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SYNTHESIS AND ANTILEISHMANIA EVALUATION OF LIMONENE β-AMINOALCOHOLS AND DEVELOPMENT OF NANOSTRUCTURED SYSTEMS FOR TREATMENT OF LEISHMANIASIS.

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Introduction: Leishmaniasis is endemic in tropical regions, affecting over 12 million people in 88 countries and its clinical manifestations can occur in cutaneous, mucocutaneous and visceral forms. The main health organizations are concerned about that due to the significant number of cases. Despite of this, the therapeutic arsenal available to treat this illness is deficient, antique, and most of the drugs present several side-effects. Moreover, the widespread development of resistance by certain strains of leishmaniasis to antimonial compounds, contribute to the bad health condition of the underdeveloped countries. Natural Products (NPs) are very important for human therapy and the strategy of searching new leads to treat parasitic diseases starting from natural sources is widely used by medicinal chemists. Among the NPs, Limonene is a main constituent of essential oils with a number of pharmacological activities and as a flavor in cosmetics industry. Arruda *et al.* showed that limonene was effective in *in vitro* and *in vivo* assays against Leishmania species (IC_{50}=185 mM, MTT test).[1] Recently, we have synthesized several limonene β-aminoalcohol derivatives at the cyclic double bond and evaluated its leishmanicidal activity against isolated parasites.[2] We observed that the inhibitory action against promastigotes is greater than pentamidine, and two of the synthesized compounds were found to be 100-fold more potent. This same library showed a good carrapaticide activity against both larvae and eggs of *R. microplus*[3] indicating the high potentiality of these compounds.

Objetives: Synthesize aminoalcohols derived from limonene and development of nanostructures with these compounds in order to test *in vivo* topically in mice with cutaneous leishmaniasis.

Materials and methods: The synthesis of β-aminoalcohols were achieved using protocols published before.[2] The nanocapsules were prepared by interfacial deposition of pre-formed polymers[4] and by cavitation using high pressure homogeneizer[5]. We have initially analyzed by laser diffraction (Mastersizer 2000, Malvern, UK) to exclude the presence of micrometer particles in the formulations. The determination of the assay of drugs in suspensions and the amount of active ingredient associated with the nanostructures were determined by HPLC using detector UV-VIS S-200. The average diameter and polydispersity of nanocapsules suspension was determined by dynamic light scattering Zetasizer nanoseries, Malvern Instruments, model ZEN 3600. The stability of suspensions of nanocapsules was analyzed in Turbiscan LAb (Formulaction, France). The viscosity of suspensions of nanocapsules was conducted in Brookfield rotational viscometer and the pH of the formulations was measured in calibrated pot.

Results and discussion: We have selectively synthesized 7 β-aminoalchools with moderate to good yields. The nanostructures don't shown micrometer particles in the formulations. In dynamic light scattering (DLS), the particle size analyses showed diameters ranging from 0.133 to 0.244 nm. The nanoparticles were stable, with little tendency to the occurrence of creaming, sedimentation or coalescence when analyzed with Turbiscan. The viscosity of NPs remained around 0.71 MBPS and pH remained around 5.0.

Conclusions: The characterization of the nanopartucles showed similars nanometrics distributions with laser diffraction and DLS. The nanostructures were enabling for further antiparasitic activity assays.

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