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ABSTRACT BOOK

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MP-133 / PHARMACOKINETIC OF MYRIOCIN IN RABBIT'S EYES

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Keywords: myriocin,pharmacokinetic,drug delivery, eye, qTrap

Introduction
Myriocin (Myr) is a suicide inactivator of ceramide synthesis with a complex lipid multifunctional structure. Its biological activity is exerted at very low doses, and thus highly performing quantitative method are needed [1]. The pharmacological development of Myr to modulate ceramide levels also requires currently unavailable ADME information in healthy and pathological animal models.

Methods
A 3200 qTRAP system was operated under manufacturer's instructions to perform extensive tandem MS studies. LC and MS were optimized for the separation, detection, identification and quantification of Myrin aqueous humour, vitreous humor and retina of rabbit after different treatments. MRM scan mode was used as protocol, to tackle the ambiguities of some samples, EPI scan, MS3 and the use of HR-MS on a 6600 qTOF was also crucial.

Results
Tissue levels of Myrare related to the dose, pharmaceutical formulation, administration route, and administration schedule. Four type of eye drop formulations were evaluated in rabbits: Myr in buffer solution, Myr in two different types of liposomes (neutral and cationic), Myr encapsulated in a novel type of solid nanolipid particles. In particular, solid nanolipid particles was found to be extremely efficacious for the delivery of Myrin the different areas of the eye. The slow release formulation produced a Tmax between 180-240 minutes, with a maximum concentration respectively of 10 μg/mL in vitreous and 1.7 μg/g in retina. Biological activity of Myr was always confirmed in rabbit's retina by a significant decrease in ceramides levels, compared to the physiological level established from untreated animals. Some untreated animals demonstrated the presence of a peak with spectroscopic and chromatographic characteristics of Myr. EPI scan, MS3, and the use of a HR-MS as protocol confirmed an upstream contamination.

Conclusions
A new pharmaceutical delivery system, such as solid lipid nanoparticles, allows Myr to accumulate into the retina by a non-invasive eye-drops administration, and to modulate sphingolipid levels. These results would be promising to study its efficacy in mouse pathological model of retinitis pigmentosa. MRM measurement needs alternative and/or complementary techniques to confirm eventual false-positives samples.

Novel Aspect
The use of HR-MS as protocol should be quite advantageous for predicting new metabolites and for

removing unwanted matrix interferences.

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MP-134 / COMPARISON OF ESI, APCI AND APPI IONIZATION TECHNIQUES FOR TESTOSTERONE (T), DIHYDROTESTOSTERONE (DHT) AND ESTRADIOL (E2) LCMS/MS ASSAY

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Keywords: Comparing ionization techniques for steroids

Introduction

High sensitivity measurement at low concentrations of non-derivatized testosterone (T), dihydrotestosterone (DHT) and estradiol (E2) requires optimizing ionization technique but few matrix-specific comparisons are available. We compared electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) for sensitivity and matrix interference in neat solutions and human serum.

Methods

LC instrumentation and conditions

A Shimadzu Prominence HPLC system was used and consisted of a DGU-20A5 degasser, three LC-20 AD pumps, a SIL-20AT HC autosampler and a CTO-20A column oven (Shimadzu Scientific Instruments, Kyoto, Japan). The column was an Agilent Poroshell 120 SB-C18 (2.1 × 50 mm; 2.7 µm) with 0.3 µm in-line filter (Agilent Technologies). For the determination of LLOQs with standard solutions, column temperature was 40°C, injection volume 20 µl, and mobile phase of 70% methanol/water, containing 0.1% (v/v) of formic acid for positive ESI and 2.5 mM ammonium hydroxide for negative ESI. APCI and APPI were used without mobile phase additions. For serum and tissue samples, a following gradient was employed (A: water, B: methanol): 0–1 min: 20% B, 1–8 min: 20 > 70% B, 8–10 min: 70% B, 10–12 min: 100% B, 12–16 min: 20% B. Flow rate was 0.3 ml/min, injection volume 40 µl and same mobile phase additions were used as for the isocratic separations. A flow-line selection valve was used to divert the eluent to waste during 0–7 min and 11–16 min. For all experiments with APPI, toluene was used as a dopant solvent, delivered with an LC-20 AD pump with a flow rate 10% of that of the mobile phase.

MS instrumentation and conditions

An API 5000 triple quadrupole MS was used with Turbo V (ESI, APCI) and PhotoSpray (APPI) ion sources (AB Sciex, Toronto, Canada). The APPI lamp was a DC-driven 10.0 eV krypton discharge lamp model PKS100 from Heraeus (Hanau, Germany). Nitrogen was employed as ion source, curtain and collision gas (Peak NM20ZL, Peak Scientific, Inchinnan, UK). For the precursor ion selection and optimization of the MS parameters, 5 µ M solution of E2 in methanol was infused post-column into the mobile phase (70% methanol/water).

The E2 infusion flow rate was kept at 5% of the mobile phase flow. Precursor and product ion selection was based on ion intensity. After establishing the MRM conditions, further optimization of the ion source parameters and the mobile phase flow rate was made with on-column injections, which enabled signal-to-noise (S/N) calculations. MS parameters not related to ionization were optimized and kept identical for each MRM transition. Both quadrupoles were set at unit resolution, cycle time was 250 ms and no signal