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# Quality control of commercial tablets containing the novel antipsychotic quetiapine

Vincenzo Pucci [a], Roberto Mandrioli [a], Anna Ferranti [a], Sandra Furlanetto [b], Maria Augusta Raggi [a,*]

[a] *Department of Pharmaceutical Sciences, University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy*
[b] *Department of Pharmaceutical Sciences, University of Florence, Via G. Capponi 9, 50121 Florence, Italy*

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**Abstract**

Quetiapine (bis [2-(2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl]ethoxy)ethanol]fumarate) is the most recent agent introduced on the drug market for the treatment of psychotic disorders. Two different analytical methods for the quality control of quetiapine in commercial formulations have been developed and compared: a spectrophotometric method and a capillary zone electrophoretic (CZE) method. The spectrophotometric assay was carried out measuring the absorbance at a wavelength of 246 nm. The CZE method used an uncoated fused-silica capillary and a pH 2.5, 50 mM phosphate buffer as the background electrolyte. The detection wavelength was 205 nm, the separation voltage was 15 kV, and a complete electrophoretic run lasts less than 2.5 min. Extraction of quetiapine from the commercial tablets consisted of a simple one-step treatment with a pH 2.5, 50 mM phosphate buffer. Linearity was observed in the 5–25 μg $ml^{-1}$ concentration range of quetiapine for the spectrophotometric method, and in the 5–50 μg $ml^{-1}$ concentration range for the electrophoretic method. Both methods gave satisfactory results in terms of repeatability and intermediate precision (RSD < 1.9%). Also accuracy values were very good for both methods, the recovery being between 98.2 and 100.5%.


*Keywords:* Quetiapine; Quality control; Tablets; CZE; Spectrophotometry

## 1. Introduction

Quetiapine fumarate (bis [2-(2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)]ethoxy)ethanol] fumarate, Fig. 1), a dibenzothiazepine derivative, is a recent antipsychotic drug with an atypical neuropharmacological profile [1]. Quetiapine is the antipsychotic that has the highest serotonin/dopamine binding ratio [2,3], being the serotonin type 2 ($5\text{-}HT_2$)-receptor blocking effect about twice as strong as the dopamine $D_2$-receptor blocking effect [4]. Thanks to this binding pattern, quetiapine causes minimal extrapyramidal side effects [5]. It appears as effective as the older antipsychotics producing side effects no worse than those

* Corresponding author. Tel.: +39-051-209-9739; fax: +39-051-209-9734.
*E-mail address:* raggima@alma.unibo.it (M. Augusta Raggi).

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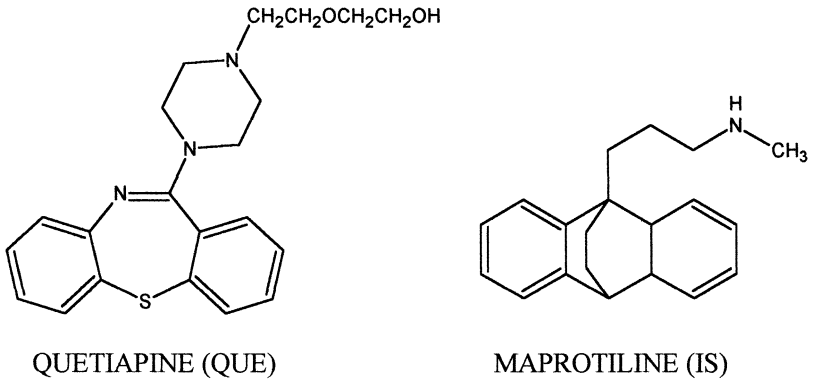


Fig. 1. Chemical structures of quetiapine (QUE) and maprotiline (IS).

encountered with standard antipsychotics [5,6]. This characteristic makes quetiapine well tolerated and effective in patients who are particularly susceptible to these severe side effects, including the elderly and adolescents and those with pre-existing dopaminergic pathologies, such as Alzheimer's disease and Parkinson's disease [7]. Like other antipsychotic agents, quetiapine is extensively metabolized by the hepatic cytochrome P 450 (CYP) system [8] and primarily by the CYP3A4 isoenzyme; it has a relatively low protein binding (83%) and an elimination half-life of 7 h (range of 4–12 h) [9,10].

The recommended quetiapine dosage for reducing positive symptoms of schizophrenia is in the 150–750 mg $day^{-1}$ range and for reducing negative symptoms is of 300 mg $day^{-1}$ [11]. Lower doses of quetiapine ($\sim$150 mg $day^{-1}$) may be more appropriate for management of psychosis in the elderly [1,12]. Quetiapine has an excellent side effect and safety profile [13]. The drug's most frequent side effects are agitation, somnolence, headache, dry mouth, insomnia, postural hypotension, dizziness [14,15]. Some of these effects are caused by its known α-adrenergic receptor and hystamine receptor blockade and are the only side effects observed even in overdose situations (30 tablets of 100 mg) [16].

Only a few papers concerning the analysis of quetiapine in biological samples are present in the literature, while no papers are found on quality control of quetiapine tablets. A gas chromatographic method coupled to a nitrogen–phosphorus detector has been recently implemented for the quantitation of quetiapine plasma levels. The sample pretreatment consists of a liquid–liquid extraction by means of *n*-butylchloride [17]. Another paper describes an HPLC method for quetiapine analysis in human plasma by means of spectrophotometric detection [18], using a liquid–liquid procedure extraction with ethyl acetate. Recently, a more feasible and rapid HPLC method for the analysis of quetiapine in plasma of schizophrenic patients has been developed [19]. This method uses a careful pretreatment of the biological samples carried out by means of a SPE procedure.

Quetiapine has been available in the United States since September 1997, but until now official pharmacopoeias have not reported any monograph on this drug. No official or published method is available for the determination of quetiapine in pharmaceutical preparations.

In the last few years, our research unit has worked intensively on the quality control of pharmaceutical formulations containing atypical antipsychotics [20–24]. The aim of the present investigation is the quality control of commercial tablets containing the novel antipsychotic quetiapine. Two analytical methods based on Vis–UV absorbance spectrophotometry and capillary zone electrophoresis have been developed.

## 2. Experimental

### 2.1. Chemicals

Quetiapine fumarate was kindly provided by AstraZeneca UK Limited (Macclesfield, Cheshire, UK). Maprotiline (9-[γ-methylaminopropyl]-9,10-dihydro-9,10-ethanoantracene) used as internal standard (IS) in the capillary electrophoresis method was purchased from Sigma Chemical CO. (St. Louis, MO). Methanol HPLC grade, sodium hydroxide 2 mol $l^{-1}$ and phosphoric acid analytical grade were from Carlo Erba (Milan, Italy). Ultrapure water (18.2 MΩ cm) was obtained by means of a Millipore MilliQ apparatus (Milford, MA).

The pharmaceutical formulation Seroquel® 200 containing 230.26 mg of quetiapine fumarate corresponding to 200 mg of quetiapine free base was obtained from AstraZeneca S.p.A. (Basiglio, Milan, Italy). Inactive ingredients are: povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

### 2.2. Instruments

Quantitative analysis of quetiapine was performed with a $^{3D}$CE capillary electrophoresis automated apparatus (Agilent Technologies, Palo Alto, CA), equipped with a diode array detector set at 205 nm. Capillary zone electrophoresis was run in untreated fused-silica capillaries (Composite Metal Service Ltd. The Chase, Hallow, Worcester, UK) of 38.5 cm (effective length 8.5 cm) and 50/363 μm I.D./O.D. The cartridge was maintained at 25.0 °C. The sample solutions were loaded into the capillary at the anodic end by pressure injection at 50 mbar for 10 s. The instrument was operated at 15 kV with typical currents of about 40 μA. Before use, the new capillary was purged with deionized water for 5 min, then washed with 1.0 N sodium hydroxide for 10 min, with 0.1 N sodium hydroxide for 10 min, with water for 20 min, and finally with capillary zone electrophoretic (CZE) buffer for 10 min. Careful washing of the capillary was essential in order to obtain reproducible results. Thus, at the beginning of every working day the capillary was rinsed with: water (5 min), 0.1 N NaOH (3 min), water (6 min) and background electrolyte (BGE) for 5 min. After each electrophoretic run the capillary was flushed with BGE for 2 min. At the end of the day the capillary was washed with water (2 min), with 0.1 M NaOH (5 min) and with water (5 min). It was then air-dried for 3 min. Preliminary spectrophotometric assays were carried out using a Jasco (Tokyo, Japan) Uvidec-610 double-beam spectrophotometer. The quantitative analysis was performed using a Jasco Uvidec-4 Digital spectrophotometer (Jasco, Japan Spectroscopic CO., Ltd, Tokyo, Japan). Quartz cuvettes with an optical path of 1 cm were used.

### 2.3. Solutions and sample pretreatment

The stock solutions of quetiapine (1 mg $ml^{-1}$) were prepared from pure compound by dissolving 23.03 mg of quetiapine fumarate in 20 ml of methanol. The stock solution of maprotiline was obtained dissolving 20 mg of pure compound in 20 ml of methanol. Standard working solutions were prepared by diluting each stock solution with a phosphate buffer (5 mM, pH 2.5) for the CZE method and with a phosphate buffer (50 mM, pH 2.5) for the spectrophotometric method. The standard solutions were prepared every day.

Quetiapine was extracted from the tablets using the following procedure. First, 20 tablets were accurately weighed, finely ground to a powder and thoroughly mixed. Then, an aliquot of this powder corresponding to 20 mg of declared active principle (calculated as quetiapine free base) was weighed and transferred into a volumetric flask. A 20 ml volume of 50 mM, pH 2.5 phosphate buffer was added, the mixture was agitated for 15 min on an ultrasonic bath and then centrifuged for 15 min at 3000 rpm. The supernatant (with a final concentration of 1 mg $ml^{-1}$ of quetiapine) was used for preparing the working solutions diluting the stock mixture with phosphate buffer. The BGE was a phosphate buffer (50 mM, pH 2.5) prepared by dissolving the appropriate volume of *o*-phosphoric acid in water and adjusting the pH with sodium hydroxide (1 mol $l^{-1}$). The buffer was

always filtered through cellulose acetate syringe filters (0.20 μm, Albet–Jacs-020-25) prior to use.

### 2.4. Precision assays

Quetiapine standard and tablets solutions were prepared and analysed six times within the same day to obtain the repeatability, and six times over different days to obtain the intermediate precision, according to USP requirements [25]. Each assay was carried out on a different extraction of quetiapine from the commercial tablets of Seroquel. The percentage relative standard deviations (RSDs%) of the data obtained were calculated with both methods. The LOQ and the LOD were calculated according to USP guidelines [25].

### 2.5. Accuracy

The accuracy of the methods was evaluated by means of recovery determinations, adding a known quantity of the reference powder to a certain amount of the pharmaceutical formulation, in order to obtain three different levels of addition. The samples were analysed and the mean recovery, as well as the repeatability was calculated on six assays for each concentration added.

## 3. Results and discussion

### 3.1. Spectrophotometric analysis

The spectra of a 10 μg $ml^{-1}$ quetiapine standard solution in methanol and in a 50 mM, pH 2.5 phosphate buffer (two candidates as solvents for the extraction of quetiapine from tablets) are reported in Fig. 2. As can be seen from the ultraviolect spectrum in methanol (Fig. 2a), quetiapine shows an absorbance band with a maximum at 210 nm and two shoulders at 248 and 294 nm. Instead, when recorded in acidic buffer medium the ultraviolet spectrum of quetiapine (Fig. 2b) presents an absorbance maximum at 210 nm and two absorbance shoulders at $\lambda = 246$ and 291 nm, with somewhat different morphology. Since the detection at 210 nm would have been difficult because of the many potentially interfering compounds, and the detection at 291 nm would have been scarcely sensitive, we chose to carry out the analyses at $\lambda = 246$ nm. A calibration curve was set up by plotting the absorbance values against the quetiapine concentration (μg $ml^{-1}$), in the 5–25 μg $ml^{-1}$ range. A good linearity was found in the examined concentration range; the linearity equation, calculated by means of the least square method, was $y = 0.04109\ x = 0.0007$ ($r = 0.9997$; error for the slope $= 5.3 \times 10^{-4}$; error for the intercept $= 8.1 \times 10^{-3}$).

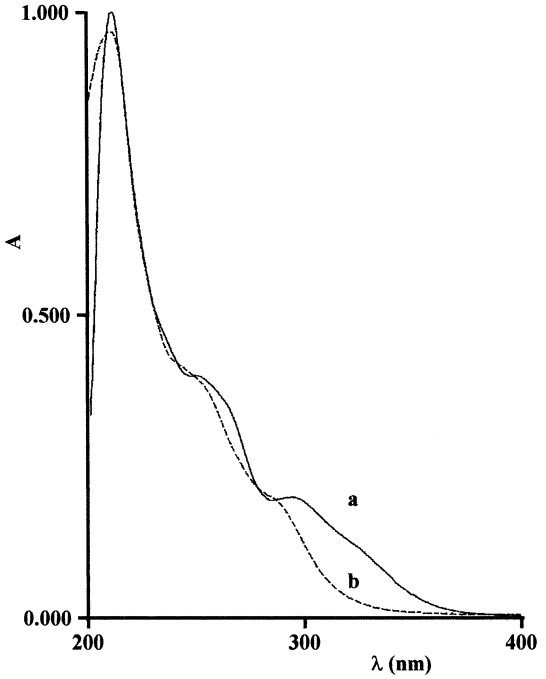


Fig. 2. Ultraviolet spectrum of a 10 μg $ml^{-1}$ quetiapine standard solution a) in methanol, and b) in 50 mM, pH 2.5 phosphate buffer.

In order to verify the method precision, quetiapine standard solutions at three different concentrations (5–15–25 μg $ml^{-1}$) were subjected to spectrophotometric analysis for six trials. The intraday assays (repeatability) for the 5 μg $ml^{-1}$ gave a RSD value of 1.2%, while the interday assays (intermediate precision) gave a RSD value of 2.0%. For the solution with a concentration of 15 μg $ml^{-1}$ the RSD% values for repeatability and the intermediate precison were 0.5 and 0.8, respectively, while for the solution with a concentration

of 25 μg $ml^{-1}$ the RSD% values for repeatability and the intermediate precison were 0.4 and 0.8, respectively. The limit of quantitation was 2.5 μg $ml^{-1}$ and the limit of detection 1.5 μg $ml^{-1}$. Having thus validated the method in terms of precision on standard solutions, it was applied to the assay of quetiapine in Seroquel® tablets as described in Section 2. The choice of the solvent used for the extraction of quetiapine from Seroquel® tablets was of great importance. Preliminary spectrophotometric assays on Seroquel® tablets were carried out dissolving quetiapine from the powdered formulation either in methanol, methanol-water (50:50, v/v), or acidic buffer, centrifuging it and subjecting the resulting solution to spectrophotometric measurements. The extraction performed using methanol as the solvent led to percentage recoveries (drug found of declared) of 109%, clearly indicating the presence of interference. The interference was decreased by using methanol-water (50:50, v/v) as solvent, however, this procedure gave unsatisfactory results as well. Interference was completely eliminated by using 50 mM phosphate buffer pH 2.5, as solvent for a quantitative extraction of quetiapine. The spectrum of a solution obtained from the extraction of Seroquel® tablets is morphologically identical to the spectrum of the standard solution. The percentage of label claim (quetiapine found of declared) is high and close to 100% for measurements carried out at the wavelength of 246 nm. Under these conditions, the mean value of percentage of drug found of declared was 98.8% at three different concentrations (5–15–25 μg $ml^{-1}$) of quetiapine with a repeatability RSD $\leq$ 1.2% and an intermediate precision RSD $\leq$ 1.9% (Table 1). The accuracy of the method was verified by adding known amounts of quetiapine pure substance to powdered formulation, obtaining additions of 5, 15 and 20 μg $ml^{-1}$ (total concentrations of 10, 20 and 25 μg $ml^{-1}$). All the spectrophotometric assays gave satisfactory results: the mean percentage recovery obtained was 99.4% with good repeatability (RSD $\leq$ 1.2%). The detailed results are reported in Table 2.

The proposed extraction method is rather robust: small variations ($\pm$0.2) in the pH value of the phosphate buffer did not bring about any change in the recovery of quetiapine from formulations; the same can be said of the time of extraction/sonication and the temperature: variations of $\pm$5 min and $\pm$5 °C, respectively, did not change significantly the results of the analysis.

### 3.2. CZE analysis

The analysis of quetiapine was carried out using a capillary electrophoresis apparatus with a UV detector set at 205 nm. Quetiapine has at least one amino group in its structure (see Fig. 1) which can be easily charged at low pH. For this reason an acidic BGE was used because the cationic form, which is in equilibrium with the more lipophilic non-charged species, has a better solubility in water. Preliminary assays were performed using a 100 mM, pH 2.5 phosphate buffer and an uncoated fused-silica capillary with a total length of 38.5 cm and an effective length of 8.5 cm, ID 50 μm. The short capillary used led to high currents during the separation runs, due to the high BGE ionic strength. For this reason, the total ionic concentration of the BGE was reduced from 100 to 50 mM, in order to minimise the negative effects of the current. The result of the adjustment of the BGE concentration gave a baseline separation of the analytes in a short time when a 50 mM

Table 1
Quality control of Seroquel® tablets

| Method | Spectrophotometry | | | CZE | | |
|---|---|---|---|---|---|---|
| Quetiapine concentration (μg $ml^{-1}$) | 5 | 15 | 25 | 5 | 20 | 50 |
| % Drug found of declared[a] | 97.8 | 98.6 | 99.8 | 98.9 | 99.4 | 100.1 |
| Repeatability (RSD%)[a] | 1.2 | 1.0 | 0.9 | 1.0 | 0.7 | 0.4 |
| Intermediate precision (RSD%)[a] | 1.9 | 1.8 | 1.6 | 1.8 | 1.6 | 1.5 |

[a] $n = 6$

Table 2
Accuracy of methods

| Method | Spectrophotometry | | | CZE | | |
|---|---|---|---|---|---|---|
| Quetiapine concentration added (μg ml$^{-1}$) | 5+5 | 5+15 | 5+20 | 10+5 | 10+10 | 10+20 |
| Recovery (%) | 98.6 | 100.1 | 99.6 | 98.2 | 99.5 | 100.5 |
| Repeatability (RSD%) | 1.1 | 1.0 | 1.2 | 1.8 | 1.6 | 1.3 |

Each value is the result of six independent assays.

phosphate buffer, pH 2.5 was used. This system was taken further for the determination of the analyte in pharmaceutical formulations and the quantitative analysis was performed using a 50 mM phosphate buffer, pH 2.5, applying a constant voltage of 15 kV, and requiring only a few minutes for a complete electrophoretic run. Intentional variations ($\pm$3 kV) to the experimental voltage of the analysis caused the proportional modification of migration times, however they did not cause any change in the analysis results.

In order to choose a suitable IS, different substances were investigated, namely maprotiline, paroxetine, protriptiline, triprolidine, dibenzepine, amitriptiline, loxapine and chlorpromazine, which have quite similar molecular structures. All the substances were well separated from quetiapine, except the loxapine. The migration times of the tested substances are reported in Table 3. Maprotiline was chosen as the IS because it can be better quantitatively extracted using the extraction procedure of quetiapine from pharmaceutical tablets. The electropherogram of standard solutions containing quetiapine and maprotiline 20 μg mL$^{-1}$ shows (detection wavelength is 205 nm) two peaks, with quetiapine peak at migration time of 1.4 min and the peak of maprotiline with a migration time of 1.9 min.

Table 3
Compounds tested as possible IS for CZE analysis

| Compound | Migration Time (min) |
|---|---|
| Quetiapine | 1.40 |
| Loxapine | 1.41 |
| Dibenzepine | 1.76 |
| Protriptiline | 1.79 |
| Amitripline | 1.82 |
| Chlorpromazine | 1.82 |
| Triprolidine | 1.85 |
| Maprotiline | 1.90 |
| Paroxetine | 1.93 |

The calibration curve was obtained by plotting the value of the ratio between the area of quetiapine and that of the IS (maprotiline) against the quetiapine concentration. Linearity was observed in the 5–50 μg ml$^{-1}$ quetiapine concentration range. The equation of the calibration line, obtained by the least-square regression was: $y = -0.00118 + 0.03008\ x$ (error for the slope $= 7.9 \times 10^{-4}$; error for the intercept $= 2.0 \times 10^{-2}$), where $x$ is the quetiapine concentration, expressed as μg ml$^{-1}$, and $y$ is the ratio between the area of quetiapine and that of the IS (maprotiline, 20 μg ml$^{-1}$). The linearity, expressed by the linear correlation coefficient, $r$, was 0.9991. The LOQ value was 0.100 μg ml$^{-1}$ and the LOD value was 0.050 μg ml$^{-1}$, calculated according to USP [25]. The precision assays gave RSD% values of 0.9 for repeatability and 1.9 for the intermediate precision on 5 μg ml$^{-1}$ quetiapine standard solution ($n = 6$); RSD% values of 0.6 for repeatability and 1.5 for the intermediate precision on 20 μg ml$^{-1}$ quetiapine standard solution ($n = 6$); RSD% values of 0.3 for repeatability and 1.3 for the intermediate precision on 50 μg ml$^{-1}$ quetiapine standard solution ($n = 6$).

Application of the method to commercial formulations gave good results. The electropherogram of an extract having a nominal concentration of 20 μg ml$^{-1}$ of quetiapine, is shown in Fig. 3. It is apparent that the peak of quetiapine is very neat, with a migration time of 1.4 min, and is well separated from that of maprotiline (20 μg ml$^{-1}$), used as IS, which has a migration time of 1.9 min; no interference from the formulation matrix is present. The overall morphology of the electro-

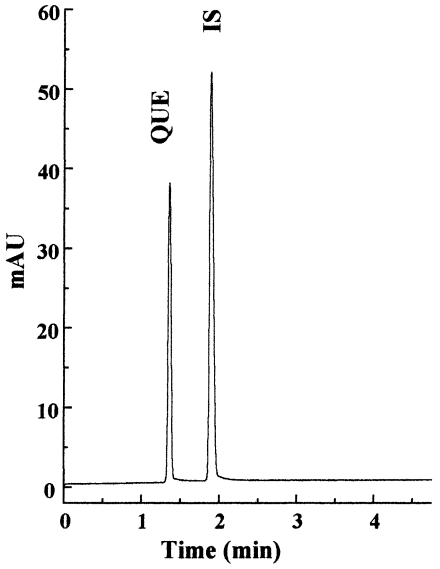


Fig. 3. Electropherogram of a 20 μg ml$^{-1}$ (quetiapine nominal concentration) Seroquel® 200 tablet extract containing 20 μg ml$^{-1}$ of IS (maprotiline). Conditions: BGE phosphate buffer 50 mM, pH 2.5. Capillary length 38.5/8.5 cm, ID 50 μm. Voltage 15 kV. Temperature 25.0 °C. Detector wavelength 205 nm.

pherogram is nearly identical to that of a standard solution at the same concentration. The extraction procedure of the drug from the tablets is very simple and feasible being based only on a one-step treatment of the powder obtained from the tablets with a pH 2.5 phosphate buffer, followed by centrifugation. This method assures a good efficiency and selectivity. In fact, it can be seen that no interference from excipients was revealed.

The quality control assays carried out in several trials gave very satisfactory results as shown in Table 1: the percentage of label claim found of quetiapine is higher than 98.9% for every concentration analysed; this indicates that the amount of drug found is in accordance with the claimed value, and within the limit prescribed by USP [25]. Precision assays were carried out analysing extracts of Seroquel® 200 tablets in order to evaluate the RSD% data of intraday and interday assays. These were both satisfactory (Table 1). In fact, the highest RSD values were 1.0 and 1.8% for the repeatability and intermediate precision, respectively, for a nominal concentration of 5 μg ml$^{-1}$. The accuracy of the method was evaluated by means of recovery studies by adding to a known amount of the pharmaceutical formulation known quantities of pure quetiapine at three different concentrations (5–10–20 μg ml$^{-1}$). The results are summarised in Table 2. As one can see, high recovery values were obtained (mean recovery was 99.4%). The quantitative recovery results of the analyte indicate the high accuracy of the proposed CZE method. The precision of the recovery assays (repeating the procedure six times) was also very satisfactory; in fact, the values of RSD% intra-day, calculated on six trials, varied between 1.3 and 1.8.

### 3.3. Stability of quetiapine solutions

The assays carried out indicated that quetiapine stock solutions (1 mg ml$^{-1}$) in methanol are stable for at least 6 months when stored at −20 °C; these results were confirmed by the data obtained by means of CZE method, which did not show any change in the electropherograms, even when injecting solutions prepared from a 6-month old quetiapine stock solution. In all cases peak identity and peak purity were assessed from the spectra recorded by the diode array detector of the electrophoretic apparatus. The stability of the standard solutions was tested by analysing them at the beginning and the end of the working day: identical results (within the precision limits) were obtained. The same assays were carried out on the samples extracted from pharmaceutical formulation yielding equivalent results.

Thus, it can be concluded that quetiapine solutions (both standard solutions and solutions extracted from formulations) are stable in the proposed experimental conditions.

## 4. Conclusions

The two proposed methods, one based on spectrophotometry and the other on capillary zone electrophoresis, are suitable for the determination of quetiapine in commercial tablets. The sample treatment is very rapid, consisting of a simple one-step extraction with 50 mM, pH 2.5 phosphate buffer, centrifugation and dilution. The same extract from Seroquel® 200 tablets was

analysed by means of the two methods, giving similar and satisfactory results in terms of repeatability, intermediate precision, and accuracy. Considering the obtained data, it is possible to affirm that both proposed methods are fast, simple and suitable for the accurate determination of quetiapine in commercial tablets. The electrophoretic method in particular is very rapid, while the spectrophotometric method is simpler and requires less expensive instrumentation. Furthermore, the proposed methods are inexpensive and non-polluting, because small volumes of buffer are needed for the preparation and analysis of the sample and because organic solvents are not used at all.

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