SUPERAGREGATES FROM AMPHOTERICIN B MICELLES: A NEW WAY TO DECREASE ITS TOXICITY

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INTRODUCTION
The Amphotericin B in a micellar system (AmB) is a drug largely used for the treatment of systemic fungal infections, especially in immune-compromised patients. However, its use is limited due to its high toxicity, which is the main cause of side effects such as nephrotoxicity (1). There are several intravenous amphotericin B lipidic formulations that are less toxic, but presenting high cost. According to the literature, in aqueous solution there are the monomeric and aggregated forms of AmB, these latter being responsible for its side effects (2). Lately, it has been observed that the heating of AmB solutions generates “superaggregates” forms, which are produced by the condensation of monomeric and aggregate forms. This new state has been demonstrated to be less cytotoxic while keeping its activity (1). The aim of this work was not only to investigate the changes in the spectrum of the unheated and heated AmB solutions, following the bands of “superaggregates”, monomer and aggregates forms, but also to evaluate its toxicity.

MATERIALS AND METHODS
A spectroscopic study was performed in the wavelengths from 300nm to 450nm at four different concentrations (from 50 to 0.05mg.L⁻¹) of unheated and heated AmB. It is important to attempt that those values to the blood concentration following intravenous administration. For the in vitro toxicity assay, red blood cells from healthy human donors were used representing a mammalian (cholesterol containing) cell model. Then, potassium and hemoglobin leakage from red blood cells were monitored, respectively, as a measure of acute and chronic toxicity. Such protocol was previously approved by the UFRN’s Ethical Committee.

RESULTS
The spectrum of heated AmB revealed a decrease in the monomers concentration (409nm) at high concentrations, and an increase on the “superaggregates” form (323nm) when compared to the unheated ones. Concerning the toxicity, unheated and heated AmB showed different behavior: the hemoglobin leakage from unheated AmB, especially at high concentrations, was higher than the one found to the heated AmB, whose values tended to zero. Similar profile was found to the K⁺ leakage.

CONCLUSIONS
The heated AmB showed to be much less toxic than the unheated ones, highlighting this new procedure as a simple, inexpensive and safe alternative for the future treatment of systemic fungal infections.

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REFERENCES
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