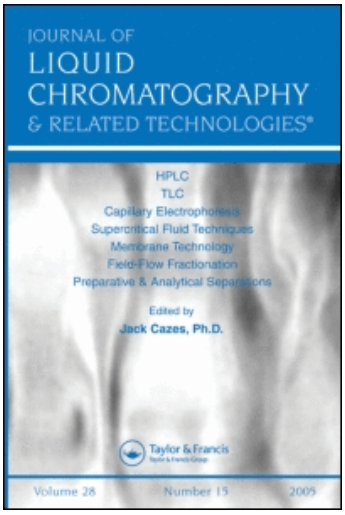

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RAPID AND ACCURATE SIMULTANEOUS DETERMINATION OF FOSINOPRIL SODIUM AND HYDROCHLOROTHIAZIDE IN TABLETS BY HPLC

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ABSTRACT

A new, simple, precise, accurate, and rapid reverse-phase high performance liquid chromatographic (RP-HPLC) method has been developed for the simultaneous determination of fosinopril sodium and hydrochlorothiazide from tablets. The procedure is based on the use of the RP-HPLC method with a UV detector. Each analysis requires no longer than 6 minutes. A reversed phase C_{18} column with a mobile phase composed of a mixture of methanol: water (40:60, v/v), adjusted to pH 4 with 10% orthophosphoric acid, was used to separate both compounds with

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sulfamethoxazole, as an internal standard, in a reasonable time period.

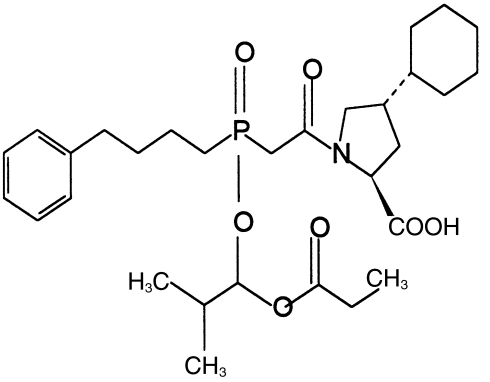
The linearity range for fosinopril sodium and hydrochlorothiazide was 1.6–30 μg/mL and 1–30 μg/mL, respectively. The detection limits for fosinopril sodium and hydrochlorothiazide were 0.29 μg/mL and 0.26 μg/mL, respectively.

INTRODUCTION

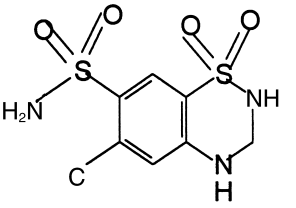
Fosinopril sodium (FS) is an angiotensin-converting enzyme inhibitor with action and use similar to that of captopril. It is converted in the body to its active metabolite, fosinoprilat. Fosinopril is given as the sodium salt. hydrochlorothiazide, which is a member of thiazide diuretics, and is most widely used for the treatment of hypertension, either alone or in combination with other antihypertensive drugs, i.e. fosinopril.[1,2]

A literature survey reveals very few analytical reports for the analysis of FS, individually based on capillary electrophoresis[3,4] and liquid chromatography,[4] or in its combination with HCT based on spectrophotometry.[5]

There have been several reports on the determination of HCT, individually or in its combination with other drugs, including the use of liquid chromatography,[6–9] capillary zone electrophoresis,[10] and spectrophotometry.[11–14]



Fosinopril



Hydrocholorothiazide

In this work, a binary mixture of FS and HCT was analysed employing, simple, fast, and accurate reversed-phase high performance liquid chromatography in bulk material and in tablet dosage forms at a single wavelength.

EXPERIMENTAL

Apparatus

A liquid chromatographic system consisted of a Waters Isocractic LC pump 510, with an automatic sample injection system (Waters 717 plus Autosampler), equipped with a Waters 996 photodiode array detector. A Bondapak C_{18} reverse phase column packed with 10 μm dimethyl octadecylsilyl bonded amorphous silica (300 mm × 3.9 mm) was used as the stationary phase.

Chemicals and Reagents

Fosinopril sodium in tablet dosage forms (Monopril Plus) were kindly supplied by Bristol Myers Squibb Pharm. Ind. (Istanbul,Turkey). Hydrochlorothiazide was procurred from Nobel Drug Inc. (Istanbul, Turkey) and internal standard sulfamethoxazole was kindly supplied by Fako Drug Inc. (Istanbul, Turkey).

Chromatographic grade, double distilled water, methanol, and analytical reagent grade orthophosphoric acid (Merck) were used.

Standard Stock Solution

Accurately weighed 10 mg of standard FS and HCT were taken separately in a 10 mL volumetric flask. 10 mL methanol was added and kept in an ultrasonic bath for 5 min. Standard solutions for HPLC were prepared with a mobile phase by varying the concentration of FS in the range of 1.6 – 30.0 μg/mL and HCT in the range of 1.0–30.0 μg/mL.

The concentration of sulfamethoxazole (internal standard) was maintained at a constant level of 30.0 μg/mL. The calibration curve for the HPLC analysis was obtained by plotting the peak area ratio of the drug to the internal standard against the drug concentration.

Chromatographic Conditions

The mobile phase consisted of a mixture of methanol:water (40:60, v/v) adjusted to pH 4 with 10% orthophosphoric acid. The mobile phase was prepared daily, filtered, sonicated before use, and delivered at a flow rate of 1.0 mL/min and the effluent was monitored at 245 nm. 50 μL of each solution was injected and chromatograms were recorded.

Analysis of Tablets

The average weight per tablet was calculated from the weight of 10 tablets. Ten tablets were weighed and reduced to a fine powder. A quantity of composite equivalent to 20 mg of FS (12.5 mg of HCT) was weighed and transferred into a 10 mL flask, stirred with methanol, made up to volume with the same solvent, and filtered. An appropriate volume of the filtered solution was taken in a 10 mL flask. An appropriate amount of internal standard was added and diluted up to the mark with the mobile phase. The amount of FS and HCT per tablet was calculated from a linear regression equation.

Recovery Studies

To study the accuracy, precision, reproducibility, and to check the interference from excipients used in the formulation of the above method, a recovery experiment was performed. The known amounts of the pure sample solution was added to the preanalysed formulation of each drug, including a constant level of the internal standard, and the mixtures were analysed by the proposed method. From the total amount of drug found, the percentage recovery was calculated. Each determination was performed in 10 replicate injections.

RESULTS AND DISCUSSION

The reversed phase HPLC method was developed to provide a specific procedure suitable for the rapid quality control analysis of FS and HCT in the binary mixtures. Chromatographic investigations revealed that a mixture of FS and HCT could be resolved from the coformulated excipients using C_{18} stationary phase and the above described mobile phase. The system was found to be suitable to separate FS and HCT from the common excipients. The mobile phase was choosen after several trials with methanol:water in various proportions and at different pH values with different internal standards.

The chromatographic system described above allows complete baseline separation for every two adjacent peaks. At a flow rate 1.0 mL/min, the retention times of FS and HCT and internal standards were 3.3, 4.2, and 6.1 min, respectively. The optimum wavelength for detection at 245 nm for both samples was obtained.

Figure 1 shows a typical chromatogram obtained, followed by analysis of FS and HCT in tablets. As shown in Figure 1, the substances were eluted, forming well shaped symmetrical single peaks, well separated from the solvent front. No interfering peaks were found in the chromatogram due to tablet excipients.

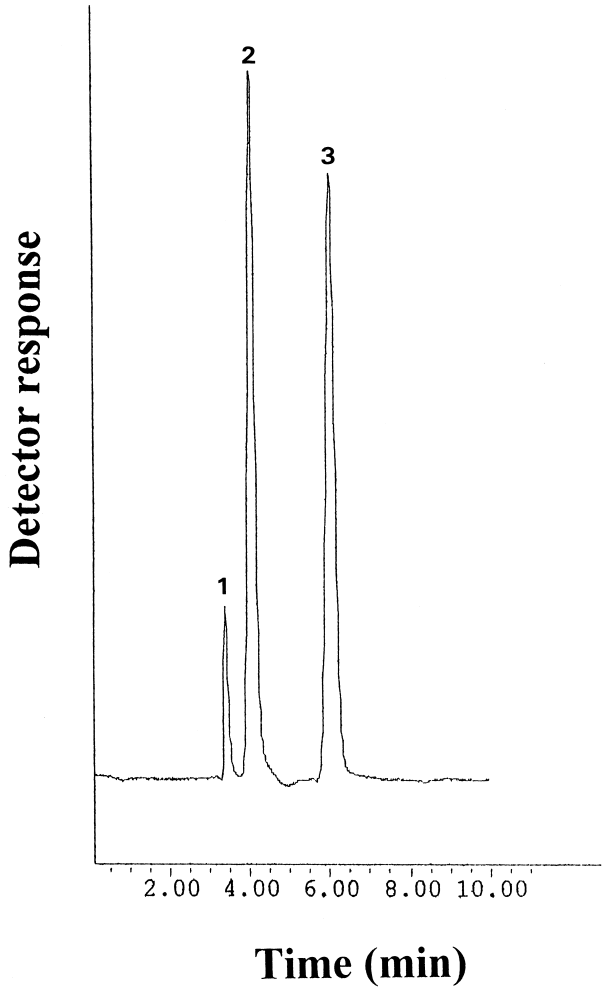


Figure 1. The chromatogram of a solution of FS **(1)** (8 μg/mL) and HCT **(2)** (10 μg/mL) with Sulfamethoxazole (IS) **(3)** (30 μg/mL).

Linearity was obtained for FS in the concentration range 1.6 – 30.0 μg/mL and HCT in the concentration range 1.0 – 30.0 μg/mL. The regression equation was shown in Table 1. The limit of detection of the procedure was shown in Table 1, which was calculated as the blank response plus three times the blank standard deviation devided by the slope of the calibration curve.

Table 2 represents the results obtained for intra- and inter-day variability studies of FS and HCT samples. These results show the accuracy and repro-

Table 1. Statistical Analysis Results of the Calibration Plots of FS and HCT by RP-HPLC

Sample	Linearity Range * (μg/mL)	Slope	Intercept	S.E. of Slope	S.E. of Intercept	Correl. Coeff.	Detection Limit (μg/mL)	Determination Limit (μg/mL)
FS	1.6-30	0.029	−0.019	0.0030	0.013	0.998	0.29	0.97
HCT	1.0-30	0.022	−0.00069	0.00075	0.0004	0.999	0.26	0.87

* Data represents 10 replicate injections of standard solutions.

ducibility of the assay. Thus, it was concluded that there was no significant difference for the assay which was tested within day and between days.

In order to demonstrate the validity and applicability of the proposed methods, recovery studies were performed by analysing synthetic mixtures of FS and HCT which reproduced different composition ratios (Table 3).

Assay in Tablet Dosage Forms

When working on synthetic mixture, results encouraged the use of the methods described for the assay of FS and HCT in commercial tablet dosage forms. The results obtained from the proposed method of the analysis of FS and HCT tablets indicate that the proposed assay can be used for quantitation and routine quality control analysis of this binary mixture in commercial samples. The results are shown in Table 4.

Table 2. Intra-Day and Inter-Day Precision of FS and HCT Standards

Compound	Theoretical Concentration (μg/mL)	Intra-Day Concentration Mean	Measured* (μg/mL) RSD %	Inter-Day Concentration Mean	Measured** (μg/mL) RSD %
FS	4.0	3.95	0.20	3.98	0.24
	8.0	7.90	0.80	7.94	0.55
HCT	2.5	2.49	0.33	2.49	0.06
	5.0	4.97	0.23	4.97	0.22

* Mean values represent five different sample standards for each concentration.

** Inter-day reproducibility was determined from five different runs over a 3-week period.

Table 3. Resolution of FS and HCT Laboratory-made Mixtures by RP-HPLC

Added (μg/mL)		Found (μg/mL)		Recovery %		Mean (μg/mL)*		RSD %	
FS	HCT	FS	HCT	FS	HCT	FS	HCT	FS	HCT
8.0	10.0	7.99	9.9	99.9	99.0				
8.0	10.0	7.92	9.8	99.0	98.0				
8.0	10.0	7.97	10.0	99.6	100.0	7.96	9.90	0.45	1.01
16.0	5.0	15.7	4.99	98.1	99.8				
16.0	5.0	15.72	5.0	98.3	100.0				
16.0	5.0	15.8	4.97	98.8	99.4	15.74	4.99	0.33	0.31

* Average of three experiments.

There is no HPLC method reported in pharmacopoeias and literatures so far for the simultaneous determination of FS and HCT in drug dosage forms. In order to know whether the excipients in the tablet show any interference with the analysis, known amounts of the pure drug were added to the same aliquot portions of the same powdered tablets, and mixtures were analysed by the proposed method. The recovery study shows a recovery average of 98.2% and 98.8% with a RSD of 0.45% and 0.34% for FS and HCT, respectively. It is concluded, that the proposed method is sufficiently accurate and precise in order to be applied to pharmaceutical dosage forms. High percentage recovery data shows that the method is free from the interferences of the excipients used in the formulations.

Table 4. Assay of FS and HCT Pharmaceutical Dosage Form

Compound	Labelled amount (mg per tablet)	Amount found	Mean*	RSD %
	20.0	19.84		
	20.0	19.85		
FS	20.0	19.75		
	20.0	19.76		
	20.0	19.78	19.80	0.23
	12.5	12.43		
	12.5	12.48		
HCT	12.5	12.50		
	12.5	12.50		
	12.5	12.45	12.47	0.25

* Average of five experiments.

CONCLUSION

The proposed method for the determination of FS and HCT, simultaneously, in the presence of each other and, also in pharmaceutical dosage forms, give accurate and precise results. This RP-HPLC method gives a good resolution between FS and HCT within a short analysis time (< 7 min). No interferences from excipients were observed in any of tablet samples. Therefore, the proposed HPLC method can be used for routine simultaneous analysis of these drugs, and can be used as an alternative tool for the drug quality control laboratories.

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