The Effect of Water on Particle Size, Porosity and the Rate of Drug Release from Implanted Titania Reservoirs

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ABSTRACT

A new strategy in the treatment of several neurodegenerative illnesses is the implantation of devices to be used in controlled drug release. Sol-gel titania implants filled with valproic acid, have being used for this purpose, to treat epilepsy induced in rats. The kinetics of drug release depends on: (a) porosity and (b) chemical interactions between valproic acid and the surface hydroxyl groups of titania. The concentration of water used in the hydrolysis reaction is an important variable in the degree of porosity, hydroxylation and structural defects of the nanostructured titanium oxide reservoir. The titanium n-butoxide/water ratio was systematically varied during the sol-sol-gel synthesis, while maintaining the amount of valproic acid constant. Characterization studies were performed using DTA-TGA, FTIR, Raman, TEM, SEM, BET and *in vitro* release kinetic measurements. The particle size and porosity were found to depend on the amount of water used in the sol-gel reaction.

Keywords: sol-gel, titania, valproic acid, controlled drug release, epilepsy

1 INTRODUCTION

Controlled drug delivery systems have been intensely investigated for their therapeutic effectiveness, by directing drugs towards specific tissues[1]. Within the major benefits of this procedure are: an increase in the chemical stability of the drug and the elimination of side effects in the patient. Inorganic porous materials such as functionalized silica and titania xerogels are emerging as a new category of drug host systems[2]. Recently the implantation in the brain of biocompatible sol-gel ceramic devices, filled with valproic acid (VPA), has been proposed as a therapy for epileptic disorders, in contrast to standard systemic therapies that are required to cross the blood-brain barrier (BBB).

The application of these sol-gel titania inorganic matrixes as a drug delivery system in the brain is determined by: its biocompatibility with the surrounding brain tissue and its capability to release a constant amount of the drug for long periods[2,3]. It can be shown that the diffusion process depends on the morphology of the system as well as on matrix-drug interactions[3] . In this paper we study the effect of the water content in the gelation reaction on the chemical and morphological properties of the drug reservoir.

2 EXPERIMENTAL

Three types of TiO_2-VPA samples have been prepared by using alkoxide:water molar ratios of 1:4, 1:8 and 1:16 in the sol-gel process, with a constant amount of VPA (30mg of VPA/1g TiO_2). VPA was dissolved in a mixture of t-butanol and water with a constant alkoxide/t-butanol ratio of 1/8. Titanium n-butoxide was added drop-wise, maintaining the mixture under constant stirring at 30 °C.The solution was stirred for 24 hours. Finally, alcohol was eliminated and the Titania-VPA materials were dried at 30 °C for three weeks.

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The Raman spectra of the powders were recorded at room temperature by a Jobin-Yvonne Labram micro-Raman apparatus, using the 632.8 nm line of a He-Ne laser for excitation. The laser power on the sample was kept below 1 mW by the insertion of optical filters, in order to avoid undesired heating effects. The spectra collection times and the number of scans were optimized in order to have an acceptable signal/noise ratio. The FTIR studies were performed using a Nicolet Nexus 770 infrared spectrometer with a DTGS detector with a resolution and wavenumber precision of 0.09 cm^{-1}.
TEM images were recorded on a Zeiss EM910 electron microscope operated at 100 kV, with a side entry goniometer and a 0.4 nm point to point resolution, attached to a CCD Mega Vision III image processor. For the SEM studies a JEOL 5600LV scanning electron microscope equipped with an EDS for chemical analysis was used to perform both the morphological and chemical composition of the samples.

The specific surface areas were obtained using a Quantasorb sorptometer and calculated from the nitrogen isotherms at 77K using the BET method. The mean pore diameter was determined using the BJH analysis.

VPA release tests from TiO_2-VPA samples were performed at 25 °C in an aqueous medium. A tablet of ~50 mg was immersed in 7 ml of deuterated water. The quantity of VPA released was measured by considering the resonances at 4349 cm^{-1} in the near-FTIR spectrum, which correspond to CH2 vibrations. Approximately 0.5 ml of the solution were removed for spectroscopic analysis and then returned to the system. The absorbance obtained was referenced to a calibration curve of concentration *vs*. % absorbance.

3 RESULTS AND DISCUSSION

Figure 1 show the IR spectra in the range between 3000 to 3800 cm^{-1} where stretching vibrations of OH are observed. In all cases the spectra shows two bands around 3640 cm^{-1} and 3270 cm^{-1}.However, in the sample 1:16 the low energy band is displaced to 3258 cm^{-1}. For pure valproic acid, the stretching vibrations appear at 3181 and 3431 cm^{-1} which correspond to the acid group = COOH and water OH's[4]. We assume that this strong displacement is due to hydrogen bond interactions between the TiO_2 matrix and the valproic acid. Qualitatively we observe that, when the spectra are integrated, the highest concentration of OH's corresponding to the 1:4 sample decreasing with an increasing water/alkoxide ratio. This is confirmed with the TGA study on these samples shown in Table 1

Sample	ΔT(°C)	% Loss weight
Valproic 1:4	209-300	17.36
Valproic 1:8	203-300	11.6
Valproic 1:16	186-300	9.21

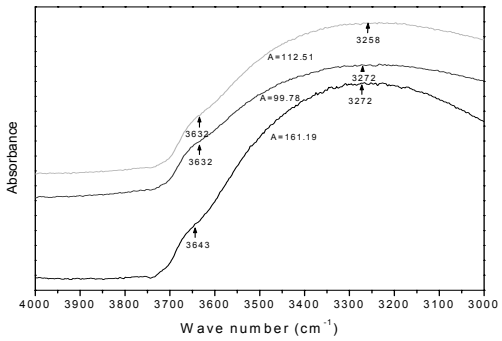

Figure 1. The infrared spectra in the 3000-4000cm^{-1} showing the OH stretching vibrations.

The origin of this paradoxical behavior is due to the fact that the lower the pH the higher the hydroxylation[5] .

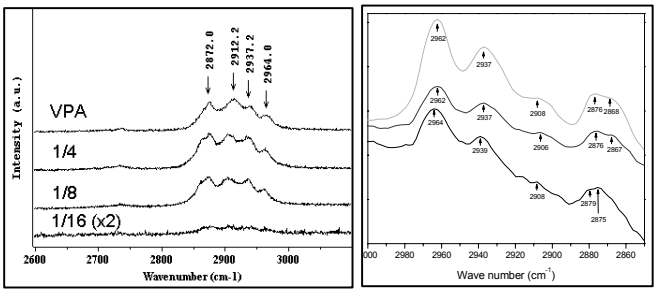

Figure 2. The Raman fig (2a) and infrared (2b) spectra corresponding to the CH stretching region.

The high wave-number region of both Raman (figure 2a) and FTIR(figure 2b) of pure VPA, TiO2-VPA 1:4, TiO2-VPA 1:8 and TiO2-VPA 1:16. All the spectra show very similar structures that can be assigned to the stretching C-H vibrations in CH, CH_2 and CH_3 groups of the VPA confirming the presence of VPA in the reservoir.

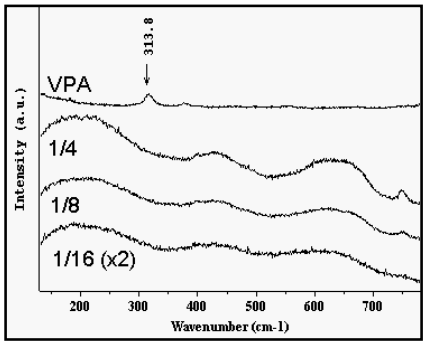

Figure 3. The 200-700 cm^{-1} infrared region showing the amorphous phase of titania is shown.

In the low wave-number region (figure 3, 100-750 cm^{-1}), the three broad bands typical of amorphous titania are evident, at 201, 433 and 629 cm^{-1}. The amorphous nature of TiO_2 based samples is confirmed by XRD analysis as shown in Figure 4.

The VPA peak at 314 cm^{-1}, due to a low frequency vibration of the crystalline phase of the pure VPA powders, is absent in the three TiO_2-VPA samples, suggesting that VPA is well dispersed in the host, without substantial aggregation. The XRD analysis (fig 4) also confirms this result, as the crystalline features of VPA are not found in the TiO_2-VPA samples. This is a remarkable phenomenon since in most of the TiO_2 synthesized by sol-gel under acid conditions[6], the three forms of crystalline TiO_2 (brookite, anatase and rutile) are present at room temperature. Somehow the valproic acid is interfering with the crystallization process at the molecular level. For example hydrogen bridges such as ≡Ti-O^-●●●HO=C-R could hinder the formation of crystallites. Further study of this phenomenon should shed more light on the interactions between the TiO_2 matrix and VPA .

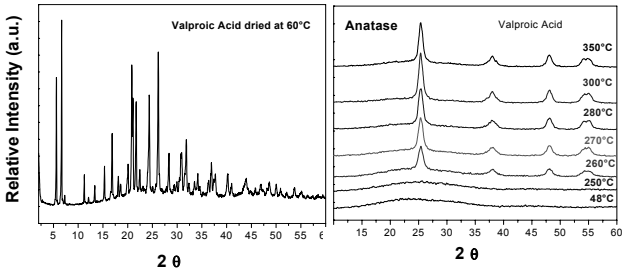

Figure 4. XRD spectra of (a) pure valproic acid and (b) valproic acid occluded in the titania at various temperatures. Note the appearance of the anatase phase at260^{0}C

Table 2 summarize the results of the BET and BJH analysis on the TiO_2-VPA samples. The higher the content of water in the initial sol, the lower is the pore size and specific surface area. This can be explained because it is known that as we increase the acidity of the initial sol, we obtain larger pore sizes and areas in the final product[7]. However, what is quite surprising is the large areas found which are six times larger than conventional titanias.

Sample	Area (m2/g)	Volume (cm3/g)	Mean pore diameter (Å)
TiO2-VPA 1-4	456.7039	0.557	48
TiO2-VPA 1-8	398.1301	0.291	29
TiO2-VPA 1-16	378.0474	0.194	20

Figures 5 and 6 illustrate the kind of morphologies, particle and pore size obtained in the three samples. As Figure 5 shows the agglomerate particle size has a minimum at 1:8 alkoxide/water content. As the water content increases furthermore, the agglomerates increase in size as shown for the 1:16 sample.

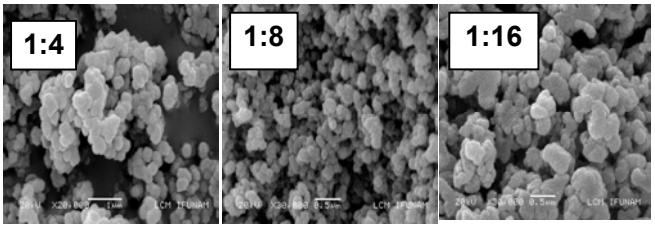

Figure 5. Each particle in this figure is in itself an agglomeration of primary particles. They differ by the amount of water used in the sol-gel reaction.

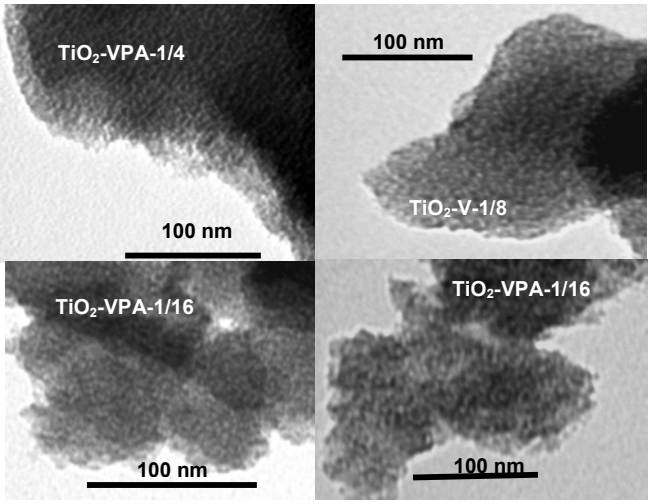

Figure 6. TEM micrographs of the different samples. As one can see each particle of Figure 5 is in itself an agglomeration of primary particles.

3.4 Release kinetics measurement

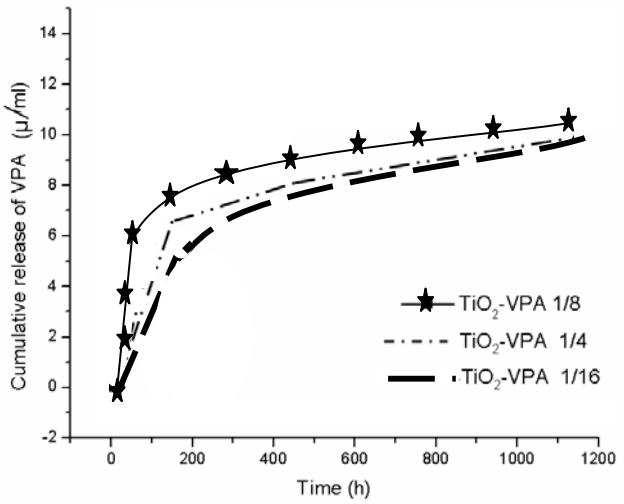

Figure 7: Cumulative release profiles of VPA from TiO2-VPA samples.

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The VPA release test for the TiO_2-VPA samples was performed at 25°C in an aqueous medium. A pellet of ~ 50 mg was immersed in 7 ml of deuterated water. The quantity of VPA released was measured in the NEAR-FTIR spectrum at 4349 cm^{-1} which corresponds to CH_2 vibrations. Approximately 0.5 ml of the solution was removed for spectroscopic analysis. Following analysis the solution was returned to the system. The absorption obtained was referenced to a calibrated curve.

Figure 7 shows the cumulative release profiles of VPA in deuterated water. It can be observed that the release has a two-step behavior: an initial fast release and a relatively slow subsequent release. The initial burst lasts for 312 hours (13 days). The subsequent release was observed for up to 1068 hours (44 days). An interesting feature is that in the first step, the 1:8 alkoxide/water content samples has a larger rate of delivery than the other two, indicating that the kinetics of this stage is governed by a competition between pore size effects and the degree of hydroxylation. For example, the 1:4 sample, has the largest pore size, yet it also had the largest degree of hydroxylation which implies that, in this case, the OH interactions are dominating the rate of delivery. In contrast the 1:16 sample has both the smallest pore size and the lower degree of hydroxylation signifying that for this sample the pore size effect is the main factor governing the rate of delivery. In the second stage the rate of delivery has almost the same slope and probably this stage is regulated by absorption-desorption equilibrium.

Finally, it is interesting to note that the drug delivery extends over a large period of time.

4 CONCLUSIONS

In this paper we report the characterization of TiO_2-VPA powders obtained with different initial molar ratios between alkoxide and water. Raman spectroscopy, FTIR, XRD and calorimetric studies indicate that the TiO_2-VPA samples are in the amorphous phase in a temperature interval between room temperature and 250°C. Moreover, BET and BJH analysis together with FTIR and TGA show that as we increase the initial water content the pore size, the specific surface area and the degree of hydroxylation decreases. Furthermore, it was found that the synthesis of TiO_2 with VPA using sol-gel methods has unusually large specific surface areas, as large as six times that of those for conventional titanias. Finally, the release kinetics measurements evidenced a two-step behavior: an initial fast release and a relatively slow subsequent release . The first lasted for approximately 13 days and we provided evidence that it is probably governed by a competition between OH-VPA interactions and the steric constraints that pore size imposes. The second stage, with a slow but constant delivery rate, can last for months, although here we only report 44 days.

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