

**Artigo Original**

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## **Biocompatible glassceramic applied in drug release system**

*Vitrocerâmico biocompatível aplicado em sistemas de liberação de medicamentos*

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**Abstract**

The anorthite is an intelligent material which degrades only in acid medium. This behavior along with its biocompatibility is interesting for clinical applications where degradation of a biomaterial is desired, such as in drug delivery systems. The aim of this work is the assessment of the application of anorthite capsules as drug delivery system using L-Dopa plus benserazide as a test drug. Spherical capsules were manufactured, weighted, filled with the drug, sealed and immersed in buffer solution with pH 3.5 for 120 hours, which was kept in permanent movement to simulate corporeal environment. At the end of the test the capsules were emptied, washed, dried and weighted again. The mean weight loss was  $0.004 \pm 0.001$  g, which demonstrates the degradation of the glassceramic in acid environment. An UV/VIS spectrophotometer was used to measure the quantity of drug released in the solution from samples collected at 24, 72 and 120 hours after the test started. The drug was found in the solution after 24 hours, increasing its concentration until 72 hours when the drug release rate seems to have decreased. From the samples analyzed, it was possible to conclude that a continued release of the drug occurred through the capsule walls due to its porosity. The results showed the possibility of use of the anorthite in drug release system keeping a continued liberation of the drug in the organism.

**Keywords:** Anorthite, Drug delivery system, Intelligent glassceramic, Degradable biomaterial, Parkinson's disease.

**Resumo**

A anortita é um material inteligente que se degrada apenas em meio ácido. Este comportamento, juntamente com a sua biocompatibilidade, é interessante para aplicações clínicas onde a degradação do biomaterial é desejável, como em sistemas de liberação de medicamentos. O objetivo deste trabalho é avaliar a aplicabilidade das cápsulas de anortita como sistemas de liberação de medicamentos, usando L-Dopa mais benserazida como medicamento de teste. Cápsulas esféricas foram confeccionadas, pesadas, preenchidas com o medicamento, seladas e imersas em solução tampão com pH = 3,5 durante 120 horas, mantida em movimento constante para simular o ambiente corpóreo. No final do ensaio as cápsulas foram esvaziadas, lavadas, secas e pesadas novamente. A perda de massa média foi de  $0,004 \pm 0,001$  g, demonstrando a degradação do vitrocerâmico em meio ácido. Um espectrofotômetro UV/VIS foi usado para medir a quantidade de medicamento liberada na solução, através de amostras coletadas em períodos de 24, 72 e 120 horas após o início do ensaio. O medicamento foi detectado na solução após 24 horas, com concentração crescente até 72 horas, quando a taxa de liberação do medicamento pareceu diminuir. Através das amostras analisadas, foi possível concluir que ocorreu uma liberação contínua do medicamento através das paredes das cápsulas devido à sua porosidade. Os resultados mostraram a possibilidade de utilização da anortita em sistemas de liberação de medicamentos mantendo a liberação contínua da droga no organismo.

**Palavras-chave:** Anortita, Sistema de liberação de medicamentos, Vitrocerâmico inteligente, Biomaterial degradável, Doença de Parkinson.

## Introduction

Glassceramics are polycrystalline materials produced by controlled crystallization of glasses which guarantee the formation of a desired microstructure with superior mechanical properties than those achieved by ceramic and glass materials (Ferreira *et al.*, 2002).

The patented glassceramic anorthite as biomaterial (MU 8702682-1) considered in this work, is obtained by fusion of raw materials which contain silicon oxides, aluminum and calcium to form glass with characteristics of an intelligent material. Intelligent materials can be defined as those that respond, in a desired way, to the environment changes in order to perform an appropriate function (Cavalheiro, 2005).

The anorthite is an intelligent material, since it is capable of dissolving itself in acid environment in different rates depending on the pH. This characteristic, as well as its biocompatibility (Cavalheiro, 2005) makes the anorthite an appropriate material for biomedical applications.

Some chronic conditions like Parkinson's disease need a continuous treatment during a long period and require the drug therapeutic index to be kept constant in the organism. Therefore, various researchers have been dedicated a great effort to develop a carrier system for drugs with the purpose of a continued release of them, maintaining a constant therapeutic index (Kong *et al.*, 2000).

Presently, L-Dopa is the most effective oral drug for treatment of Parkinson's disease. However, its effect lasts only for few hours, becoming necessary the repetition of the intake along the day. As the disease progresses, the effect of the drug lasts for shorter periods and complications like motor fluctuations appear. It is believed that such motor fluctuations are consequence of the periodic intakes which cause intermittent release of dopamine with consequent pulsatile stimulation of postsynaptic neurons. Therefore, researchers hypothesize that continuous release of L-Dopa can minimize the risk of motor dysfunctions. In clinical reality, L-dopa is usually combined with benserazide which allow reduction of the doses in about ten times, therefore, reducing secondary effects (Thanvi and Lo, 2004).

Controlled drug release systems are generally useful to deliver the drug in the organism continuously and with a well established kinetics, maintaining the therapeutic index for long periods, improving the efficiency of the drug (Kong *et al.*, 2000). Consequently, it is possible to achieve similar effect as those of conventional methods as injection and oral administra-

tion (Ogawa and Plepis, 2002). Besides, it is possible to apply the therapeutic agent directly at the site of action, producing high located concentrations and preventing systemic effects.

All implanted biomaterial triggers a sequence of physiological events in the organism (Tang and Eaton, 1995), defined as "reactions to the strange body". During those reactions the pH of the injured tissue varies from 3.5 in healing process, to 7.4 when the healing is completed (Ratner *et al.*, 1996).

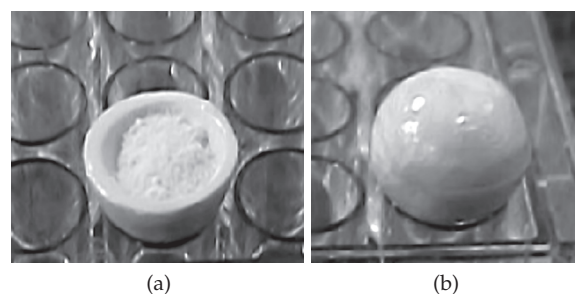
Since the glassceramic anorthite is biocompatible and degrades in acid environment (Cavalheiro, 2005), it can, potentially, be applied in a drug delivery system. So, the aim of this work is the assessment of the application of spherical anorthite capsules as drug delivery system using L-Dopa plus benserazide as the test drug.

## Materials and Methods

Hollow spherical glassceramic capsules with diameter of 10 mm, were designed and manufactured at the Grade Institute of Basic Sciences (IGCB, Schroeder, Brazil) using the conventional glassceramic manufacturing process, that is, components mixing in predefined ratios, mixture heating until fusion temperature in order to obtain a glassy material, molding, controlled crystallization to form the glassceramic material and cooling. The molds were made in two hollow half spheres of stainless steel.

In order to proceed to the *in vitro* test, three capsules were weighted, filled with 30 mg of Prolopa® HBS (Roche, Brazil), as illustrated in Figure 1a, sealed with surgical silicon, as shown in Figure 1b, and immersed in buffer solution of pH 3.5, in separate recipients (one capsule in each flask) suspended by a thread, as indicated in Figure 2.

During the test, the solutions were maintained at 20 °C in permanent movement by means of a magnet-



**Figure 1.** a) Half capsule filled with Prolopa® HBS (Roche, Brazil); and b) The two half sealed with surgical silicon, forming the capsule for the *in vitro* test.



**Figure 2.** Experimental setup of the *in vitro* test showing the capsules suspended in solution of pH 3.5 in the UNICAMP's Biochemistry Department.

ic stirrer (100 rpm) aiming to simulate the corporeal environment (Silva Jr. and Orefice, 2001).

The investigation of the drug released through the pores was carried out by measuring the drug concentration in the solution during 120 hours of immersion. For this purpose, two samples of 1 ml were removed from the flasks 24 hours, 72 hours and 120 hours after the beginning of the test. The volume of the removed sample was replaced by the same buffer solution, so the total amount of solution in the flasks remained the same throughout the test. This method is a standard procedure at the UNICAMP's Biochemistry Department (University of Campinas, Brazil) where this part of the experiment was carried out. The drug release was analyzed with a UV/VIS spectrophotometer. In this study, the spectrophotometer was tuned to the wavelength of 270 nm, which is the main absorption spectrum of L-Dopa-benserazide.

At the end of the *in vitro* test, the capsules were emptied, washed, dried and weighted.

## Results

The mass of each capsule at the beginning and at the end of the experiment, as well as the difference between them are shown in Table 1. At the end of the test protocol, the mean weight loss was  $0.004 \pm 0.001$  g. This data demonstrates the dissolution of the glassceramic in acid environment.

**Table 1.** Capsules mass before and after the *in vitro* test.

Capsules	Mass before the test ( $\pm 0.001$ g)	Mass after the test ( $\pm 0.001$ g)	Lost mass ( $\pm 0.001$ g)
1	1.241	1.237	0.004
2	1.309	1.304	0.005
3	1.269	1.267	0.002

The absorbance magnitude of 30 mg of Prolopa® HBS diluted in 100 ml of buffer solution with pH 3.5 was 1.312 units ( $\lambda = 270$  nm), which allowed to estimate the mass of the drug in the 1 ml sample of the solution extracted during the test and, consequently, due to the continuous mixture, the mass of the drug in 100 mL of solution in each period analyzed. The results are shown in Table 2, where it is possible to observe that the drug was already dispersed in the solution after 24 hours of capsules immersion with a more intense liberation during the first 72 hours. After that, drug release rate tends to decrease.

## Discussion

In order to simulate the corporeal environment, with fluids and electrolytes in movement, corresponding to the concept of bioactivity (Silva-Jr. and Orefice, 2001), it was used a buffer solution in permanent movement in which the capsules of anorthite were immersed during 120 hours. The fluid movement created drug's concentration gradient around the capsules allowing its diffusion to the solution.

The pH 3.5 buffer solution was chosen in order to mimic the physiological conditions of healing processes and the reaction to a strange body which will occur as a response of the organism to an implanted capsule (Guyton and Hall, 2002; Ratner *et al.*, 1996; Silva-Jr. and Orefice, 2001). The glassceramic capsules behaved as a reservoir system where drug was stored, working as a release regulator. It differs from a polymeric system where the drug is dispersed in its matrix being released only due to its degradation (Dash and Cudworth, 1998; Kimura and Ogura, 2001).

It is important to remind that the behavior of the capsule in the acid solution and the liberation of its

**Table 2.** Absorbencies and corresponding delivered masses ( $\pm 0.001$  g) measured with the UV/VIS spectrophotometer. Buffer solution pH 3.5,  $\lambda = 270$  nm ( $\text{mg} \cdot 100 \text{ mL}^{-1}$ ).

Capsules	24 hours		72 hours		120 hours		Total mass (mg)
	Absorbance	Mass (mg)	Absorbance	Mass (mg)	Absorbance	Mass (mg)	
1	0.0130	0.297	0.0261	0.597	0.0263	0.601	1.495
2	0.0132	0.302	0.0788	1.802	0.0917	2.097	4.201
3	0.0130	0.297	0.0524	1.198	0.0525	1.200	2.695

content were the focus of this research. The results depicted in Table 2 show clearly that drug diffusion occurred. Therefore, one can suppose that the capsules pores are interconnected, an important requirement for the suggested application. Although the amount and size of the pores influence the kinetic of the drug release, these parameters were not investigated in the present work, but are being analyzed and will be presented in forthcoming publications. It is well known that the size and quantity of pores can be controlled by thermal treatment during the crystallization of the glassceramic, and this feature is being investigated as well.

Regarding the weight loss of the capsules, the results of this work agreed with previous results found in the literature (Cavalheiro, 2005), conducted in agreement with the standard ISO 10993-14, which showed that the anorthite dissolves in acid environment and, therefore, the drug release took place along with capsules degradation, which implies in the wall thickness reduction and increasing of the pores size. The modest weight loss was due to the short immersion period and the slow degradation, which is a feature of the material. It is a very relevant behavior since the deliverance of the drug and the complete degradation of the capsule are desirable for implantable drug release systems.

In the present work, the experiment was carried out in the temperature of 20 °C (controlled environment temperature) due to the operations characteristics of the equipment available for the test. However, considering that the main purpose was to evaluate the diffusion of the drug through the pores of the material, while its dissolution occurs, the temperature of 20 °C was satisfactory and the results obtained were encouraging. Certainly other experiments shall be carried out in order to better describe the anorthite behavior under more realistic conditions, such as body temperature, body fluid simulation systems and dynamic changes of pH.

The release system in this work is a complex one since it involves simultaneously the dissolution of the drug inside the capsule, the diffusion of the drug through the capsule wall and the dissolution (degradation) of the capsule itself. Therefore, to establish a theoretical framework in order to model this process would be a complex task. The Ritger-Peppas empirical model could be, with some assumptions, adjusted to this system in order to analyze the fraction of drug released as function of time. The constant of proportionality, in this model, is defined according to the

matrix used to disperse the drug. However, since the drug is not impregnated in anorthite, the Ritger-Peppas model is not completely appropriate. Another approach could be the Fick's second law, which considers that the matrix or capsule does not dissolve itself and, therefore, the wall thickness of the reservoir remains constant. The influence of the temperature on the diffusion rate is implicit in the kinetic and diffusion constant in the first model and in the diffusion coefficient in the second one.

The glassceramic capsules behaved as a reservoir system and its cavity worked as a regulator of the drug release rate. The results showed the possibility of application of the glassceramic anorthite as vehicle in a controlled drug delivery system which can be confirmed by an *in vivo* test. The production of the capsules was a simple process and can be used to manufacture capsules of various geometries and sizes in order to achieve better anatomical adaptation to the implantation site, as well as a better control of drug delivery dynamics.

Although only three samples were analyzed, the good results related to the drug release through the pores of the material, its simultaneous degradation and the currently importance of the subject encouraged the publication of the present work. Besides, the *in vivo* test carried out in previous work (Cavalheiro, 2005) showed that the products of the anorthite degradation do not cause local or systemic effects. In order to test the release kinetics in other immersion conditions and material porosity it was necessary to confirm the real possibility of using anorthite in drug release systems, which was provided by this study.

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