Metabolic Stability in vitro Assay of new drug candidates for tuberculosis

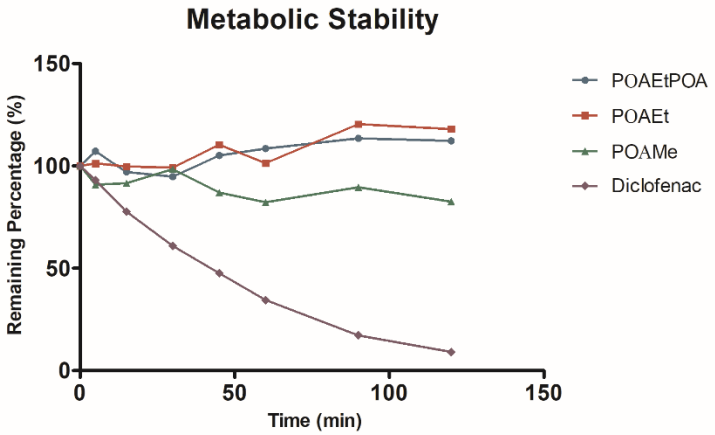
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Abstract

Introduction: The development of new drugs is a complex process, with only 0,027% of new synthesized molecules being approved by regulatory agencies. Inadequate pharmacokinetic properties and toxicity are responsible for half of the failures in this process and the in vitro screening of new molecules assists in the selection of the best candidates and to understand the results of in the in vivo studies. In the metabolic stability assay the molecules are submitted to a microsomal system to evaluate their degradation by the microsomal enzymes. Considering that tuberculosis is still responsible for millions of deaths and cases of bacterial resistance to the drugs used in the treatment only increase, esters of pyrazinoic acid, the active metabolite of pyrazinamide, have been developed as a novel alternative for this treatment, and the present work aimed to evaluate the metabolic stability of POAEt POAEtPOA and POAMe. Methodology: The compounds were incubated with 0,5mg/mL rat microsome for up to 120 minutes in buffer, with and without NADPH regenerating system. They were tested in concentrations of 2, 5 and 10µM. The samples were quantified by UHPLC, with previously developed methods. Diclofenac was used as a control of the system. Results: The control were adequate, indicating the system operation, showing a half-life of 33 minutes. The quantification was not possible in the 2µM, while the concentrations of 5 and 10µM presented the same profile, thus, the concentration of 5µM was choose to perform the experiment. The compounds showed no decay in any of the situations referred to it, making it impossible to calculate the elimination half-life, and therefore the extrapolated clearance. Conclusion: It was observed that the three molecules were stable in this system and there was no activity of the microsomal enzymes on these compounds.

Image



References

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Biography

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