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Pre-clinical investigation of the modulation of quetiapine plasma pharmacokinetics and tissues biodistribution by lipid-core nanocapsules

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ABSTRACT

This study aims to investigate the changes in plasma pharmacokinetics and liver and brain distribution of quetiapine (QTP) due to its encapsulation into a polymeric nanocarrier. For this reason a bioanalytical method was developed and validated in order to quantify QTP in plasma, liver and brain tissue samples. The method was linear over the concentration range of 0.025–3.0 μg.mL ($r^2 > 0.98$), accurate, precise (R.S.D < ± 15%) and the recoveries, stability and validation parameters are within the acceptable limits determined by international guidelines. Plasma pharmacokinetics, cerebral and hepatic distribution of the drug were carried out after intravenous administration of 5 mg kg^{-1} of nanoencapsulated (QLNC) or free-QTP to male Wistar rats. Increasing half-life was observed for QLNC in relation to free-QTP due to o significant decrease in total clearance. QTP volume of distribution was not altered due to encapsulation. An increase in QTP liver exposure was observed after nanoencapsulation probably due to a reduction in drug metabolization process.

1. Introduction

Development of drug delivery systems involves different technological approaches in order to modify the drug release profile, pharmacokinetics and pharmacodynamics *in vivo* aiming to improve products safety and efficacy and reduce unwanted effects or toxicity [1,2].

The use of polymeric nanoparticles, matricial or vesicular colloids containing biocompatible polymers in the system domain, as drug carriers has attracted great attention in recent years [3] due to their advantages like biodegradability [3], capability of controlling the release of drugs [1,2] and increasing half-life in the systemic circulation [4], and targeting drugs to specific organs as brain, liver or kidneys, as well as tumor cells [5]. Furthermore, the use of nanoparticles is a promising approach for administration of insoluble or sensitive drugs such as taxol, peptides or DNA [4–6].

Lipid-core nanocapsules (LNC) is a specific type of polymeric nanocarrier proposed by Jäger et al. [7] in 2009. These nanocapsules suspension are prepared by self-assembling mechanism [8] and are constituted by a polymeric shell containing polysorbate-80 fitted around a dispersion of capric/caprilic triglycerides and sorbitan monoestearate. These systems have higher encapsulation efficiency for lipophilic drugs, are capable to protected the drug from chemical or enzymatic degradation and to prevent early *in vivo* metabolization and elimination altering the drug pharmacokinetic (PK) disposition [3,9–11]. Due to the equilibrium between plasma and tissues, changes in drug plasma PK profiles due to nanoencapsulation can lead to changes in tissues biodistribution [4].

Quetiapine (QTP, Fig. 1), an atypical antipsychotic, is a drug used for the treatment of schizophrenia, acute mania and episodes of depression associated with major depressive disorders [12]. The drug is extensively metabolized in the liver by the cytochrome P450 (CYP) enzymes, primarily by CYP3A [13,14]. QTP side effects include weight gain and metabolic disorders, such as increasing glucose levels and dyslipidemias during chronic use [15,16]. The use of nanocarried QTP could targeting the drug to the brain, pos-

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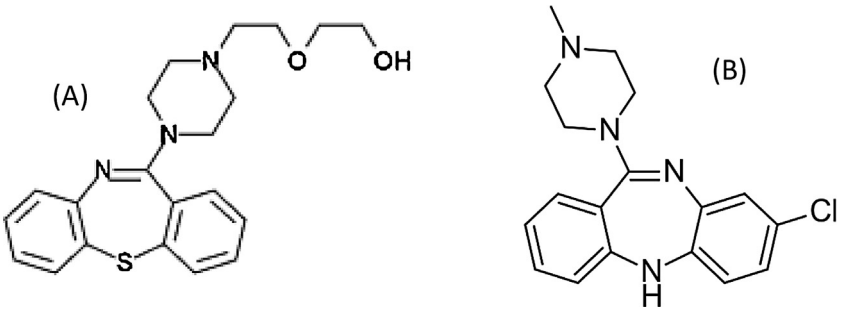

Fig. 1. Chemical structures of quetiapine (A) and the internal standard clozapine (B).

sibly reducing systemic side effects due to a decreased systemic exposure.

A previous study from our group had shown that QTP is a suitable drug to load into LNC with high encapsulation efficiency due to its physicochemical properties such the partitioning coefficient logD [17]. The efficiency of this formulation to increase QTP brain penetration and reduce its liver metabolization has yet to be investigated.

A literature review showed that previous methods have been described to quantify QTP in plasma samples from humans and rats [12,16–23]. However, the use of liquid chromatography in tandem with mass spectrometry (LC-MS/MS) [22], solid-phase extraction [23] or the necessity of large samples volume [18] turns these methods expensive for application in an initial pre-clinical pharmacokinetic investigation.

The most commonly used technique to access drug concentrations in biological samples such as total blood, plasma, urine and tissue biopsy in pharmacokinetic investigation is the high performance liquid chromatography (LC) [24]. The use of ultraviolet detection enables the quantification of drugs after extraction from biological samples and is cheapest comparing to fluorescence detector or LC-MS/MS [25].

In the present work a validated a simple LC-UV method was developed and validated to quantify QTP in rat plasma, brain and liver tissue viewing to investigate the alterations in plasma and tissue pharmacokinetics due to QTP nanoencapsulation into LNC.

2. Materials and methods

2.1. Materials

QTP fumarate (>99.0%) was kindly provided by Pratti Donaduzzi Pharmaceutical Laboratory (Toledo, Brazil). Clozapine (>99.0%), used as internal standard, was a donation from Cristália Pharmaceutical Laboratory (Itapira, Brazil). Acetonitrile and methanol (LC grade) were obtained from Tedia (Fairfield, USA), triethylamine was obtained from Merck (Darmstadt, Germany). Water was purified by a Mili-Q system (Milipore, MA, USA). Other chemicals were of analytical grade.

2.2. Equipment

All LC runs were performed using a Waters® HPLC system equipped with a Waters® 2487 dual λ absorbance detector, automatic injector (717 Plus Waters®) and a Waters® 600 pump controller. Results were acquired and processed using the Waters® Empower software. QTP was resolved from endogenous compounds on a C_{18} column (Phenomenex Luna® 150 mm × 4.6 mm i.d.; particle size 5 μm) coupled to a C_{18} Phenomenex security guard® pre-column.

2.3. Chromatographic conditions

Chromatographic separation was accomplished in isocratic mode with a flow of 1.2 mL min^{-1}. The mobile phase consisted in thryetilamine aqueous solution (0.4%, v/v):methanol:acetonitrile (60:25:15, v/v); pH 3.0 ± 0.3 (adjusted with phosphoric acid (H_3PO_4 85%). Sample injection volume was 35 μL and detection wavelength was 246 nm for QTP and clozapine (CZP, IS—internal standard). All experiments were performed at room temperature and the total run time was 12 min. QTP/clozapine peak area ratios were used for the drug quantification in plasma and tissue samples using a matrix-matched standard curve.

2.4. Preparation of standard solutions, analytical curves and quality controls

QTP and CZP standard stock solutions (1 mg mL^{-1}) were prepared in methanol and stored at −80 ± 1 °C.

QTP standard working solutions of 0.25; 0.5; 1.0; 3.5; 5.0; 10; 20.0; 30.0; 100.0 μg mL^{-1} were obtained diluting QTP standard stock solution in methanol:water (50:50, v/v). The standard working solutions were used in order to generate the standard curves (0.025; 0.05; 0.1; 0.35; 0.5; 1.0; 2 and 3 μg mL^{-1}) by spiking 90 μL of rat blank plasma with 10 μL of the aforementioned standard working solution.

CZP stock solution was also diluted in methanol:water (50:50, v/v) obtaining a 3 μg mL^{-1} solution. 10 μL of this solution was used as the internal standard for the bioanalytical method resulting in a final concentration of 0.3 μg mL^{-1} in each plasma sample.

Quality controls (QC) of the drug in this matrix were prepared in low (QCL: 0.75 μg mL^{-1}), medium (QCM: 1.2 μg mL^{-1}) and high (QCH: 2.5 μg mL^{-1}) concentrations as described previously using 7.5, 12 and 25 μg mL^{-1} working solutions.

To ensure that plasma samples above 3 μg mL^{-1} were adequately quantified a dilution assay was performed. Diluted samples (DS) were prepared diluting plasma samples containing QTP 5 μg mL^{-1} with blank plasma to reach the concentration of 0.5 μg mL^{-1}.

In order to expand the method scope to liver and brain tissues6 samples of the calibration curves and 6 QCs samples (low and high QC) were prepared spiking QTP working solutions in liver or brain tissue homogenate from untreated animals. The diluted samples were processed and analyzed in the same manner as the plasma samples. Working solutions, calibration curves and quality controls were freshly prepared every day during ongoing analysis.

2.5. QTP extraction from plasma and tissues samples

QTP was extracted from plasma by liquid–liquid extraction using ethyl acetate as the extraction solvent. First, 10 μL of IS and 10 μL of ammonium hydroxide (30%) were added to 100 μL of plasma or tissue sample and vortex-mixed for 30 s. Then, 1 mL