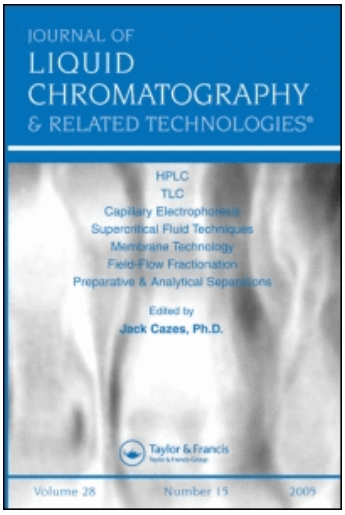

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Determination of Carbamazapine by Flow-Injection Analysis: Its Application to Tablet Analysis and Dissolution Studies

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Determination of Carbamazapine by Flow-Injection Analysis: Its Application to Tablet Analysis and Dissolution Studies

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Abstract: Flow injection analysis (FIA) of carbamazepine (CBZ) and its relevant application to the conventional CBZ tablets, e.g., content uniformity test and tablet dissolution, is described in this study. An aqueous solution of 1% sodium dodecyl sulphate (SDS) was employed as a carrier solvent. The best parameters were determined for FIA analysis; flow-rate of 1 mL · min^{-1}, detection wavelength of 288 nm, and an injection volume of 20 μL. Validation tests (intra- and inter-day) were realized with highly good repeatability (RSD% = 1.92) and linearity, limit of detection (LOD) and limit of quantification (LOQ) were calculated to be 8.34×10^{-7} M and 2.5×10^{-6} M, respectively. Results of analysis which were achieved on the tablets were compared to those methods that were suggested by USP 28. Each step was examined by statistical testing, and it seems that the proposed method is applicable, as well as the methods in the pharmacopoeia.

Keywords: Carbamazepine, Flow-injection analysis, Tablet analysis, Dissolution studies, Analytical method validation, HPLC analysis

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INTRODUCTION

Carbamazepine (5H-dibenz(b,f)azepine-5-carboxamide) is a tricyclic drug, which is frequently used for the treatment of trigeminal neuralgia and as an anticonvulsant. The chemical structure of CBZ is illustrated in Fig. 1.

This drug is preferred by many physicians for generalized tonic-clonic seizures (grand mal) and simple partial (focal, Jacksonian) seizures, particularly in patients who have not responded to other less tonic anticonvulsants. It sometimes is effective in patients who have mixed seizure patterns, which include the above, or other partial or generalized seizures. It is also functional in the treatment of pain associated with true trigeminal neuralgia. Beneficial results have also been reported in gloss pharyngeal neuralgia. CBZ has also been used with some benefit for the management of acute mania, maintenance therapy of bipolar effective disorder, and for the management of aggression and alcohol withdrawal syndrome.[1,2]

Certain methods have been employed for the determination of CBZ. These are classified as in the following: spectrophotometric determination using partial least square method,[3] chemometric assisted UV-spectrophotometric method,[4] flow injection photochemical spectrofluorimetric method for pharmaceutical tablets,[5] LC-MS/MS for the analysis of CBZ, oxcarbazepine (OXCBZ) and metabolites in several body materials,[6–9] HPLC analysis.[10–19] There has been no report on a FIA technique employed for the determination of CBZ amount.

The present study is based on two different aims. The first one is to develop a FIA method for the determination of CBZ and to validate it by employing common analytical and statistical tests depending on the suggestions of ICH guidelines.[20] The second part of the study is to test the application of the mentioned method to the tablet content uniformity test using HPLC and FIA and the dissolution behavior of the CBZ tablets determining the samples by spectrophotometry, as proposed in NF/USP 28 monograph[21] and FIA.

EXPERIMENTAL

Apparatus

FIA and HPLC experiments were made by removing or fixing the column to an HPLC combined with an LC-6A pump, SIL-6B auto injector, SPD-10 A

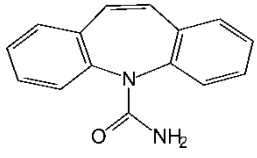

Figure 1. The chemical structure of CBZ.

UV-detector, SCL-6B system controller, and C-R7A integrator, all Shimadzu, (Kyoto, Japan). During the HPLC analysis a C_{18} column having a length of 100 mm, inner diameter (ID) of 4.6 mm, and particle size of 3 μm was used. A 2401 UV spectrophotometer, Shimadzu (Kyoto, Japan) was employed using quartz cells. All solutions were sonicated in a Branson B-220 (Shelton, U.S.A.) sonicator.

Chemicals

Standards of CBZ and OXCBZ, which is the internal standard in the HPLC studies, were kindly supplied from Novartis (Istanbul, Turkey). Other chemicals and solvents were analytical grade and provided from Merck GmbH (Darmstadt, Germany). Distilled water was produced in our laboratory using only a glass apparatus. Conventional CBZ tablets were purchased from local drugstores and given codes as CBZ A (Lot: 043), CBZ B (Lot: 01), CBZ C (Lot: 041), and CBZ D (Lot: 05).

Procedures

Preparation of the Carrier Solvent and Standard Solutions

A stock solution of 1.08×10^{-5} M CBZ was prepared for FIA in an aqueous solution of 1% SDS and utilizable solutions were diluted from that solution. Repeatability, linearity (in the range of $7 \times 10^{-6} - 3 \times 10^{-4}$ M), and calibration studies ($1.08 \times 10^{-5} - 6.48 \times 10^{-5}$ M) were prepared by dilutions from the stock solution.

FIA Analysis

By removing the column, the same HPLC system was used for the FIA studies. The carrier solvent consisted of an aqueous solution of 1% SDS. Certain FIA parameters were examined to find the optimum conditions, such as wavelength of detection, flow rate, and injection volume.

Spectrophotometric Analysis

The solvent system consisted of an aqueous solution of 1% SDS and it was also used as a blank during the spectrophotometric measurements. The measurements were made at 288 nm in quartz cells.

HPLC Analysis

Three sets of CBZ solutions were prepared by increasing the concentration in the range of 3.70×10^{-5}–7.40×10^{-6} M and fixed amount (7.73×10^{-6} M)

of OXCBZ as an internal standard (IS). IS was prepared to be used only in HPLC studies. Mobil phase consisted of 50% methanol:acetonitrile:H_3PO_4 (20:25:0.5). A C_{18} column having a length of 100 mm, inner diameter (ID) of 4.6 mm, and particle size of 3 μL was used during the HPLC analysis. Injection volume was always 5 μL and the signals were detected at 288 nm.

Tablet Sample Preparation

Ten CBZ tablets from each tablet sample (containing 200 mg active drug, CBZ) were weighed and finely powdered in a mortar. The average weight of a tablet was calculated. A sufficient quantity equivalent to the average weight of a tablet content was accurately weighed from the tablet powder and water containing 1% SDS was added to dissolve the active material and made up to the volume of 25 mL in a volumetric flask. It was sonicated for 10 min. Then, the tablet sample solution was centrifuged at 5000 rpm for 10 min. The supernatant was diluted following the same procedure as in the preparation of standard solutions to fulfill spectrophotometry and FIA.

Dissolution Procedure

The dissolution studies on conventional CBZ tablets were carried out according to USP 28[21] the paddle method at 75 rpm. The dissolution medium was 900 mL of distilled water containing 1% SDS at $37 \pm 0.5^{\circ}C$. The samples were withdrawn at definite time intervals for one hour and assayed both spectrophotometrically and with the FIA technique at 288 nm. CBZ amounts released from the tablets were calculated.[22]

RESULTS AND DISCUSSION

CBZ is a highly non-polar chemical and it has a low solubility in common polar solvents. USP 28[21] suggests an aqueous solution of 1% SDS for dissolution studies of CBZ. Thus, it can be evaluated that this medium is a good solvent for CBZ, and the tablets containing CBZ at an amount of 200–400 mg can be dissolved without any problem in this medium.

UV spectrum of the stock solution of CBZ prepared in aqueous solution of 1% SDS at a concentration of 1.08×10^{-5} M CBZ, was scanned in the range of 200–400 nm and a maximum wavelength at 288 nm was obtained.

The variation of the flow rate on the UV signals of 1.08×10^{-5} M CBZ as its integrated area was examined by detecting the signals at 288 nm. It was determined that $1.0\ mL \cdot min^{-1}$ of flow rate is at the plateau where the area against flow rate is very low or the little changes do not affect the concentration of CBZ. Therefore, the flow rate was decided to be $1\ mL \cdot min^{-1}$ and the rest of the experiments were conducted at that flow rate. The variation of the area against flow rate is demonstrated in Fig. 2.

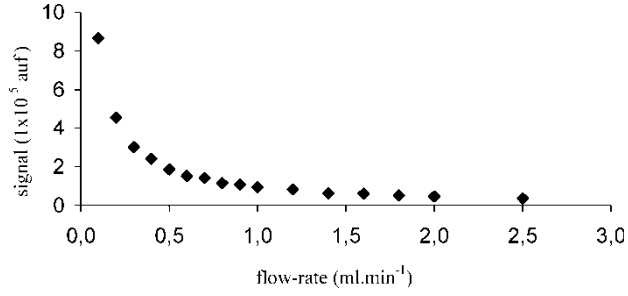

Figure 2. The variation of flow-rate versus integrated area of 1.08×10^{-5} M CBZ.

The effect of loop volume on the area of the signal of 1.08×10^{-5} M CBZ was examined by injecting the samples in the range of 5–100 μL. They were plotted versus loop volume and it was observed that the linearity was in the range of 5–50 μL. The variation of area against loop volume is demonstrated in Fig. 3. Thus, it was decided that a reasonable injection volume is 20 μL for this study.

Repeatability

After finding the optimum conditions, the following experiments were conducted to get the validation studies. Three groups of each set of 1.08×10^{-5} M CBZ were prepared and each of them was injected 8 times, and the results were evaluated regarding intra-day and inter-day precision. The results are given in Table 1.

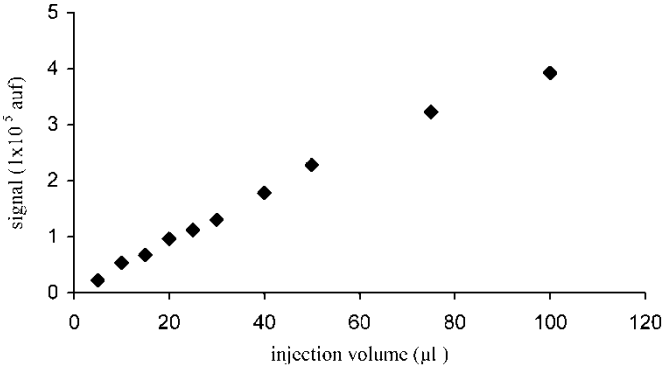

Figure 3. The variation of peak area versus loop volume. Injection range: 5–100 μL; concentration of CBZ sample: 1.08×10^{-5} M; flow rate: 1 mL · min^{-1}; signal detection: 288 nm.

Table 1. Precision test of 1.08×10^{-5} M CBZ solution in optimum FIA conditions

	Intra-day precision (n = 8)			Inter-day precision pooled (n = 24)
	First day	Second day	Third day	
$\bar{x}$	97947	96081	97427	97139
SD	2594	1345	1508	1863
RSD%	2.65	1.40	1.55	1.92

$\bar{x}$: mean; SD: standard deviation; RSD: relative standard deviation.

The RSD% values explain the repeatability results which are determined between 1.40 and 2.65%. Pooled values of inter-day results are lower than 2%. This shows that the method is completely reliable.

Linearity and Range

Limits of the linearity were investigated in a wide concentration range. The starting point of deviation was detected with 7×10^{-5} M CBZ concentration. A linear relationship was obtained in the range of 1.08×10^{-5} and 6.48×10^{-5} M as shown in Table 2, the r value found for intra and inter-day is 0.9995, which indicates the linearity in the studied concentration.

The calibration results indicate that the FIA is a reliable method for the determination of CBZ, depending on the statistical elements.

LOD and LOQ were calculated by multiplying (standard deviation of repeatability, SD/slope of the calibration equation, a) with 3.3 and 10, respectively. They were calculated to be 8.34×10^{-7} for LOD and 2.5×10^{-6} M for LOQ.

Table 2. Linearity results of CBZ solution in the range of 1.08×10^{-5} and 6.48×10^{-5} M for intra- and inter-day precision with their statistical results

	Intra-day (n = 5)			Inter-day (pooled values, n = 15)
	First day	Second day	Third day	
a	7.31×10^9	7.40×10^9	7.41×10^9	7.37×10^9
b	6630	2791	4551	4675
r	0.9994	0.9996	0.9995	0.9995
$\pm S_r$	9.61×10^3	9.35×10^3	6.80×10^3	1.59×10^3
S_e	2.12×10^8	2.07×10^8	1.50×10^8	1.79×10^8
CL (p = 0.05)	$\pm 1.75 \times 10^8$	$\pm 1.70 \times 10^8$	$\pm 1.24 \times 10^8$	$\pm 7.34 \times 10^7$

a: slope; b: intercept; r: correlation coefficient; S_r: standard deviation of intercept; S_e: standard deviation of slope, CL: confidence limits.

Accuracy

Accuracy or intermediate precision of the method was tested at three concentrations in the linearity range using six replicate injections. In the case of the drug product, accuracy was determined by the application of the analytical method to synthetic mixtures of the drug product components, known amounts of analyte had been added within the studied method range. Percent error was calculated by (found concentration-spiked concentration)/ spiked concentration) × 100 and precision was studied by the coefficient of variation with the confidence interval at the low central and high concentration levels of linearity ranges (Table 3).

The % recoveries were found to be almost 100% for drug substance and drug product and accuracy was much less than the acceptance criteria, which is in the range of −0.59 and 0.88 for the drug substance and 0.86 and 1.61 for the drug product. The same concentration levels were used to evaluate the precision as a degree of repeatability performing six replicates. The values of RSD were in the range of 8.47 and 9.02% for drug substance and 7.79 and 5.12% for the drug product. It is stated that the acceptance criteria are not higher than 15% deviation from the nominal value for accuracy and not more than 15% C.V. for precision.[23]

Content Uniformity Test of CBZ Tablets

The determination of the CBZ amount in conventional CBZ tablets was achieved by the progressed method. FIA was also used, besides an HPLC method for the determination of CBZ, and their results were compared to each other. The protocol of the analytical procedure, both FIA and HPLC, is given in the experimental section (Table 4).

When FIA–HPLC results of conventional CBZ tablets are compared, good parallelism can be seen in both FIA and HPLC methods. Regarding the content uniformity test, CBZ-D does not provide the official requirements.[24] Thus, the CBZ-D tablet was not considered for further testing, because of its invalid results.

Dissolution Studies of Conventional CBZ Tablets

The dissolutions of conventional CBZ tablets were tested according to USP 28[21] and the amounts of CBZ released were determined by UV-spectrophotometrically[22] and FIA methods which are proposed with this study.

Dissolution testing of drug formulations was introduced in the 1960s and accepted by health regulatory authorities in the 1970s. Since then, the importance of dissolution testing has grown rapidly, as have the number of tests and demands in quality control laboratories.[24,25]

Table 3. Results as recovery, accuracy, precision and bias values for added to the carrier solvent and spiked CBZ onto the matrix

		CBZ amount (M) (Mean ± SD, n = 6)	Recovery (%)	Accuracy (%)	RSD (%)	Bias
Added CBZ (M)	3.24×10^{-5}	$3.22 \times 10^{-5} \pm 1.61 \times 10^{-8}$	99.41	−0.59	8.47	0.34
	6.48×10^{-5}	$6.51 \times 10^{-5} \pm 2.92 \times 10^{-8}$	100.50	0.50	9.02	0.33
	9.72×10^{-5}	$9.81 \times 10^{-5} \pm 7.44 \times 10^{-8}$	100.88	0.88	8.69	0.37
CBZ spiked to matrix (M)	3.18×10^{-5}	$3.22 \times 10^{-5} \pm 2.68 \times 10^{-8}$	101.22	1.22	6.91	0.32
	6.36×10^{-5}	$6.41 \times 10^{-5} \pm 4.27 \times 10^{-8}$	100.86	0.86	7.79	0.29
	9.54×10^{-5}	$9.69 \times 10^{-5} \pm 7.85 \times 10^{-8}$	101.61	1.61	5.12	0.32

Table 4. Content uniformity test results of CBZ tablets each containing 200 mg active material

	CBZ-A		CBZ-B		CBZ-C	
	FIA (n = 6)	HPLC (n = 10)	FIA (n = 6)	HPLC (n = 10)	FIA (n = 6)	HPLC (n = 10)
$\bar{x}$ (%)	96.02	100.7	102.82	102.7	95.76	100.8
SD	1.21	1.86	0.84	4.72	1.08	3.82
RSD (%)	1.26	1.85	0.81	4.60	1.13	3.79
CL ($p < 0.05$)	±1.62	±1.95	±0.88	±3.37	±1.14	±2.72

$\bar{x}$: mean CBZ amount (%); SD: standard deviation; RSD: relative standard deviation; CL: confidence limits.

The release of the active material, CBZ from CBZ A, B, C tablets against time was determined by the methods mentioned above and the plots of the variations are demonstrated in Fig. 4.

According to USP 28[21] conventional CBZ tablets have to release at least 75% of the labeled amount in 60 min. All tested conventional CBZ tablets (CBZ A, B, C tablets) provided the drug release criteria that is given in the USP.[21]

One way to evaluate dissolution studies is the application of kinetic models to the dissolution data.[26] There are several kinetic models; zero order, first order, Higuchi, Weibull (RRSBW) kinetics, etc. These models are useful to understand the dissolution characteristics of the dosage form and also give an idea about the in vivo behavior of the preparation. For these reasons, in this study we applied zero and first order, Hixson-Crowell, Higuchi, and Weibull kinetics in order to evaluate the in vitro dissolution behavior of the conventional CBZ tablets (Table 5).

By the application of the dissolution data to kinetic models, the best harmony was determined with Weibull Kinetics because the highest determination coefficient and the lowest residual mean square (RMS) values were obtained by Weibull Kinetics.

Weibull kinetics is a kinetic model that is used for making the dissolution profiles linear and defining the system by parameters. An important parameter in this system is β factor. β characterizes the shape of the original dissolution curve numerically. If the slope of the line is found to be bigger than 1 ($\beta > 1$), this means a slow drug release occurs at the beginning and then it is followed by a fast plateau value. If the slope of the line is equal or less than 1 ($\beta \leq 1$), this means there is a faster drug release at the beginning, which is followed by a first order release profile which reaches the plateau.[27,28]

Since drug release from conventional CBZ tablets showed a release profile fitting Weibull kinetics with $\beta < 1$, a faster drug release occurs at the beginning which is followed by a first order drug release. This initial

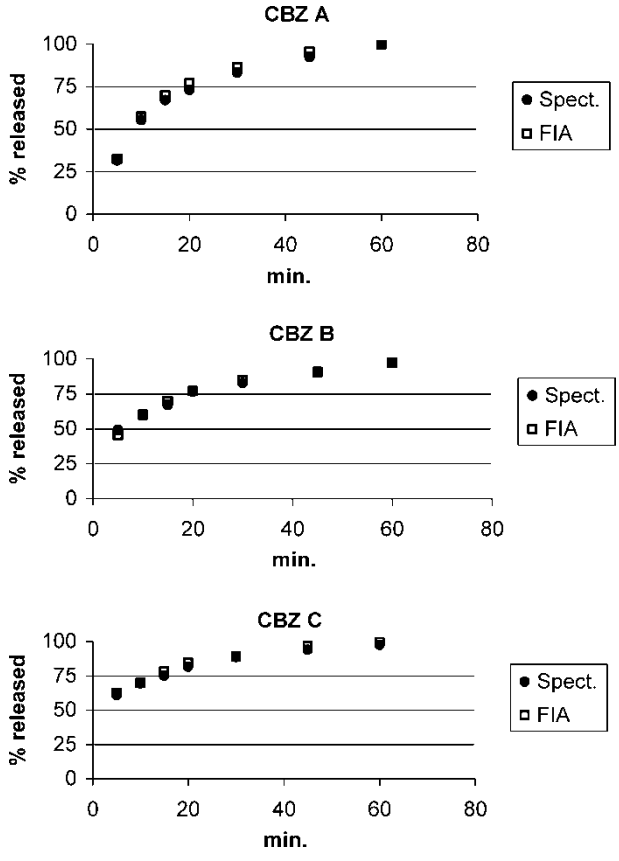

Figure 4. The released amount (%) of CBZ from conventional CBZ A, B, C tablets.

"faster drug release" meets the criteria of conventional CBZ tablets that are defined in pharmacopoeia.[21] All conventional CBZ tablets that are used in our study are in agreement with its criterion.

These results proved that the values for the measurement of CBZ release from tablets exhibited very good parallelism both UV spectrophotometry and in the FIA technique. Thus, it can be said that there is an insignificant difference between the two methods.

As is known, FIA has gradually gained much interest for the development of analytical methods because of its simplicity, feasibility, high sampling frequency, and degree of automation and low expense of reagents and samples. Apart from chemical reactions, many other chemical processes can be put into practice and automated in flow systems. Among them, ionic exchange, preconcentration, clean up, liquid–liquid extraction, solid phase extraction, gas diffusion, dialysis, precipitation, etc., can be mentioned.

Table 5. Kinetic results and fitting criteria of conventional CBZ tablets dissolved in aqueous solution of 1% SDS medium

	CBZ tablet					
	CBZ A		CBZ B		CBZ C	
Kinetic model	UV-spect.	FIA	UV-spect.	FIA	UV-spect.	FIA
First order						
RMS	5.529	5.681	6.140	6.077	6.674	6.750
k_1	0.857	0.856	0.846	0.847	0.838	0.838
r^2	0.735	0.732	0.715	0.718	0.703	0.702
Zero order						
RMS	700.398	800.399	970.755	957.979	1375.810	1439.985
k_0	0.936	0.930	0.914	0.915	0.892	0.892
r^2	0.875	0.865	0.835	0.838	0.795	0.796
Hixson-Crowell						
RMS	4.148	4.304	4.725	4.671	5.301	5.385
k_4	0.870	0.868	0.856	0.858	0.846	0.846
r^2	0.757	0.753	0.733	0.736	0.796	0.717
Higuchi						
RMS	67.197	91.089	150.249	141.254	301.560	315.819
k	0.994	0.992	0.987	0.988	0.977	0.977
r^2	0.988	0.985	0.974	0.976	0.955	0.955
Weibull						
RMS	$8.560 \cdot 10^{-4}$	$7.687 \cdot 10^{-4}$	$2.067 \cdot 10^{-3}$	7.37810^{-4}	$1.214 \cdot 10^{-3}$	$2.720 \cdot 10^{-3}$
β	0.996	0.997	0.986	0.995	0.988	0.971
r^2	0.992	0.993	0.972	0.991	0.976	0.943

RMS: Residual mean square; k: Rate constant of the investigated kinetic (k_0: $mg \cdot h^{-1}$, k_1: h^{-1}, k_4: $mg^{1/3} \cdot h^{-1}$, k: $h^{-1/2}$); r^2: Determination coefficient; β: shape factor.

Another effective characteristic is the possibility of using unstable reagents or analyzing unstable compounds that decompose when using conventional procedures. This feature makes the technique suitable for satisfying the increasing demand for control and routine analysis in many fields of analytical chemistry.[29] For these reasons the FIA technique seems to be an alternative method when compared with spectrophotometry as very similar results were obtained for drug content in the study.

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