BJPS

Brazilian Journal of
Pharmaceutical Sciences
vol. 50, n. 2, apr./jun., 2014
http://dx.doi.org/10.1590/S1984-82502014000200012

Article

Development of dissolution test method for a telmisartan/ amlodipine besylate combination using synchronous derivative spectrofluorimetry

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The dissolution process is considered an important *in vitro* tool to evaluate product quality and drug release behavior. Single dissolution methods for the analysis of combined dosage forms are preferred to simplify quality control testing. The objective of the present work was to develop and validate a single dissolution test for a telmisartan (TEL) and amlodipine besylate (AML) combined tablet dosage form. The sink conditions, stability and specificity of both drugs in different dissolution media were tested to choose a discriminatory dissolution method, which uses an USP type-II apparatus with a paddle rotating at 75 rpm, with 900 mL of simulated gastric fluid (SGF without enzymes) as the dissolution medium. This dissolution methodology provided good dissolution profiles for both TEL and AML and was able to discriminate changes in the composition and manufacturing process. To quantify both drugs simultaneously, a synchronous first derivative spectrofluorimetric method was developed and validated. Drug release was analyzed by a fluorimetric method at 458 nm and 675 nm for AML and TEL, respectively. The dissolution method was validated as per ICH guidance.

Uniterms: Combined dosage forms/quality control. Dissolution test/combined dosage forms. Telmisartan. Amlodipine besylate. Spectrofluorimetry/quantification analysis.

O processo de dissolução é considerado como uma importante ferramenta *in vitro* para avaliar a qualidade do produto e o comportamento de liberação do fármaco. Prefere-se um ensaio único de dissolução para formas farmacêuticas contendo associação de fármacos pela simplificação dos testes de controle de qualidade. O objetivo do presente trabalho foi desenvolver e validar um teste de dissolução único para forma farmacêutica comprimidos contendo telmisartana (TEL) e besilato de anlodipino (AML) associados. Condições "sink", estabilidade e especificidade de ambos os fármacos nos diferentes meios de dissolução foram avaliadas para selecionar um método de dissolução discriminatório, que utiliza um aparato do tipo II da USP, com pás girando a 75 rpm e 900 mL de fluido gástrico simulado (SGF sem enzima) como o meio de dissolução. Estas condições proporcionaram bons perfis de dissolução para ambos, TEL e AML, sendo capaz de discriminar as mudanças na composição e processo de fabricação. Para quantificar os dois fármacos simultaneamente, um método de fluorescência derivada sincronizado foi desenvolvido e validado. A quantidade de fármaco liberado foi analisada pelo método fluorimétrico em 458 e 675 nm para a AML e TEL, respectivamente. O método de dissolução foi validado de acordo com a orientação da ICH.

Unitermos: Forma farmacêutica com associação/controle de qualidade. Teste de dissolução/forma farmacêutica com associação. Telmisartana. Besilato de anlodipino. Espectrofluorimetria/análise quantitativa.

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INTRODUCTION

Drug dissolution testing an important analytical technique to evaluate product quality, to assess drug release behavior and to discriminate changes in the formulation and manufacturing process (Kulkarni *et al.*, 2012). The strategy to determine the solubility and permeability properties of drugs uses a biopharmaceutical classification system to classify drugs into four basic groups (Amidon *et al.,* 1995). The development of a dissolution method for a drug product with limited water solubility and combinations of drugs has been a challenge for both the pharmaceutical industry and regulatory agencies (Soni *et al.*, 2008; Dressman *et al.*, 1998; Oliveira *et al.,* 2009). Currently, there is increased demand for biorelevant dissolution media, which have the ability to discriminate changes in the formulation and manufacturing process (He *et al.,* 2004; Panikumar *et al.,* 2012; Menegola *et al.*, 2007). *In vitro* dissolution media is formulated to be biorelevant, as it should be able to serve as a surrogate of the *in vivo* environment. *In vitro* dissolution media are made biorelevant by adding various levels of bio-salts, lecithin and fatty acids (Galia *et al.,* 1998). A single dissolution method for the analysis of multiple API active components in combinations present in a dosage form is preferred to simplify quality control testing procedures (Vignaduzzo *et al.*, 2010; Huang *et al.*, 2011; Panikumar *et al.*, 2013; Zongyun *et al.*, 2011).

Telmisartan (TEL) (Figure 1A), chemically known as 4′-[(1,4′-dimethyl-l-2′-propyl[2,6′-bi-1*H*-benzimidazol]-1′yl)methyl]-[1,1′-biphenyl]-2–carboxylic acid**,** is a angiotensin–II (AT_1) receptor antagonist used in the treatment of hypertension and myocardial infarction. Amlodipine besylate (AML) (Figure 1B), chemically known as 3-ethyl-5-methyl 2-(2-amino ethoxy methyl)-4-(2-chloro phenyl)-1,4-dihydro-6-methyl pyridine-3,5-dicarboxylate benzene sulfonate, is a calcium channel blocker used in the treatment of hypertension and angina pectoris (Anthony , David, Brian, 2004). TEL and AML have been formulated in a fixed-dose combination used in the treatment of hypertension. To the best of our knowledge, no single dissolution test has been reported for TEL and AML in a combined tablet dosage form. Therefore, the objective of the present investigation was to develop and validate a single discriminating dissolution test method for TEL and AML in a combined tablet dosage form. A literature survey revealed that a few analytical methods are available for the simultaneous quantification of TEL and AML by spectrophotometry (Pratap *et al.*, 2012) and high performance liquid chromatography (Mhaske *et al.*, 2012; Kottai *et al.*, 2010). Chromatographic methods are complex, as they require expensive instrument setup and skilled operators (Basavaiah, Raghu, Vinay, 2012). Spectrophotometry methods are unsuitable for the evaluation of drugs in multi-component analysis because of the lack of specificity (Mark, Workman Jr., 2003).

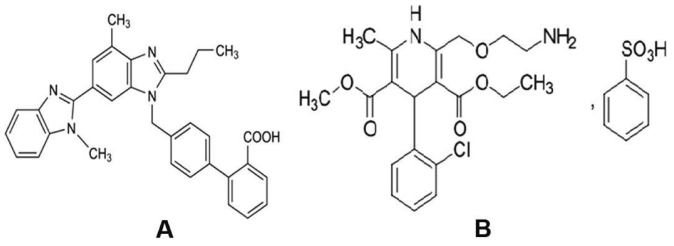

FIGURE 1- Chemical structure of telmisartan (A) and amlodipine besylate (B).

Spectrofluorimetry has assumed a major role in drug analysis because of its greater sensitivity and selectivity than absorption spectrophotometry (Gomez-Hens, 1991). The synchronous first derivative spectrofluorimetry technique is superior in terms of sensitivity, spectral discrimination, and provides more reliable identification of chemical species in multi-component analysis without interference from formulation excipients and components of the dissolution media (Andrade *et al.*, 2010; Belal *et al.*, 2011; Ei-wassef *et al.*, 2009). Therefore, we developed and validated a simple synchronous first derivative spectrofluorimetric method for the simultaneous quantification of TEL and AML in dissolution samples.

MATERIAL AND METHODS

Material

All chemicals and reagents were of analytical grade. Telmisartan (TEL) and amlodipine besylate were gift samples from Dr. Reddy's Laboratories Ltd, Hyderabad. Telsartan-AM and Sartel-AM formulations (TEL 40 mg and AML 5 mg) were purchased from local pharmacies. Hydrochloric acid, ortho-phosphoric acid, potassium dihydrogen orthophosphate, sodium hydroxide and sodium chloride were purchased from SD Fine Chemicals Ltd, Mumbai, India; sodium lauryl sulfate (SLS), Tween 80, cetrimide, lecithin and sodium taurocholate were purchased from Himedia Ltd, Mumbai, India.

Instrumentation

The fluorescence spectra and measurements were recorded using a Shimadzu (Japan) RF-5301 PC

spectrofluorophotometer, equipped with a 150 W Xenon arc lamp. A 1 cm quartz cell was used, connected to RFPC software. The instrument was operated both at low and high sensitivity with the excitation and emission slit width set at 5 nm. A dissolution apparatus (Electro lab TDT-08L), analytical balance (Shimadzu AUX 220, Japan), pH meter (Elico), tablet compression machine (Lab Press, CIP Machineries, Ahmedabad, India) and hardness tester (Secor, Hyderabad, India) were used for the study.

Analytical method

Standard solutions of TEL and AML were diluted appropriately with 1 molar (M) hydrochloric acid (HCl) to obtain solutions containing TEL (4 µg/mL) and AML (4 µg/mL). The fluorescence spectra of these diluted solutions were scanned in the spectral range of 350 to 800 nm. The normal spectra of TEL and AML were transformed to corresponding synchronous first derivative spectra in the range of 350 to 800 nm and overlapped. The first derivative spectrum of TEL had zero intensity at 458 nm, whereas AML gave a significant derivative response. The derivative spectrum of AML had zero intensity at 675 nm, whereas TEL gave a significant derivative response. Therefore, 458.0 nm was selected for the estimation of AML and 675 nm was selected for the estimation of TEL in the co-formulation and *in vitro* dissolution studies.

Dissolution test conditions

Dissolution testing of TEL (40 mg) and AML (5 mg) bulk drug-filled capsules (12 units) was performed using a paddle-type USP tablet dissolution apparatus, in 900 mL of various buffers, such as 0.1 M HCl, acetate buffer (pH 2.7 and 4.7), phosphate buffer (pH 3.6/5.6/6.8 and 7.4) and like simulated gastric fluid without enzymes (SGF); modified fasted and fed state intestinal fluids (MFaSSIF and MFeSSIF) and blank fasted and fed state intestinal fluids (FaSSIF and FeSSIF) at 50 rpm and at 37±0.5 °C for 60 min. Aliquots of 5.0 mL were withdrawn at 5 min interval up to 60 min, and replaced with an equal volume of fresh medium to maintain sink conditions. At the end of the test, the withdrawn samples were filtered, diluted with 1 M HCl and quantified by the developed and validated spectrofluorimetric method. The dissolution studies were conducted three times using four capsules in each of the media (12 units). The amount of dissolved drugs was computed from the respective calibration curves and then plotted against time. The media in which highest drug release occurred for the TEL and AML bulk drugs was the medium chosen for the *in vitro* dissolution studies of the tablet dosage form (Telsartan-AM and Sartal-AM).

Validation of the dissolution method

The method was validated by the analysis of specificity, linearity, accuracy and precision as per ICH guidelines (2005).

The specificity of the proposed method was evaluated through the analysis of a placebo solution, which was prepared with the common excipients (lactose, starch, microcrystalline cellulose, magnesium stearate, titanium dioxide and talc) of the pharmaceutical formulation. Thus, the mixture of inert components was prepared in their usual concentrations employed in tablets (concentrations were determined based on the Handbook of Pharmaceutical Excipients and calculated for the medium weight of the contents) (Raymond, Paul, Sian, 2007). The developed method was applied in order to check if any component of the formulation could generate a response or generate an emission band similar to the drugs.

Linearity was determined by constructing the plot between analyte intensity *vs*. concentration to calculate the regression line for standard dilutions of 4-14 (TEL) and 1-6 µg/mL (AML) using the linear least squares methodology.

The precision of the method was determined by intra-day precision and inter-day precision variations as per ICH guidelines. The intra-day precision and inter-day precision were assessed after subjecting six tablets to the dissolution test conditions, on the same day and on three different days respectively. The % RSD was calculated.

The accuracy was carried out by adding known amount of standard drug at 80, 100 and 120% of the nominal assay of TEL and AML to the placebo sample in the dissolution media and then subjected to the proposed dissolution method. The experiment was conducted in triplicate. The percentage recovery and percentage relative standard deviation (%RSD) were calculated for each concentration.

Stability determination

Sample solutions were prepared in the optimized dissolution media and at the same dissolution test conditions. Aliquot samples were collected initially and at 24 h intervals for 2 days and analyzed by the proposed analytical method. The drug concentrations were compared after 0, 24 and 48 h.

RESULTS AND DISCUSSION

Development of dissolution method

The selection of a dissolution test method was based on screening studies using a USP type II apparatus at a paddle speed of 50/75 rpm. The selection of a dissolution medium to provide adequate solubility and stability of both TEL and AML was critical for the selected dissolution method. The log P values of TEL and AML were 6.66 and 3.0, respectively, indicating the poor water solubility and lipophilic character of both drugs. TEL is soluble in strong acid and basic media, but strong basic media are not suitable as dissolution media because of the gastrointestinal pH range of 1.0-7.4. AML solubility was similar in all buffered media (pH 1.2-7.5). The screening results showed that the dissolution rates of both bulk drugs were higher in simulated gastric fluid (SGF) media (pH 1.2) than other media (Table I), due to the interaction between lone pairs of electrons on nitrogen atoms and the ionizable groups present in TEL and AML with NaCl, HCl molecules present in SGF media (prepared as per USP-2007, without enzymes, consisting of 2 gm sodium chloride, 0.2M hydrochloric acid to adjust pH to 1.2 and volume make upto 1000 mL). Thus, this media was useful for the quality control testing of both drugs in tablets. The pH of the dissolution medium was 1.2, i.e. within the range of gastrointestinal tract pH levels, and therefore mimicked the gastrointestinal tract environment (biorelevant). This assay was designed to provide information for pharmaceutical researchers involved in the development of new biorelevant dissolution media and in predicting the *in vivo* performance of poorly soluble drugs. Therefore, the selected dissolution test conditions were: USP type II apparatus at a paddle speed of 75 rpm in 900 mL of simulated gastric fluid (pH 1.2).

TABLE I - Screening study results for dissolution of TEL (40 mg) and AML (5 mg) bulk drug using a USP type II apparatus at 50 rpm, temperature 37 ºC±0.5 for 60 min

Dissolution media	% Drug release Mean± RSD (n = 12)	
	TEL	**AML**
0.1 N Hydrochloric acid	73.57±0.30	100.50±1.92
Acetate buffer, pH 2.7	7.11±0.28	94.88±0.35
Acetate buffer, pH 3.6	12.03±1.30	97.37±4.66
Acetate buffer pH 4.7	14.91±2.41	100.98±0.03
Phosphate buffer, pH 5.6	13.81±1.22	98.86±2.05
Phosphate buffer, pH 6.8	19.73±0.62	98.88±4.03
Phosphate buffer, pH 7.4	9.27±0.30	71.89±6.18
SGF (simulated gastric fluid without enzymes)	79.17±2.12	98.18±5.44
BFaSSIF (Blank fasted state simulated intestinal fluid)	11.89±0.825	95.42±2.58
BFeSSIF (Blank fed state simulated intestinal fluid)	5.08±0.445	98.42±2.88
MFaSSIF (Modified fasted state simulated intestinal fluid)	11.48±0.45	99.42±2.59
MFeSSIF (Modified fed state simulated intestinal fluid)	5.17±0.33	100.0±1.10
Telsartan-AM Tablets		
50 rpm, SGF media	86.66±0.29	99.28±0.01
75 rpm, SGF media	96.86±1.22	98.28±0.02
Sartel-AM Tablets		
50 rpm, SGF media	88.03±1.20	99.05±2.03
75 rpm, SGF media	93.81±1.59	99.01±2.05

In vitro dissolution studies from tablet dosage forms

Dissolution studies on Telsartan-AM and Sartel-AM tablets were performed under the optimized dissolution test conditions. These results are shown in Figures 2 and 3, and reveal that more than 90% of both TEL and AML were released from the two products.

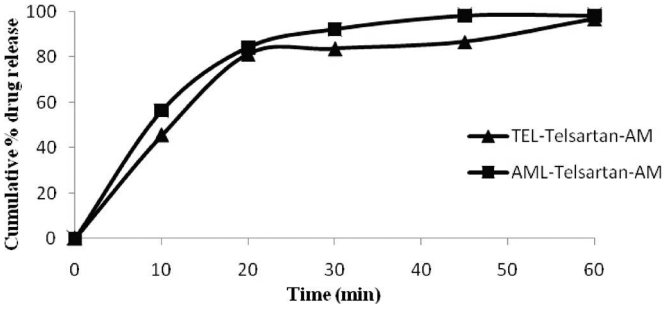

FIGURE 2 – *In vitro* dissolution profile of Telsartan-AM tablets in SGF media at 75 rpm (n = 12).

Stability studies

Both TEL and AML were found to be stable under dissolution test conditions and the measured derivative absorbance of the initial time and after 24 and 48 h was similar. There was no evidence of degradation of the drugs under the dissolution test conditions, indicating that the solutions were stable for more than 48 h.

Discriminatory power of the dissolution method

The discriminatory power of the dissolution method was determined by manufacturing tablets under different

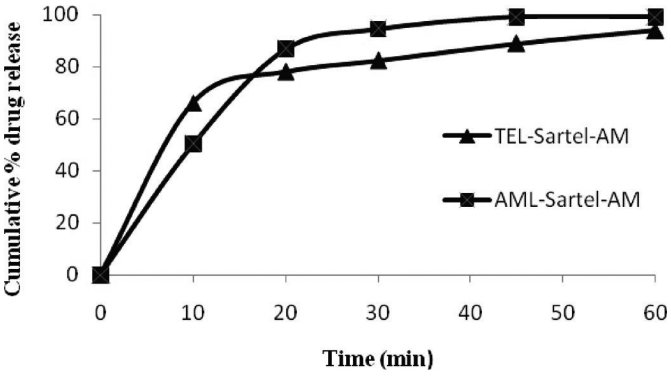

FIGURE 3- *In vitro* dissolution profile of Sartel-AM tablets in SGF media at 75 rpm (n=12).

TABLE II - Data obtained from stability studies

	% Amount of drug found		
Drug	initial time	after 24 h	after 48 h
TEL	98.01	98.05	99.05
AML	99.06	100	99.06

conditions and checking the dissolution behavior in the presence of the proposed dissolution test conditions. The effect of tablet hardness (5 kg/cm^2 *vs*. 8 kg/cm^2) and the disintegrant (with disintegrant *vs*. without disintegrant) are shown in Figures 4 and 5, revealing that dissolution rate of both drugs was slightly faster for tablets with less hardness and with a disintegrant. Therefore, this dissolution method has the ability to discriminate changes in the composition and manufacturing process. The dissolution profile data were also compared mathematically using the similarity fit factor (f_2).

$$f_2 = 50 \cdot \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n} w_t (R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

If f_2 is less than 50, then two dissolution profiles are considered dissimilar. The similarity increases as the f_2 value increases above 50 and approaches 100 (FDA 1997). The similarity factor f_2 was calculated from the dissolution profile, using five points for telmisartan and three points for amlodipine besylate. Among these, one point was found to indicate more 85% of drug release.

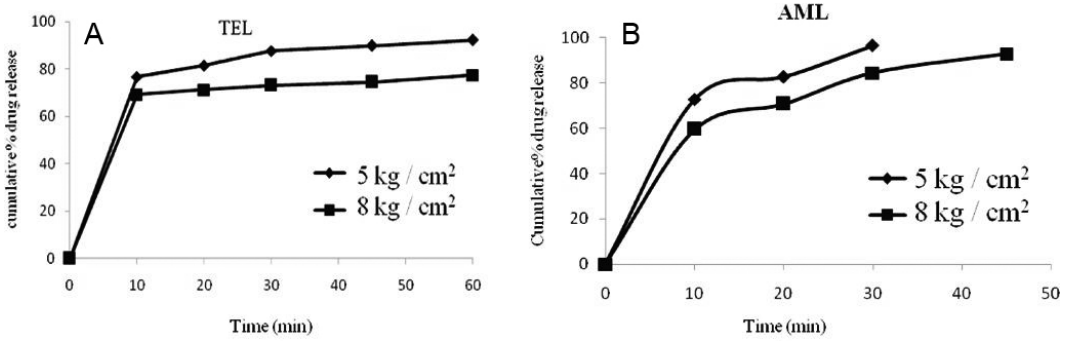

FIGURE 4 - Comparison of dissolution profiles of TEL/AML tablets manufactured with different hardness.(A) Profile for TEL and (B) for AML.

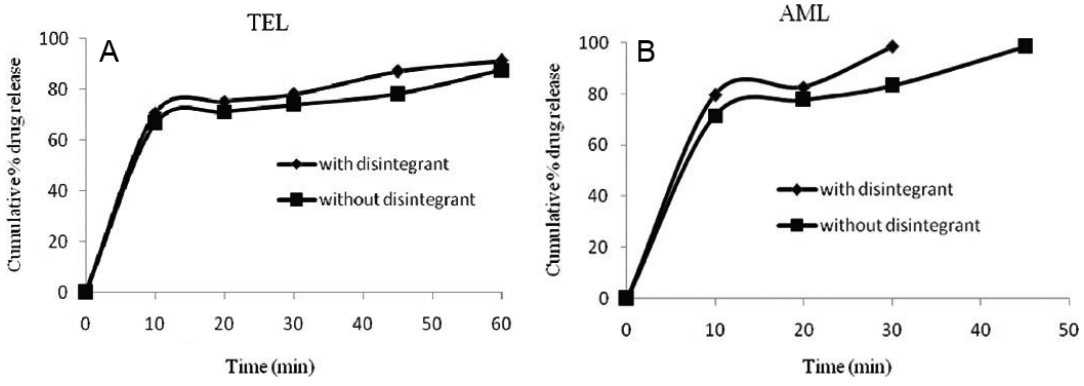

FIGURE 5- Comparison of dissolution profiles of TEL/AML tablets manufactured with and without a disintegrant.(A) Profile for TEL and (B) for AML.

Table III lists the f_2 values used for the comparison of the dissolution profiles for each of the process parameters evaluated. These results confirm that the dissolution test procedure has discriminating power regarding variation in the composition and manufacturing process.

TABLE III - Similarity factor (f_2) for dissolution profiles of tablets with different parameters

	f_2 Value	
Process parameter	Tablets with hardness of 5 kg/cm^2 vs. 8 kg/cm^2	Tablets containing disintegrant vs. no disintegrant
TEL	44.47	63.14
AML	46.14	49.21

Method validation

Specificity

The synchronous fluorescence derivative spectra of the placebo, TEL and AML in the dissolution medium are shown in Figure 6. Perusal of the figure shows that there was no interference from the excipients in the tablets and dissolution medium with the derivative response of either of the drugs (TEL and AML) at their respective analytical wavelengths. Therefore, the proposed method is specific.

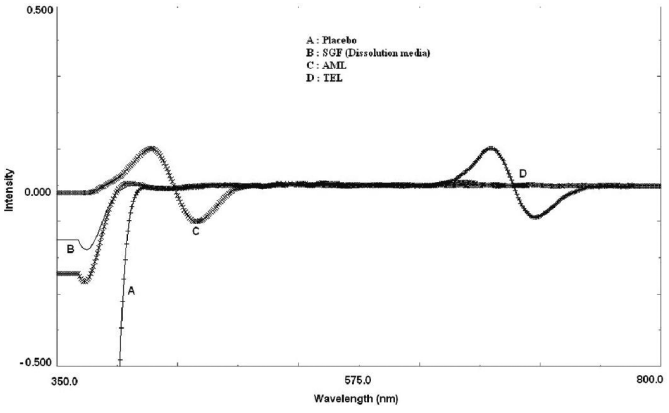

FIGURE 6 - Synchronous first order derivative spectrum of placebo (A), blank dissolution medium (B), AML (C) and TEL (D).

Linearity

The linearity was evaluated by the least square regression method. The responses for TEL at 675 nm were found to be linear in the concentration range of 4-14 µg/mL, with a correlation coefficient (r) value of 0.997. Similarly, the responses for AML at 458 nm were linear in the concentration range of 1-6 µg/mL, with a correlation coefficient (r) value of 0.999. The results indicate a good linear relationship between the derivative response and concentration. Linearity plots are shown in Figure 7.

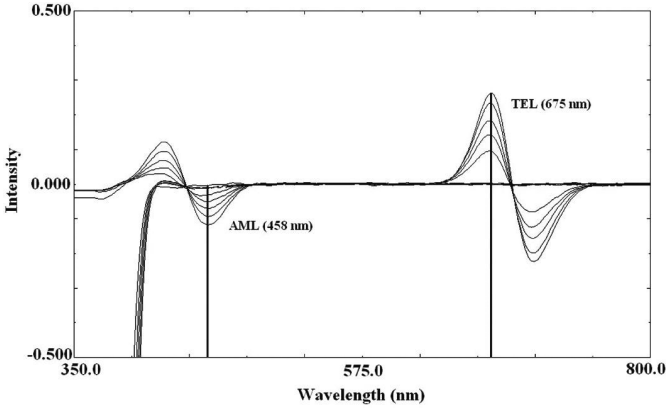

FIGURE 7 - First derivative synchronous linearity spectrum of amlodipine besylate (AML) and telmisartan (TEL).

Precision

The percent relative standard deviation values for intra and inter day precision studies were found to be less than 2 and there was no significant difference observed between the intra- and inter-day values, which indicates that the proposed method was reproducible and precise. The results are reported in Table IV.

Accuracy

Accuracy shows the agreement between the standard value and the observed value. The accuracy results of the proposed dissolution method are reported in Table V. Percent recovery was from 97.0-99.0% and percent relative standard values were less than 2; this signifies that the dissolution method is accurate for its intended use.

CONCLUSION

The discriminating and dissolution test developed and validated for TEL/AML tablets was considered satisfactory. The best conditions optimized for dissolution testing for TEL/AML tablets were: 900 mL of simulated gastric fluid (SGF without enzymes), a paddle-type apparatus, stirring speed of 75 rpm, a temperature of 37 ºC±0.5 and collection time of 60 min. The dissolution studies for TEL and AML combination tablets in the proposed dissolution media were found to be better, because of their discriminating power, utility as a surrogate of the gastrointestinal tract environment (biologically relevant). In addition, these studies provide information for pharmaceutical researchers involved in the development of new biorelevant dissolution media and predicting the *in vivo* performance of poorly soluble drugs. The

TABLE IV - Precision data for the proposed dissolution method

Product	TEL				AML			
	Intra-day (%)		Inter-day (%)		Intra-day (%)		Inter-day (%)	
	Mean±SD	%RSD	Mean±SD	%RSD	Mean±SD	%RSD	Mean±SD	%RSD
Telsartan-AM	96.86±1.07	1.11	97.28±0.78	0.80	98.28±0.11	0.11	99.98±0.99	0.99
Sartel –AM	93.81±0.59	0.63	99.10±0.98	0.98	99.01±1.05	1.06	98.89±1.25	1.264

TABLE V - Results for accuracy for the proposed dissolution method

Analyte	% level of recovery	Amount (mg)			
		Added	Recovered	%Recovery	%RSD
TEL	80	32	31.56	98.62	1.10
	100	40	38.82	97.05	0.89
	120	48	47.52	99.0	1.24
AML	80	4	3.90	97.5	1.02
	100	5	4.85	97.0	0.98
	120	6	5.89	98.16	0.85

results obtained from validation show that the proposed dissolution method was scientifically sound. These advantages encourage the routine use of the developed dissolution method in the quality control analysis of TEL and AML in tablet dosage forms.

ACKNOWLEDGMENTS

The authors are thankful to the management of Gokaraju Rangaraju College of Pharmacy for providing necessary facilities and infrastructure to carry out this research work.

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Received for publication on 21st May 2013
Accepted for publication on 21st January 2014