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**Article** *in* Journal of Nano Research · January 2016

DOI: 10.4028/www.scientific.net/JNanoR.38.47



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*Journal of Nano Research* *Online: 2016-01-06*
*ISSN: 1661-9897, Vol. 38, pp 47-51*
*doi:10.4028/www.scientific.net/JNanoR.38.47*


# Use of pseudoboehmite nanoparticles for drug delivery system of glucantime®

A.H. Munhoz Junior[1,a], J.S. Martins[1,b], R.R. Ribeiro[1,c], L.F. Miranda[1,d], R.C. Andrades[1,e], K.C. Bertachini[1,f] L.G.A. Silva[2,g]

[1]Depto. Engenharia de Materiais, Universidade Presbiteriana Mackenzie – R. da Consolação, 930 – ZIP CODE 01302-907 - São Paulo – SP – Brazil - [2]Instituto de Pesquisas Energéticas Nucleares – São Paulo – SP - Brazil

[a]ahmunhoz@yahoo.com, [b]engmateriais@mackenzie.br, [c]roberto.ribeiro@mackenzie.br, [d]leila.miranda@mackenzie.br, [e]raphaelconsandrades@yahoo.com.br, [f]kelly.ambientaljk@hotmail.com, [g]lgsilva@ipen.br

**Keywords**: pseudoboehmite, sol-gel, drug delivery system.

**Abstract**: Recently, the incidence of American Cutaneous Leishmaniasis (ACL) has been grown in Latin America, especially in Brazil, where from 1980 to 2005, 605,062 cases were recorded. The drug glucantime®, whose active principle is the meglumine antimoniate (or meglumine antimonate) is used in the treatment of leishmaniasis. Its toxicity is due mainly to the presence of antimony in its structure. Therefore, it is crucial to determine the safe dose levels of this drug in the treatment. Drug delivery systems have been currently the focus of many studies due to its effectiveness in treating diseases proved to be superior compared to conventional methods. Drug delivery systems can avoid overdosing by decreasing the amount of drug intake, which results in a better therapeutic effect in addition to reducing the risks of plasma concentration reaching toxic levels. Synthetic nanomaterials have been receiving great attention due to their potential applications in pharmaceutical technology as well as the possibility of controlling their particle size and composition, which allows a better performance in drug release. Pseudoboehmite is a synthetic aluminum compound precursor of alumina [1] and a polymorph of boehmite, with active groups in its structure [2], making it an excellent adsorbent material. In this work, pseudoboehmite was prepared by using the sol-gel process for being used as an excipient. The incorporation of pseudoboehmite in glucantime® was performed in the processing of tablets. Both pseudoboehmite and the tablets were characterized via X-ray diffraction (XRD), differential thermal analysis (DTA), thermogravimetric analysis (TG), and scanning electron microscopy (SEM) using secondary electron detector and EDS detector. The release profile was obtained by UV/Vis spectroscopy for *in vitro* simulation. No reaction between the drug and the excipient was observed.

## Introduction

Pseudoboehmite is an aluminum compound that has been studied for the controlled release of drugs [1, 2]. This material can be obtained by the sol-gel process, which allows the obtaining of highly pure inorganic oxides with excellent properties, since all steps of synthesis from molecular precursors to the final product can be controlled. This process permits a good control of the stoichiometry, porosity, crystalline structure and particle size of the desired products, which interfere with their morphology and surface area [3]. E.M. Moroz *et al.* studied the structure of pseudoboehmite and have synthesized this compound using three different methods. It was observed that the pseudoboehmites with large surface area ($450 m^2/g$) were prepared from aluminum nitrate and ammonium hydroxide [4]. This procedure was adopted in this study for obtaining pseudoboehmite.

Leishmaniasis is a tropical disease neglected by governmental authorities that affects up to 10% of the world's population. Leishmaniasis is an anthropozoonosis whose worldwide spreading is related to the capacity of its insect vector, the sand-fly to adapt to different areas of the planet. Currently, leishmaniasis is endemic in 98 countries and territories over four continents: Africa, Asia, Europe and America (North to South), Oceania being free of this disease. 400 million people

live in areas at risk of contracting leishmaniasis [5]. Human visceral leishmaniasis is potentially fatal. More than 90% of visceral leishmaniasis cases occur in poorly developed or developing countries such as India, Bangladesh, Nepal, Sudan and Brazil.

The drugs first chosen for the treatment of leishmaniasis are the highly toxic pentavalent antimonials. In French-speaking countries, Spain and Brazil, the N-methylglucamine antimoniate, which is also a pentavalent antimony (glucantime®) is used. The structure of glucantime® was little known for many years, but it has been recently observed that antimonate molecules of N-methyl-D-glucamine are coordinated with one antimony atom. The World Health Organization (WHO) recommends 20 mg Sb/kg of body weight/day intramuscular or intravenous dose for at least 20 days and up to two weeks after the parasitological cure, with a maximum daily dose 850 mg of antimony as treatment for visceral leishmaniasis. For cutaneous leishmaniasis, the recommendation is a 10-20 mg Sb/kg of body weight/day dose until the lesions heal. For mucocutaneous leishmaniasis, it is recommended the administration of 20 mg Sb/kg of body weight/day for 30 days [6,7,8]. The use of a natural product, three phenylpropanoid dimers (1-3), has been recently reported as an active substance for the treatment of leishmaniasis [9].

**Experimental**

The pseudoboehmite was prepared by the sol-gel process according to the methodology described by A.H. Munhoz Junior *et al*. [3].

**Characterization of the samples:**

The pseudoboehmite samples were characterized using several techniques. Thermal analyses: the thermogravimetric analysis (TG) and differential thermal analysis (DTA) were performed in a Netzsch-JupiterSTA449F3 equipment with heating from room temperature to 1300°C at 20°C $min^{-1}$ and 50 $cm^3$/min $N_2$ flow.

X-ray powder diffraction: the samples were dried at 70° C and analyzed by X-ray diffraction. The samples were analyzed by a Rigaku MultiFlex diffractometer with a fixed monochromatic radiation. The experimental conditions were: 40kV, 20mA, $20° < 2\theta < 90°$, $\Delta 2\theta = 0.02°$, $\lambda$CuK$\alpha$, divergence slit = 0.5°, reception slit = 0.3 mm and step time = 2s.

Scanning electron microscopy: the SEM images were taken with Jeol equipment JSM 6510, using secondary electron detector and EDS detector. The powders were placed upon SEM stubs covered with double-face tape. After that, the powders were covered with gold in an Edwards Sputter Coater model S150B. The images were registered under several magnifications.

UV-vis spectrometry determination of adsorption of the drug in pseudoboehmite – "*in vitro* analysis": the pseudoboehmite used in the production of tablets contained 4 (wt%) of meglumine antimoniate. The UV-vis analysis showed that the molecules underwent molecular electronic transitions. In ultraviolet spectroscopy, the drug molecule must contain chromophore groups so electronic transitions can occur. Otherwise, it is necessary to use other techniques, such as complexing association to form a chromophore group or using other analytical methods, e.g., capillary electrophoresis, chromatography, etc. In order to determine the optimum wavelength for meglumine antimonate analysis, the tests were performed with white calibration (0.1M HCl solution) in a spectrophotometer Femto 800XI and subsequently scanned in the wavelength range between 190 and 250 nm. A 2500 μg/ml solution of meglumine antimoniate was employed, setting the drug wavelength value as the one with the highest peak on the chart.

Release profile of meglumine antimonate: the tests were conducted in order to know the rate at which the active principle dissolves in a liquid medium (usually aqueous) according to the "United States Pharmacopeia" USP method [10]. The standard dissolution test was performed in a constant temperature bath with rotation at 100 rpm for 30 minutes. The dissolutor "New Model 299" calibrated at 50 rpm paddle type device was the equipment used for the experiment. The dissolution media temperature was set at 37 °C (± 1 °C) to evaluate the release profile of meglumine antimonate in 0.1M HCl solution. Three tanks were used and 10 mL aliquots were removed from each tank solution after six different times: 15, 30, 45, 60, 90 and 120 minutes.

**Results and discussion**

The differential thermal analysis and the thermogravimetric analysis (Figure 1), show the characteristic behavior of pseudoboehmite.

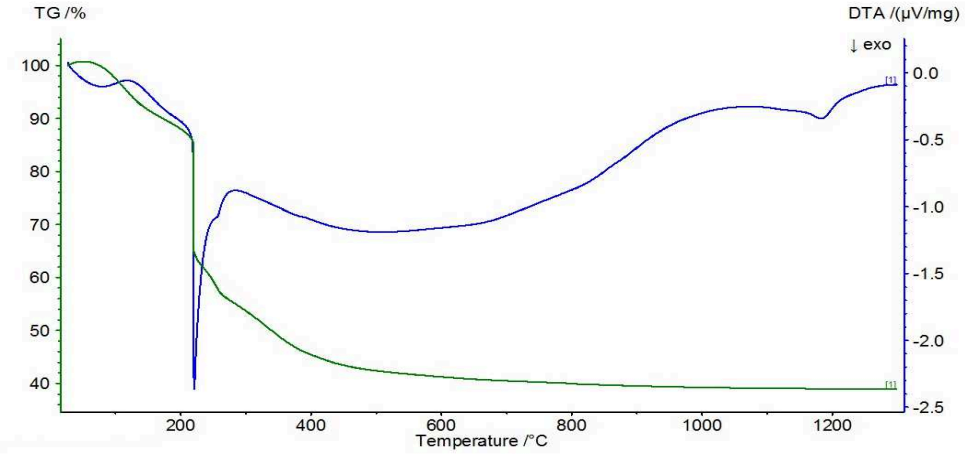


Figure 1. DTA and TG analyses of pseudoboehmite.

The DTA of the pseudoboehmite showed at approximately 80-90 ºC an endothermic peak due to water loss. At around 220-450°C the mass loss associated with the phase transformation of pseudoboehmite $(AlOOH)_n$ to $\gamma$-$Al_2O_3$ was observed. The very fast transformation of pseudoboehmite to $\gamma$-$Al_2O_3$ is an indication of the high specific surface area of this material. Powders with a large surface area exhibit faster heat transfer, which positively influences the rate of the transformation of pseudoboehmite to $\gamma$-$Al_2O_3$. About 1200$^o$ C the last phase transformation is observed in DTA analysis: an exothermic peak associated with the formation of α-alumina.

The results of X-ray diffraction of a pseudoboehmite sample are shown in Figure 2. It was observed that this sample displayed an XRD pattern similar to the one described in the literature [3].

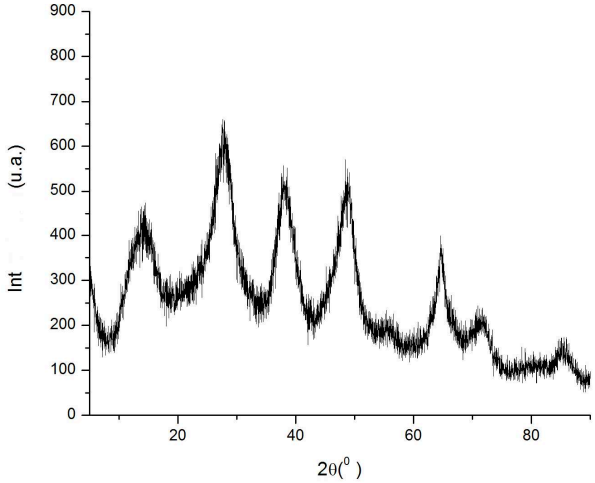


Figure 2. X-ray diffraction pattern of pseudoboehmite.

The scanning electron micrograph of pseudoboehmite (Figure 3), obtained by using secondary electron detector and a magnification of 6000 shows that the sample is a porous material. The EDS detector indicated that Sb is homogeneously distributed in the tablets. Therefore, it can be assumed that meglumine antimoniate is uniformly distributed throughout the sample.

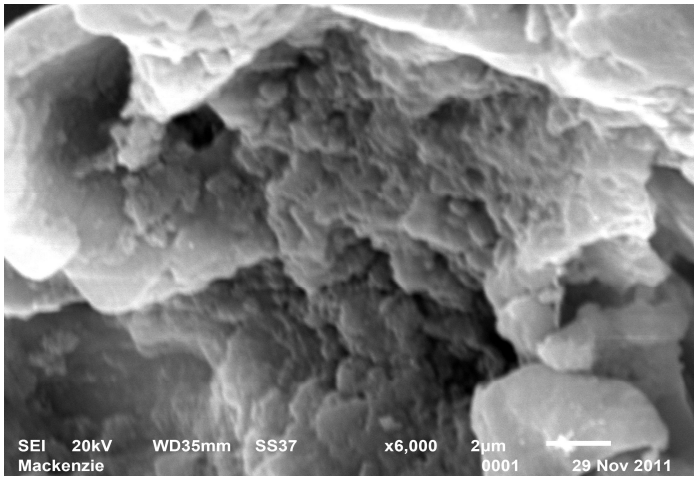


Figure 3. Scanning electron micrography of pseudoboehmite.

UV-vis spectrometry determination of the drug: by using UV-spectrophotometry analysis in a scanning range of 190-250 nm, it is observed that the 210nm value was the peak of highest absorbance. Figure 4 shows the results of the analysis.

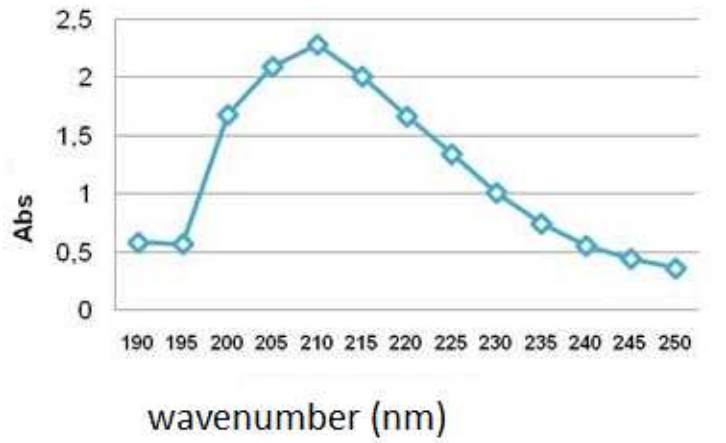


Figure 4. UV-vis spectrometry determination of drug absorbance.

The results of meglumine antimoniate release profile is depicted in Figure 5. It is observed that as time increases the concentration of n-methyl meglumine antimoniate tends to the value 275 µg/mL.

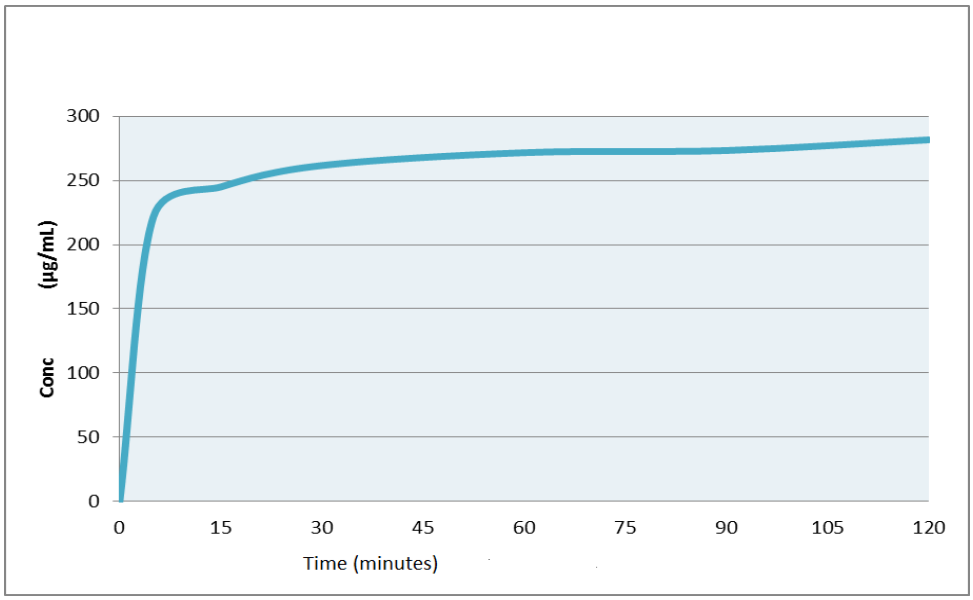


Figure 5. Drug release profile of meglumine antimonate associated with pseudoboehmite at different times.

## Conclusion

The synthesis route adopted in this work proved to be highly effective to produce pseudoboehmite. The X-ray diffraction data and other analyses together with the literature review confirm that the obtained material has the structure of pseudoboehmite.

The release of meglumine antimonate was successful, suggesting that additional studies to evaluate the efficacy of the tablet in the treatment of animals/humans infected by leishmaniasis would be fruitful.

It was observed in the electron scanning microscopy that antimony was homogeneously distributed in the analyzed tablets.

Thus the results presented in this study indicate the potential use of pseudoboehmite as a pharmaceutical excipient for drug release. Pseudoboehmite proved to be highly pure, easy to obtain, and adequate for the production of tablets.

## Acknowledgment

The authors are grateful for the supoport given by MackPesquisa, Universidade Presbiteriana Mackenzie and São Paulo Research Foundation (FAPESP, grant 2010/19157-9).

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**Journal of Nano Research Vol. 38**
10.4028/www.scientific.net/JNanoR.38

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