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published in
Chromatographia
2007

DOI (link to publisher)
10.1365/s10337-006-0166-6

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
Savaser, A., Goraler, S., Tasoz, A., Uslu, B., Lingeman, H., & Ozkan, S. A. (2007). Determination of abacavir, lamivudine and zidovudine in pharmaceutical tablets, human serum and in drug dissolution studies by HPLC. *Chromatographia*, *65*(5-6), 259-265. https://doi.org/10.1365/s10337-006-0166-6

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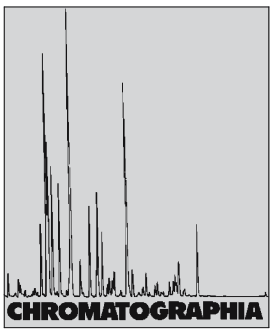
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Determination of Abacavir, Lamivudine and Zidovudine in Pharmaceutical Tablets, Human Serum and in Drug Dissolution Studies by HPLC



2007, *65*, 259–265

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Received: 31 October 2006 / Revised: 22 November 2006 / Accepted: 23 November 2006
Online publication: 10 January 2007

Abstract

A simple, accurate, precise and fully automated method for the simultaneous determination of abacavir, lamivudine and zidovudine in pharmaceutical tablets, human serum samples and drug dissolution studies has been developed. Separation was performed on a 5 μm Zorbax® C_{18} column (150 × 4.6 mm ID) with methanol:water:phosphate buffer at pH 5.65 (80:10:10; *v/v/v*) isocratic elution in less than 7 min with a flow rate of 0.6 mL min^{-1}.Good sensitivity for all analytes was observed with UV detection at 275 nm. The method allowed quantitation over the 500–3,000 ng mL^{-1} range for abacavir and 500–5,000 ng mL^{-1} range for lamivudine and zidovudine. The method has been applied, without any interference from excipients or endogenous substances, for the simultaneous determination of these three compounds in tablets. Human serum and drug dissolution studies.

Keywords

Column liquid chromatography
Tablets in dosage form
Human serum
Dissolution studies
Abacavir, lamivudine and zidovudine

Introduction

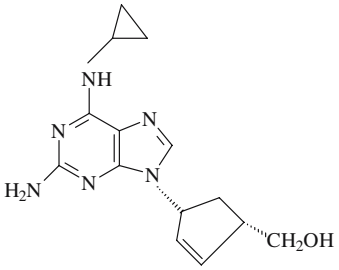
Trizivir® tablets contain three nucleoside analogues namely abacavir sulfate (ABA), lamivudine (LAM) and zidovudine (ZDV). These compounds belong to the category of HIV medicines called nucleoside reverse transcriptase inhibitors. Trizivir prevents HIV from entering the nucleus of healthy T-cells, which subsequently prevents the cells from producing new viruses and decreases the amount of virus in the body. ABA, LAM and ZDV (Fig. 1) are three synthetic nucleoside analogues.

Trizivir tablets are used for oral administration. Each film-coated tablet contains 300 mg of abacavir sulfate, 150 mg lamivudine and 300 mg zidovudine [1, 2]. ABA is converted by cellular enzymes to the active metabolite, carbovir triphosphate, an analogue of deoxyguanosine–5′ triphosphate. It inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate deoxyguanosine-5′ triphosphate and its incorporation into viral DNA [1, 2]. ABA is rapidly absorbed following oral administration with a bioavailability of about 80%. It is about 50% bound to plasma proteins. The elimination half-life is about 1.5 h following a single dose [1, 2].

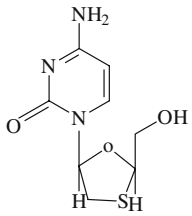
LAM is the (−) enantiomer of a dideoxy analogue of cytidine. LAM was initially developed for the treatment of HIV infection. Although, generally less potent than ZDV in inhibiting HIV-1 and -2 replication in vitro, LAM has very low cellular cytotoxicity. It is rapidly absorbed with a bioavailability of approximately 80% [1, 2].

ZDV is a synthetic nucleoside analogue and structurally similar to thymidine. The principal mode of action of ZDV triphosphate is the inhibition of reverse transcriptase via DNA chain termination after incorporation of the nucleoside analogue. ZDV is rapidly absorbed from the gastrointestinal tract with a bioavailability of about 60–70%. It passes the blood-brain barrier [1, 2].

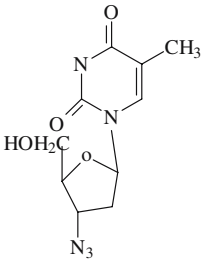
DOI: 10.1365/s10337-006-0166-6
0009-5893/07/03
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Abacavir



Lamivudine



Zidovudine

Fig. 1. Chemical structures of ABA, LAM and ZDV

There have been several publications describing analytical methods for the determination of ABA, LAM and ZDV individually. A few methods have been described for the simultaneous determination of LAM and ZDV, as binary mixtures, in biological samples and pharmaceutical dosage forms [3–6]. Most of the reported methods require solid-phase extraction or expensive equipment unsuitable for routine use in pharmacokinetic and pharmaceutical studies where many samples need to be analyzed. However, there have been no reports concerning the simultaneous determination of ABA, ZDV and LAM using HPLC except the recently published method using chemometric optimization and LC analysis in tablets [7]. Dissolution rate studies and related kinetic parameters of Trizivir® tablets and analysis of biological samples have not been reported.

Drug dissolution testing is an integral part of pharmaceutical development and routine quality control monitoring of drug release characteristics [8]. The profiles, obtained from dissolution rate studies, have also been used in an attempt to characterize the in vivo behaviour of drugs with success [9–11]. They have to be performed under precisely specified conditions (i.e., temperature, volume, and stirring rate) that mimic processes in the human gastrointestinal tract.

LC methods are widely used in the determination of drugs in pharmaceutical dosage forms and biological samples [12–14]. The goal of this work was the development of a new, rapid, sensitive and fully validated method for the direct and simultaneous determination of ABA, LAM and ZDV in raw materials, pharmaceutical dosage forms and spiked human serum samples without any time-consuming extraction or evaporation steps prior to the assay. This work also aimed at the simultaneous determination of ABA, LAM, and ZDV from drug dissolution tests.

Experimental

Equipment and Chromatographic Conditions

The chromatographic system consisted of an HP Agilent 1100 series with an Agilent series G-13158 DAD detector and an Agilent 1100 series G-1329 ALS autosampler. The data were handled with Agilent Technologies HP 1100 software. Separation was with a 5 μm Zorbax C_{18} column (150 × 4.6 mm ID) at ambient temperature. Isocratic elution was with a mixture of methanol:water:phosphate buffer at pH 5.65 (80:10:10; *v*/*v*/*v*) at a flow rate of 0.6 mL min^{-1}. The UV detector was set at a wavelength of 275 nm. An injection volume of 20 μL was used. Granisetron was used as an internal standard.

The dissolution rate studies of ABA, LAM, ZDV from tablets were performed on a Caleva 7ST dissolution apparatus (G.B. Caleva Inc., England).

Chemicals and Reagents

Abacavir, lamivudine and zidovudine and Trizivir® tablets (claimed labelled amount 300 mg ABA, 150 mg LAM and 300 mg ZDV per tablet) were kindly supplied by Glaxo-Smith-Kline Pharm. Inc. (Istanbul, Turkey). The internal standard, granisetron, was received from Roche Pharm. Inc (Istanbul, Turkey). HPLC-grade methanol was purchased from Merck (Darmstadt, Germany). All other chemicals (analytical grade) were obtained from Sigma (St Louis, MO, USA) or Merck. Double-distilled water was used throughout.

For dissolution studies, working solutions of 0.1 M HCl (pH 1.2) and 0.1 M HCl; Na_3PO_4 mixture (pH 7.4) was used to mimic the physiological conditions in gastric and enteric fluids, respectively.

Stock and Working Solutions

Stock solutions of ABA and LAM (1.0 mg mL^{-1}) were prepared by dissolving 10.0 mg of each drug in 10 mL mobile phase. The standard for ZDV was made up in methanol to obtain a final concentration of 1.0 mg mL^{-1}. The internal standard was prepared by dissolving 10 mg granisetron in 10 mL of the mobile phase. Stock solutions were appropriately diluted with the mobile phase for the preparation of working solutions (final concentration ranging between 500 and 5,000 ng mL^{-1} and the concentration of IS was maintained at a constant level of 5,000 ng mL^{-1}. Separate standard calibration graphs were constructed for each component by plotting the ratio of the peak area of the drug to that of IS against the drug concentration. The slopes, intercepts, correlation coefficient, and related validation parameters such as LOD, LOQ, standard error of slope and intercept were tabulated for each compound.

All solutions were protected from light and were used within 24 h to avoid decomposition. However, chromatograms of sample solutions recorded over a period of a week after preparation did not show any appreciable change in assay values.

Ruggedness, Accuracy and Precision

The ruggedness and intra-day and inter-day precision and accuracy of the methods were estimated by assaying five replicate samples at three different concentrations, on the same day and on five different days over a 2 weeks period. For checking the ruggedness and precision of the method, the relative standard deviations (RDSs) were calculated and tabulated. The accuracy of the methods was expressed as percentage bias [15, 16]. Accuracy of the methods was also determined by recovery studies.

Procedure for Tablets

Ten tablets, labelled as containing 300 mg ABA, 150 mg LAM and 300 mg ZDV together with excipients, were accurately weighed, crushed and finely powdered. A weight of the powder equivalent to one tablet content was accurately weighed, transferred into a 100 mL calibrated flask, diluted with a mixture of methanol:mobile phase (9:1; *v*/*v*), stirred for about 10 min and then completed to volume with the same solution. This solution was filtered and the filtrate was collected in a clean flask. After filtration, solutions were prepared by taking suitable aliquots of the clear filtrate, addition of a constant amount of IS and diluting with mobile phase in order to obtain the final solution. The amounts of ABA, LAM and ZDV were calculated from the corresponding regression equations.

Recovery Studies from Tablets and Laboratory-Made Mixtures

To verify the accuracy of the method, recovery experiments were performed by adding a known amount of pure drug to pre-analyzed tablets. The percent recovery was calculated by comparing the concentration obtained from spiked samples with the actual added concentration. Thus, the effect of common tablet formulation excipients on chromatograms (e.g., tailing, broadening) was investigated. Recovery experiments from tablets also showed the reliability and suitability of the method. Known amounts of the pure drug and internal standard, at a constant level, were added to the ABA, LAM and ZDV tablet formulation and the mixtures were analyzed. After five repeated experiments, the recoveries were calculated for each compound.

In order to demonstrate the applicability of the method, the recovery tests were also carried out by analyzing synthetic mixtures of ABA, LAM and ZDV. After five repeated experiments, the recoveries from these synthetic mixtures were calculated for each compound.

Analysis of Spiked Serum Samples

Drug free serum samples, obtained from healthy individuals, were stored frozen until assay. After gentle thawing, an aliquot of sample was fortified with ABA, LAM and ZDV dissolved in selected media as indicated above. To achieve a final concentration of 1 mg mL^{-1} and using 1 mL of acetonitrile as serum denaturating and precipitating agent, the volume was completed to 2.5 mL with the same serum sample. The tubes were vortex mixed for 5 min and centrifuged for 10 min at 5,000*g*. The supernatant was carefully taken. The concentration of ABA, LAM and ZDV was varied between 500–5,000, 500–5,000 and 500–3,000 ng mL^{-1}, respectively, in human serum and the concentration of IS was maintained at a constant level of 5,000 ng mL^{-1}. Separate standard calibration lines were constructed for each component by plotting the ratio of the peak area of the drug and the IS against the drug concentration. The related validation parameters were tabulated for each investigated anti-HIV compound.

In Vitro Dissolution Studies from Tablet Dosage Form

Drug dissolution studies were carried out in 900 mL of 0.1M HCl (pH 1.2, simulated gastric medium) according to the USP 24 [17] dissolution procedures for the single entity products with the use of a USP paddle-stirrer type of apparatus for the first 60 min at a stirring rate of 75 rpm.

As an alternative method, 700 mL, 0.1 N HCl (pH 1.2; simulated gastric medium) was used for the first 45 min. After 45 min, the medium pH was adjusted to 7.4 by adding Na_3PO_4 (pH 7.4, simulated enteric medium). The dissolution test was continued in this medium for an additional 75 min using the same stirring rate. The temperature of the cell was maintained at 37 ± 0.5 °C. At each sample time, an exact volume of the sample was withdrawn and immediately replaced with an identical volume of fresh medium. At predetermined times, (5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120 min) the concentration of each drug in the dissolution medium was determined using the related linear regression equation. The cumulative percentage of drug released in the media was plotted against time in order to determine the release profile from the tablet formulation. The dissolution test data were obtained by averaging six parallel studies.

Results and Discussion

The method provides a simple procedure to determine simultaneously the concentration of ABA, LAM and ZDV in pharmaceutical dosage forms and spiked serum samples. To develop a rugged and suitable LC method, various mobile phase compositions and different types of columns were tested. Preliminary trials using mobile phases consisting of a mixture of water, methanol and acetonitrile in different ratios did not give good peak shapes and analysis times. Addition of KH_2PO_4 buffer (7.3 mM) instead of acetonitrile improved the peak shape of all compounds as well as the IS. Finally, by using a buffer pH of 5.65 and a mobile phase consisting of a mixture of methanol:water:7.3 mM KH_2PO_4 (8:1:1; *v*/*v*/*v*) at a flow rate of 0.6 mL min^{-1}, ABA, LAM, ZDV and the IS, baseline resolution was obtained and good peak shapes observed without tailing.

The chemical structure of granisetron is not similar to the investigated compounds. However, it was chosen as the IS because it showed a shorter retention time with better peak shape and better resolution from the investigated

Table 1. Statistical data for the calibration graphs of ABA, LAM and ZDV in mobile phase and serum samples

	Mobile phase			Serum		
	ABA	LAM	ZDV	ABA	LAM	ZDV
Linearity range (ng mL^{-1})	500–3,000	500–5,000	500–5,000	500–5,000	500–3,000	500–3,000
Slope	6.483×10^{-4}	7.273×10^{-4}	2.198×10^{-4}	4.580×10^{-4}	2.150×10^{-4}	2.040×10^{-4}
Intercept	5.275×10^{-2}	0.125	9.449×10^{-2}	7.995×10^{-3}	0.421	8.660×10^{-3}
Correlation coefficient	0.999	0.999	0.997	0.999	0.999	0.999
SE of slope	1.923×10^{-5}	1.089×10^{-5}	7.886×10^{-6}	6.370×10^{-6}	5.660×10^{-6}	5.450×10^{-6}
SE of intercept	3.108×10^{-2}	2.740×10^{-2}	1.986×10^{-2}	1.610×10^{-2}	0.0091	8.810×10^{-3}
LOD (ng mL^{-1})	21.87	63.03	110.32	11.01	95.65	41.18
LOQ (ng mL^{-1})	72.90	210.09	367.74	33.36	290.47	124.79
Repeatability (RSD%)[a]	0.513	0.831	0.680	0.317	0.502	1.203
Reproducibility (RSD%)[b]	2.61	2.25	2.06	1.37	2.49	2.08

[a]Each value is obtained from five experiments
[b]Between-day reproducibility is determined from five different runs over a 2 weeks period

Table 2. Determination of ABA, LAM and ZDV in laboratory-made mixtures

Added (ng mL^{-1})			Found (ng mL^{-1})			Recovery (%)			RSD (%)			Bias (%)		
ABA	LAM	ZDV	ABA[a]	LAM[a]	ZDV[a]	ABA	LAM	ZDV	ABA	LAM	ZDV	ABA	LAM	ZDV
3,000	500	3,000	–	494.99	–	–	99.00	–	–	1.036	–	–	1.002	–
3,000	1,000	3,000	–	999.49	–	–	99.95	–	–	1.809	–	–	0.051	–
3,000	1,500	3,000	–	1,498.67	–	–	99.91	–	–	1.149	–	–	0.089	–
3,000	3,000	3,000	–	2,988.72	–	–	99.62	–	–	0.481	–	–	0.376	
Mean recovery (%)							99.51							
RSD (%)							0.382							
500	1,500	3,000	496.92	–	–	99.38	–	–	1.56	–	–	0.616	–	–
1,000	1,500	3,000	999.39	–	–	99.94	–	–	1.212	–	–	0.061	–	–
1,500	1,500	3,000	1,505.07	–	–	100.34	–	–	0.794	–	–	−0.338	–	–
3,000	1,500	3,000	2,955.90	–	–	98.53	–	–	1.924	–	–	1.47	–	–
Mean recovery (%)						99.55								
RSD (%)						0.788								
3,000	1,500	500	–	–	494.46	–	–	98.89	–	–	1.089	–	–	1.108
3,000	1,500	1,000	–	–	996.39	–	–	99.64	–	–	1.094	–	–	0.361
3,000	1,500	1,500	–	–	1,504.01	–	–	100.27	–	–	0.718	–	–	−0.267
3,000	1,500	3,000	–	–	2,963.60	–	–	98.79	–	–	1.228	–	–	1.213
Mean recovery (%)								99.40						
RSD (%)								0.699						

[a]Each value is the mean of three experiments

compounds peaks, compared with other potential internal standards. After determining the optimum conditions, a satisfactory resolution was obtained in a short analysis time. For all compounds sharp and symmetrical well-resolved peaks were obtained.

The USP suggests that system suitability tests be performed prior to analysis [17]. The parameters include tailing factor, capacity factor, theoretical plate number, retention time, asymmetry factor, selectivity and RSD% of peak height or area for repetitive injections. Typically, at least two of these criteria are required to demonstrate system suitability for the proposed method. Some of the tests were carried out on freshly prepared standard solutions including all three compounds and the IS. Tailing factors of 0.95, 1.15, 1.17, 1.28 were obtained for LAM, ABA, ZDV and IS, respectively, with asymmetry factors of 1.05; 0.95; 1.14 and 1.23. The theoretical plate number (N) and selectivity factor were 1,849 and 3.83 for LAM, 2,064.8 and 2.87 for ABA, 3,340.3 and 1.57 for ZDV. The chromatographic conditions described ensured adequate retention and resolution for all analytes. The retention times of LAM, ABA, ZDV and IS were 2.52; 2.90; 6.52 and 4.71 min. The variation in retention time for five replicate injections of all compounds reference solutions gave RSDs of 0.903% for LAM, 0.899% for ABA, 0.172% for ZDV and 0.404% for the IS. The results obtained from the system suitability tests satisfy the USP requirements.

The calibration curves and equations for ABA, LAM and ZDV in the mobile phase and serum samples were calculated by plotting the peak area ratio of compound to IS *vs* concentration of compound in the range of 500–5,000 ng mL^{-1} for all compounds in the mobile phase. Linearity was obtained in serum samples in the range of 500–5,000 ng mL^{-1} for ABA and LAM and 500–3,000 ng mL^{-1} for ZDV. Linear regression parameters of the peak area ratios versus concentration of the compounds are presented in Table 1. These results showed highly reproducible calibration curves with correlation coefficients of >0.999. The low SE values of the slope and the intercept in both media show the precision of the proposed method. The LOD and LOQ were calculated from the following equations and using the standard deviation (s) of response and the slope (m) of the corresponding calibration curve.

Table 3. Results of the assay and the recovery analysis of ABA, LAM and ZDV in tablet dosage forms and human serum

	Tablets (mg)			Serum samples (ng mL^{-1})		
	ABA	LAM	ZDV	ABA	LAM	ZDV
Labeled claim (mg per tablets)	300.00	150.00	300.00	–	–	–
Amount found (mg)[a]	300.34	149.60	300.85	–	–	–
RSD (%)	0.688	0.659	0.822	–	–	–
Bias (%)	−0.113	0.267	−0.283	–	–	–
Added (mg)	30.00	15.00	30.00	1,000	500	1,000
Found[a]	29.84	14.90	30.05	998.90	492.07	1,007.03
Recovery (%)	99.45	99.34	100.17	99.89	98.41	100.70
Bias (%)	0.53	0.67	−0.17	0.11	1.59	−0.703
RSD % of recovery	0.977	0.562	0.880	1.002	1.463	1.108

[a] Mean value of the five determination

LOD = 3.3 s/m; LOQ = 10 s/m [15, 16],

Precision, accuracy and reproducibility of the method were assessed by performing replicate analysis of standard solutions in the mobile phase and serum, Repeatability and reproducibility were characterized by RSD% (Table 1). Based on these results, there was no significant difference for the assay, as tested by within-day (repeatability) and between-day (reproducibility).

The stability of the reference compounds and sample solutions were checked by analyzing a standard solution of the compounds in the mobile phase stored at +4 °C, in the dark against a sample freshly prepared. The results demonstrated that the working reference solutions were stable for up to a week.

Recovery tests were carried out by analyzing synthetic mixtures of ABA, LAM and ZDV, with different composition ratios (Table 2).

Each film-coated tablet contains the active ingredients 300 mg of ABA as abacavir sulfate, 150 mg LAM and 300 mg of ZDV and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glyclate. The tablets are coated with a film (Opadry® green 03B11434) made of FD &C Blue No. 2, hypromellose, polyethylene glycol, titanium dioxide, and yellow iron oxide. Removal of the excipients before analysis was found to be unnecessary.

The substances were eluted as symmetrical single peaks, well separated from the solvent front. The utility of the method was verified by means of replicate estimation of pharmaceutical preparations and the results were evaluated statistically (Table 3). The results indicate that the method is suitable for simultaneous determination and routine quality control of these compounds in pharmaceutical formulations.

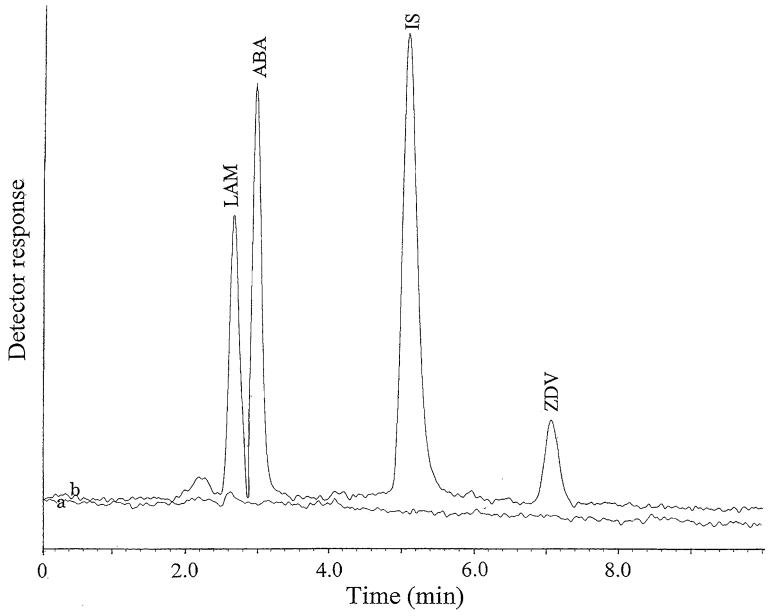


Fig. 2. Representative chromatograms of ABA, LAM, ZDV and IS *a* drug free serum sample and *b* serum samples spiked with 500 ng mL^{-1} LAM; 1,000 ng mL^{-1} ABA; 5,000 ng mL^{-1} IS; 750 ng mL^{-1} ZDV

Recovery studies were also conducted with the tablets using the standard addition method to determine the accuracy and precision. The recovery was measured by spiking the already analyzed samples of tablets with known concentrations of standard solutions of the studied compounds. The results (Table 3) indicate the absence of interferences from the common pharmaceutical excipients used in the selected formulations. It is concluded that the method is sufficiently accurate and precise in order to be applied to tablet dosage forms.

Validation with spiked human serum samples was carried out by use of the appropriate calibration equations obtained with spiked serum samples. Analysis of drugs from serum samples usually requires extensive time-consuming sample preparation and the use of organic solvents. In this study, the serum proteins were precipitated by the addition of acetonitrile followed by centrifugation at 5,000*g*. The supernatant was diluted with mobile-phase and samples, including various concentrations of ABA, LAM and ZDV and a constant amount of IS, directly injected into the LC column. A chromatogram obtained from a spiked serum sample is shown in Fig. 2b with a blank serum sample in Fig. 2a. The chromatograms show that there are no

Table 4. Kinetic assessment of release data

Kinetics	Parameter	ABA	LAM	ZDV
Zero order	k_r^0	133.16	71.25	208.45
	r^2	0.53	0.57	0.83
	SWSD	0.22	1.98	2.41
	AKAIKE's information criteria	17.82	15.38	8.51
First order	k_r	6.03	6.13	5.14
	r^2	0.70	0.70	0.63
	SWSD	5.34	7.86	788.56
	AKAIKE's information criteria	4.40	8.52	49.29
Hixson-Crowell	k	3.27	2.46	1.62
	R^2	0.67	0.67	0.75
	SWSD	0.80	0.78	8.38
	AKAIKE's information criteria	−25.94	−24.39	24.53
Weibull distribution (RRSBW)	T (min)	27.10	28.91	86.78
	β	2.21	2.34	4.51
	r^2	0.90	0.90	0.84
	SWSD	529.29	1,910.55	1.04
	AKAIKE's information criteria	−53.71	−60.92	−16.26

k_r release rate constant of first-order kinetics, k_r^0 release rate constant of zero-order kinetics, k release rate constant of Hixson-Crowell kinetics, r^2 determination coefficient, *SWSD* sum of weighed squared deviations, β shape factor, T (min) time for 63.2% release of the drug

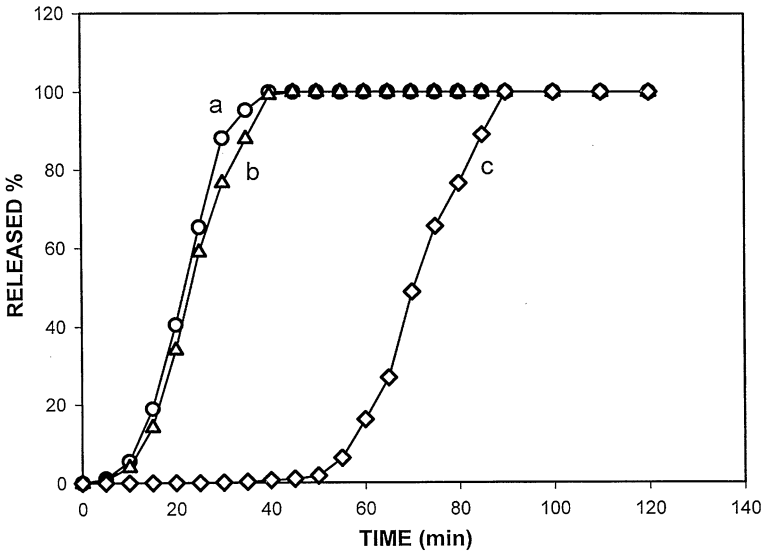


Fig. 3. In vitro dissolution profiles of ABA *a*, LAM *b*, and ZDV *c* from tablet dosage form

interferences from endogenous substances present in the matrix.

The results and recoveries of known amounts of ABA, LAM and ZDV added to serum samples are given in Table 3. The method provides reproducible results, is easy to perform, and sensitive enough for simultaneous determination of ABA, LAM and ZDV in human serum.

The amounts of ABA, LAM and ZDV found in tablets by existing analytical methods are fairly close to the labelled amounts [7]. However, the method described here is more sensitive and precise having better LOD and LOQ values and linear range. The determination of ABA, LAM and ZDV in serum and in the presence of each other by HPLC was established for the first time.

The method was also applied to the simultaneous determination of ABA, LAM and ZDV in dissolution rate studies. Trizivir® tablets, which include 300 mg ABA, 150 mg LAM and 300 mg ZDV, were investigated by the paddle dissolution method. The cumulative percentage of drug released versus the time profile is show in Fig. 3 for all compounds. As can be seen in this figure, more than 90% ABA and LAM dissolved in pH 1.2 (gastric media) within 35.0 and 40.0 min, respectively; ZDV did not dissolve in this medium.

In this first test, 900 mL 0.1 N HCl (pH 1.2) was used for 60 min at 37 ± 0.5 °C. In the second test the medium was changed. For the first 45 min, 700 mL 0.1 N HCl (pH 1.2) was used then 200 mL of 0.2 M trihydrogen sodium phosphate was added to simulate enteric fluid (pH 7.4). The concentration of the drug and the percentage released were determined at predetermined time intervals. Figure 3c shows that more than 90% ZDV dissolved in enteric medium within 85.0 min. The release data were evaluated according to different models namely zero order, first order, Hixson-Crowell and Weibull distrubution (RRSBW) [18, 19] function. All the kinetics, related rate constants and parameters are shown in Table 4. For the release profile (Fig. 3) the best compliance according to the highest determination coefficient and lowest AKAIKE's information criteria for ABA, LAM and ZDV dosage form was found with the Weibull distribution (RRSBW). The release of ABA, LAM and ZDV from tablets was determined to be 63.2%, by the end of 27.10, 28.91, and 86.78 min, respectively. The shape factor (β) value was found to be lower than 2.5 for ABA and LAM and 4.6 for ZDV. The release of compounds from the tablets tested was completed within 40.0 min, for ABA and LAM and 90.0 min for ZDV.

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