EXPERIMENTAL / LABORATORY STUDIES

Quality Control Studies on Conventional Carbamazepine Tablets Available on the Turkish Drug Market

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Abstract: Carbamazepine (CBZ) is a widely used antiepileptic drug. It is used to control grandmal seizure as well as in the treatment of neuralgia. The drug is characterised by slow and irregular gastrointestinal absorption due to its low water solubility. In clinics, for conventional dosage forms of CBZ, single daily dosing is insufficient; effective CBZ level is provided by multiple drug administration. Multiplicity of dosage causes inconsistent plasma CBZ levels leading to side effects because of narrow therapeutic and toxic levels.

In this study, quality controls of different conventional CBZ tablets which are commercially available on the Turkish drug market were examined. Quality control parameters were weight variations, diameter and thickness, content uniformity, friability and dissolution tests. Differences between conventional CBZ tablets were evaluated.

Key Words: Conventional carbamazepine tablets, quality control studies

Introduction

In the drug industry, quality control must be administered in order to prevent the kind of product which is not suitable for the aim, and at the same time it is also necessary for controlling the reliability of the production process. Quality can be defined as the suitability of the goods or service to the determined qualifications. In the establishment of quality control programmes the aim is to guarantee the determined necessities (1).

Carbamazepine (CBZ) is a widely used antiepileptic drug. It is used to control grandmal seizure as well as in the treatment of neuralgia. The drug is characterised by slow and irregular gastrointestinal absorption due to its low water solubility (2). A single daily dose of CBZ is insufficient; 2 doses per day are appropriate in most cases, but some patients may benefit from more frequent dosing to avoid side-effects (3).

In clinical studies, suspension, conventional tablets and XR (extended release) tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat more rapidly and XR tablet slightly slower than the conventional tablet. Bioavailability of the XR tablet was 89% compared to the suspension. Following a twice daily dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On following a three times daily dosage regimen, CBZ suspension affords steady-state plasma levels comparable to CBZ tablets given b.i.d when administered at the same total mg daily dose (4).

On Turkish drug market, there are conventional and controlled release of CBZ in the forms of tablets and syrups produced by different companies (5).

In this study, we worked on the quality controls of conventional CBZ tablets which are available in the Turkish drug market. For quality controls, weight variation, diameter and thickness, content uniformity, hardness, friability and dissolution tests were administered. Furthermore, difference (f_1) and similarity (f_2) tests were applied to these tablets so as to evaluate the differences and similarities of their dissolution profiles.

Materials and Method

Materials

Carbamazepine was a kind gift of Novartis Pharmaceuticals, Turkey. In our studies, four brands of commercial conventional CBZ tablets containing 200 mg of CBZ were used and coded as CBZ A (Lot:043), CBZ B (Lot:01), CBZ C (Lot:041) and CBZ D (Lot:05).

Method

Analytical method for the assay of carbamazepine

In order to determine the standard calibration curve of CBZ, a stock solution of 0.016 mg/ml was prepared in distilled water containing 1% sodium lauryl sulphate (NaLS). Then dilutions were made to prepare a series of solutions containing CBZ in different concentrations. In these solutions absorbance values at 287 nm (maximum λ) were determined UV spectrophotometrically by plotting the concentration values (x) versus absorbances (y) a calibration curve of CBZ in distilled water containing 1% NaLS was determined (6). Analytical parameters for the assay of CBZ were calculated by the ANOVA test.

LOD and LOQ determination

The limit of detection (LOD) and the limit of quantitation (LOQ) were determined by using the following equations;

LOD = 3SD/m (Equation 1)

LOQ = 10SD/m (Equation 2)

where SD is the standard deviation of the absorbance values (n=6) of the second smallest concentration, m is the slope of the calibration curve (6).

Evaluated physical characteristics for quality control studies

Weight variation: Each tablet (n=10) belonging to each brand was weighed with an electronic balance (Sartorius BL 210 S) (1).

Measurement of diameter and thickness: The diameter and thickness of CBZ tablets (n=10) from each brand were measured with a micrometer (Zeus) (1).

Hardness test: This test was applied with a hardness tester (Strong-Cobb T 100 tablet hardness tester) on 10 tablets for each brand (1).

Friability test: 10 tablets from each brand were weighed and put into the friabilitor (Roche Friabilitor). Tablets were rotated at 25 rpm, then the friability percentage was calculated for each batch (7).

Content uniformity test: The amount of CBZ in tablets from each brand was determined according to USP 28. A standard solution was prepared by dissolving pure CBZ in methanol and a sample solution was also prepared dissolving CBZ tablets (n = 20) from each batch in methanol. The absorbances of the prepared solutions were determined spectrophotometrically at 287 nm (Shimadzu 1202 UV-VIS spectrophotometer). The CBZ amount in each tablet was calculated using the equation for the calibration curve.

Dissolution studies: The dissolution rate studies on conventional CBZ tablets were carried out according to USP 28 paddle method at a stirring rate of 75 rpm. The dissolution medium was 900 ml of distilled water containing 1%NaLS at $37 \pm 0.5°C$. The samples were withdrawn at definite time intervals for one hour and assayed spectrophotometrically at

287 nm (Shimadzu 1202 UV-VIS spectrophotometer). The percentage of cumulative CBZ amounts released from the tablets were calculated. Then data were plotted and evaluated using a statistical package program (SPSS 9.0).

Comparison of the dissolution profiles

In this study, as model-independent approaches, two fit factors that compare the dissolution profiles of a pair of drug products were applied to the dissolution data. These fit factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product. The fit factors are denoted difference (f_1) and similarity (f_2) factors and are defined by equations 3 and 4 (8),

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \quad \text{(Equation 3)}$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\} \quad \text{(Equation 4)}$$

where n is the number of dissolution sample times and R_t and T_t are the individual or mean percents dissolved at each time point, t, for the reference and test dissolution profiles respectively.

Results and Discussion

Results of assay of carbamazepine

The calibration curve of CBZ was obtained by using the method which was explained in section 1.2.1 and the calibration curve was shown in Figure 1. Analytical method validation parameters for the determination of CBZ by UV spectrophotometric method were given in Table 1.

Quality control study results

The results obtained from the quality control tests were given in Table 2.

Carbamazepine tablets contain not less than 92.0 percent and not more than 108.0 percent of the labeled amount of active drug (9). Content uniformity test results showed that all conventional CBZ tablets fit this criteria (Table 2).

Although there is no official test for hardness, this property must be controlled to ensure that the product is firm enough to withstand handling without breaking or crumbling and not so hard that the disintegration time is unduly prolonged (7). The recommended value for tablet hardness is 4-8 kg (7). All tablets supply the hardness limits.
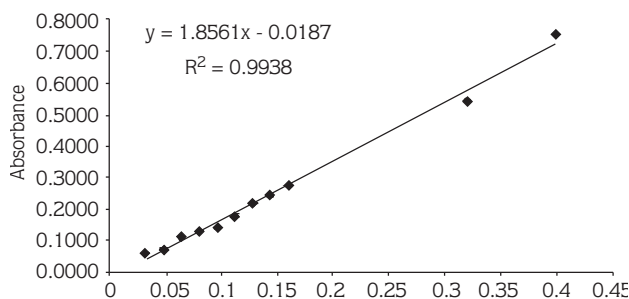
Table 1. Analytical method validation parameters for the assay of carbamazepine by UV spectrophotometric method.

Parameter	Result
Linearity range (mg/ml)	0.032 - 0.40
Slope (m)	1.8561
RSD of m (%)	0.81
SE of m	0.048
CL of m (95%)	1.7491-1.9962
Intercept (n)	-0.0187
RSD of n (%)	6.24
SE of n	0.009
CL of n (95%)	-0.0381-0.0012
Determination coefficent (r^2)	0.994
LOD (mg/ml)	0.034
LOQ (mg/ml)	0.114
RSD for precision (%)	69.79
RSD for accuracy	4.314

RSD: Relative Standard Deviation
SE: Standard Error
CL: Confidence Limits

The friability value which is also affected by the hardness value of tablets, should be in the range of 0.5-1% limits (7). Friability values of the tablets are in this range.

Difference (f_1) and similarity (f_2) tests were applied to the dissolution data. The difference (f_1) factor is proportional to the average difference between the two profiles, whereas similarity (f_2) factor is inversely proportional to the average squared difference between the two profiles with emphasis on the larger difference among all the time points (8). The use of these factors was also recommended for dissolution profile comparison

Figure 1. Calibration curve for carbamazepine.

$y = 1.8561x - 0.0187$
$R^2 = 0.9938$

Table 2. Results of quality control tests.

CBZ Tablet	Weight (g) (X mean±SD)	Diameter (cm)	Thickness (cm)	Hardness (SCU ± SD)	Friability (%)	Content uniformity (%)
CBZ A	0.280 ± 0.002	0.905	0.365	18.75 ± 2.93	0.76	105.7
CBZ B	0.399 ± 0.006	1.050	0.390	13.10 ± 3.13	0.61	101.3
CBZ C	0.402 ± 0.003	1.150	0.360	13.00 ± 1.16	0.82	104.9
CBZ D	0.258 ± 0.005	0.955	0.305	12.65 ± 2.84	0.64	98.4

SCU: Strong Cobb Unit (1 SCU = 0.643 kg)
SD: Standard Deviation

Table 3. Difference (f1) and similarity (f2) factors for reference (CBZ A) versus test products (CBZ B, C and D).

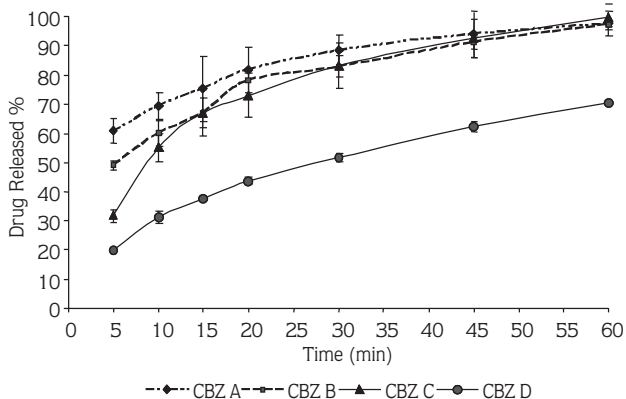|	CBZ B	CBZ C	CBZ D
f_1 values	7.36	12.24	44.12
f_2 values	57.47	51.72	22.17

Figure 2. Dissolution profiles of conventional carmabamazepine tablets.

in the FDA guide for industry (10). According to these guides, generally f_1 values vary between 0-15 and f_2 values vary between 50-100, and ensures sameness or equivalance of the curves.

The values of f_1 and f_2 factors for test products versus reference were calculated from the means of percent dissolved at each time point by using Equations 3 and 4 and listed in

Table 3. For tests (CBZ B and CBZ C)) versus reference (CBZ A), f_1 values indicate that the dissolution profiles of tests (CBZ B and CBZ C) were similar to the profile of reference

(CBZ A), and unlike the third test product CBZ D.

To release the active amount in an expected time is the primary effect of a dosage form. According to USP 28, conventional CBZ tablets have to release at least 75% of the labelled amount in 60 minutes. As can be seen in Figure 2, except for CBZ D, all other CBZ conventional tablets release the active drug according to the determined limits.

Dissolution data of conventional CBZ tablets were applied to zero order, first order, and Higuchi and Hixson-Crowell kinetics (Table 4). As seen from Table 4,

Table 4. Kinetic parameters obtained from the dissolution data for conventional CBZ tablets.

CBZ Tablet Kinetic model		CBZ A	CBZ B	CBZ C	CBZ D
First order	RMS	6.674	6.140	5.529	3.981
	k^1	0.838	0.846	0.857	0.871
	r^2	0.703	0.715	0.735	0.759
Zero order	RMS	1375.810	970.755	700.398	179.929
	k_0	0.892	0.914	0.936	0.960
	r^2	0.795	0.835	0.875	0.922
Hixson-Crowell	RMS	5.301	4.725	4.148	2.781
	k^4	0.846	0.856	0.870	0.882
	r^2	0.796	0.733	0.757	0.778
Higuchi	RMS	301.560	150.249	67.197	2.054
	k	0.997	0.987	0.994	1.00
	r^2	0.955	0.974	0.988	0.999

RMS: Residual Mean Square
k: Rate constant of the investigated kinetic
r^2 : Determination coefficent

Higuchi kinetics gives the highest determination constant and shows the best suitability for all dissolution data. CBZ D (Lot: 05) does not fit the USP 28 criteria (a conventional CBZ tablet should release at least 75% of the labelled amount in 60 minutes).

In conclusion, it can be said that, except for CBZ D (Lot:05), conventional CBZ tablets available on the Turkish drug market, fulfill the USP 28 pharmacopeia standards.

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