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Synthesis and characterization of materials loaded with Ibuprofen using a TiO_2 matrix obtained by sol-gel methods

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Abstract
Threehydroxylatedtitanium matrixloadedwith ibuprofen (TiO_2OH-IBU) were obtained by the sol-gel method using different molar ratio of alkoxide / water. These nanostructured materials (NM) were characterized by Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), scanning microscopy (SEM), Thermogravimetric analysis (TGA) and N_2 adsorption isotherm. As water/alkoxide ratio increases, the specific surface areas for the composites (TiO_2OH-IBU) and also for references (TiO_2OH-Ref),(without ibuprofen) decreased, being more pronounced in the latter case. By contrast, the average pore diameter increases following the same trend being more remarkable for references. Finally, the analysis showed mesopores and micropores. FTIR indicates the presence of hydroxyls and also water physically adsorbed, but hydroxyls free were not observed. Also, higher water/alkoxide ratios enable the production of materials with negligible non-hydrolyzed alkoxide as TGA and FTIR results indicate. It was observed that ibuprofen incorporated to the composites corresponds to 7%w. by TGA. Analysis of X-ray diffraction showed that for reference (TiO_2OH-Ref) withamolarratioalkoxide/water (1:24) the presence of anatase phase even at room temperature and that ibuprofen prevents crystallinity.Therelease of the drug for these systems was analyzed in vitro, showing typical controlled release profiles for all materials studied.This behavior could be evaluated for its use in implants near the affected area or in topical forms.

Keywords:composite, sol-gel, anti-inflammatory, nanomaterials, titanium

1. Introduction
The Sol–gel process was first described 150 years ago and it is still receiving great attention as one of the easiest ways to develop inorganic particles and hybrid materials with tuned properties. This procedure has specific advantages compared to other technologies such as: low process cost, low temperature of heat treatment, high uniformity of film and wide possibility to vary film properties by changing the composition of the solution, etc [1]. Sol–gel materials are characterized by durability and stability. Many of them are optically transparent. Currently, silica based sol–gel materials are the most widespread ones. Sol–gel materials based on other oxides — e.g. zirconium, aluminium oxides have not been extensively so far used [2]. Therefore, the study of morphological and physical chemistry properties of these materials is an important knowledge for future application in various fields.
Titanium dioxide TiO_2 has been studied mainly because of its possible applications, such as a gas sensor, in dielectric ceramics and as photocatalyst. Besides, the sol–gel process has been used as a successful synthetic route to obtain titania or titania–zirconia particles, the latter obtained from a neutral amine route, with hexagonal nanostructure and spherical morphology [3].
Materials based on titanium oxide can be characterized by their structural and physiochemical properties, such as porosity, chemical composition, chemical reactivity and surface properties [4-5]. The latter has been obtained through the layer-by-layer deposition and are characterized by a new methodology for the adsorption of n-

pentane [6-7]. Although the materials obtained have superior properties, the final product shows a narrow range of synthesis conditions [8].

The engineering of the porosity in nanostructured materials, such as TiO_2, SiO_2, etc, is an area of technological and scientific interest [9]. Sol–gel derived titania, an inexpensive, non-toxic and biocompatible material, has been studied as a carrier material for various drugs, such as sodium phenytoin, valproic acid, fluoxetine and temozolomide [10].

The aim of this study was to evaluate the effect of hydrolysis using different water/alkoxide ratios on the properties of the composite TiO2-Ibuprofen obtained by a sol-gel process. The motivation is to develop a controlled release device of drugs based on the usage of a chemically stable compatible drug. Specifically, TiO2 was chosen as matrix because it is a non-toxic and biocompatible material. We focused on its usage as a carrier for ibuprofen. A wide variety of compounds having carboxylic acid groups are biologically active, for example, the non-steroidal anti-inflammatory drugs, such as ibuprofen, naproxen, indomethacin, and diclofenac [11]. The presence of free acid groups in these compounds produces local irritation on interaction with mucosal tissues. At the same time, they are ionized at physiological pH, which makes the drug poorly absorbed through biological membrane. The nanostructured materials obtained in this research can avoid the stomach or intestinal mucosal membranes irritation.

2. Materials and Methods

Materials

Ethanol 96% (Vetec), titanium butoxide 98%$Ti(OC_4H_9)_4$ (Ti(OBut)) (Aldrich), ibuprofen 99% (MERCK) have been used as received.

Methods

2.1.Synthesis of titânia reservoirs

The encapsulation of ibuprofen (Fig1) within a hydroxylated matrix of titania was performed by a single step sol-gel procedure. Table 1 presents the components and its quantities used in each reaction for the reference titania (TiO_2OH-Ref) synthesis and ibuprofen-titania reservoirs (TiO_2OH-IBU). First, ibuprofen ratio was fixed (0.5 grams per 5grams totalmassofTiO_2OH obtained in each experiment) and this amount was dissolved in a mixture of distillated water and ethanol, under stirring at room temperature.

Then, titanium (IV) tetrabutoxide ($Ti(OC_4H_9)_4$ was added drop by drop for 4 hours to this mixture under stirring. After that, the medium was kept under stirring at 25°C for 24 h to complete theformation of the gel(see Table.2). Finally, the samples were dried under vacuum. In this work three different$Ti(OC_4H_9)_4$):water:ethanol molar ratios: 1:8:8 , 1:16:8 and 1:24:8 were evaluated.

Also, the synthesis of reference matrix reference without ibuprofen (TiO_2OH-Ref) was carried out in the same experimental conditions for comparison with other samples (TiO_2OH-IBU).

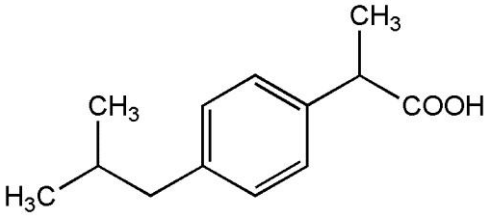

Fig 1 Chemical formula of ibuprofen

The amount of reagents used in all experiments was stoichiometrically adjusted to obtain5 gramsTiO_2OH.

2.2. Fourier transforms infrared spectroscopy (FTIR), spectra were collected with a FT-IR-THERMO NICOLET Nexus-670. The sample (~5 mg) and KBr (~ 95 mg) were ground together in an agate mortar until the sample is well dispersed. FTIR spectra were obtained in the wavenumber region between 500 and 4000 cm $^{-1}$.

2.3.Thermogravimetric analysis (TGA), were performed using a TA thermal analyzer Q50 at a heating rate of 20°C/min under nitrogen atmosphere. The TGA profiles were recorded in the temperature range 30-800°C. The weight of the sample used was about 9–11 mg in all the cases.

2.4. N_2 adsorption isotherm (BET), specific surface area was obtained from the nitrogen gas adsorption/desorption at 77.3 K, for de samples activated during 16 h at 100°C, using a Micromeritics (ASAP 2405 N). The specific surface areas and average pore diameters were determined using the Brunauer-Emmet-Teller (BET) method. Pore distributions were determined from the desorption isotherms using the Barret-Joyner-Halenda (BJH) procedure.

Table 1. Experimental conditions

Samples	Ti(OBut) (mol)	H_2O (mol)	Ethanol (mol)	Ibuprofen (mol)	Y (%)	E.E (%)
TiO_2OH-Ref (1:8:8)	0.062	0.50	0.50	-	-	-
TiO_2OH-Ref (1:16:8)	0.062	0.99	0.50	-	-	-
TiO_2OH-Ref (1:24:8)	0.062	1.48	0.50	-	-	-
TiO_2OH-IBU (1:8:8)	0.062	0.50	0.50	0.002	85.3	40.2
TiO_2OH-IBU (1:16:8)	0.062	0.99	0.50	0.002	92.5	58.3
TiO_2OH-IBU (1:24:8)	0.062	1.48	0.50	0.002	89.5	42.6

Abbreviation: Y (Yield) and E.E (Encapsulation efficiency)

*2.5.X-Ray Diffraction (XRD),*analysiswerecarried out in an X-ray diffractomer (Rigaku, model Miniflex), with a Bragg–Brentano geometry with a Cu K and radiation of wavelength of 1.5408˚A, monochromator operated at 35 Kv and 25 mA. The samples were scanned in the 2θ=2-70° range, with a step time of 2s and a step size of 0.05°.

*2.6.Scanning Electron Microscopy (SEM).*Morphology was analyzed by scanning electron microscopy (SEM JEOL-5600 LV) at 20kV Samples were coated with a layer of gold of approximately 20 nm using an EMS 550 sputter coating.

2.7.In vitro drug release, In vitro releases were performed at laboratory scale, according to the USP XXVII. The NM were suspended in 150 ml of HCl (0.1 mol dm^{-3})/Na_3PO_4 (2 mol dm^{-3}) (3:1) (pH 6.8), the dissolution medium was kept under stirring at 100 rpm . All the experiments were carried out at 37°C ± 0,2 ^{0}C. Samples (3 ml) were assessed at appropriate time intervals, and the Ibuprofen release was measured spectrophotometrically at 264 nm against a calibration curve. The calibration curve used was C= 0.1511A + 0.1134. Encapsulation efficiencies were also spectroscopically estimated. All samples were studied in duplicated.

*2.8.Encapsulation efficiency (E.E%).*The amount of Ibuprofen (IBU) loaded in the NM was directly estimated by dissolution of 5mg of (NM) in 10 ml of 0, 1M phosphate-buffered saline (PBS) at room temperature. After NM were dissolved UV absorption measurements at 264 nm were used to determine the amount of IBU. Then, the encapsulation efficiency (E.E) was calculated by using the following equation.

$$E.E\ (\%) = \frac{m_{IBUexperimental}}{m_{IBUTheoretical}}\ x100 \qquad (1)$$

$m_{IBU.\ Experimental}$: mass of IBU recovered from nanostructured materials loaded.
$m_{IBU.\ Theoretical}$:total mass of IBU calculated in each synthesis.

2.9.Yield (Y%.). The nanostructured materials (NM) yield determination (Y%) was calculated according to the following formula:

$$Y\ (\%) = \frac{m_p}{m_{IBU} + m_{Ref}}\ x100 \qquad (2)$$

$m._p$: is the total mass of nanostructured materials obtained.
$m._{IBU}$: is the mass of IBU used in each synthesis.
$m._{Ref.}$ is the mass of nanostructured materials obtained without IBU.

3. Results and Discussion

The effect of the water/ethanol molar ratio on the gelation time of the sol-gel process for the formation of TiO_2OH reservoirs and on the porous characteristics of the corresponding particles is summarized in Table 2. The gelation time decreases as the water/ethanol molar ratio increases for both systems: with and without ibuprofen(TiO_2OH-IBU), (TiO_2OH-Ref)as expected, since the water favors the hydrolysis step for the overall sol-gel process. Also, it was observed that the systems containing ibuprofen presented highergelationtimes than the systems prepared without this drug.

This couldbe attributed tohydrogen bondinginteractionformedbetweenthe OHat the surface of the TiO_2OH particles and the carboxyl group of ibuprofen.

Table 2 Gelling timesfor the sol-gel process and BET data of TiO_2OH-Refand TiO_2OH-IBU with different water ratio

Samples	Gelation Time (h)	S_{BET} (m^2g^{-1})	d_p (A^o)
TiO_2OH-Ref (1:8:8)	48	590	23
TiO_2OH-Ref (1:16:8)	28	338	26
TiO_2OH-Ref (1:24:8)	24	277	41
TiO_2OH-IBU (1:8:8)	60	375	22
TiO_2OH-IBU (1:16:8)	35	269	25
TiO_2OH-IBU (1:24:8)	30	276.	26

Figure 2 illustrates the adsorption-desorption isotherms of nitrogen of TiO_2OH-IBU systems prepared with different water/ethanol molar ratio (1:8, 1:16 and 1:24). From these experiments, the specific surface area and the average pore size diameter were calculated, thoseresults are also presented in Table 2. The results are indicating that as a rule with the increasing water concentration in the synthesis, the specific surface area decreases and the pore diameter increases. However, for all matrixes (TiO_2OH-Ref) without ibuprofen these changes are more marked. The modest surface area decreasing is suggesting that IBU is inducing some occlusion or pore mouth blocking [3].

In general,it is expected thatincreasing theproportion of water inthe reactiontheBET surface area decreases. This may be due to various reasons. The increased amount of water enhances Ostwald ripening, coalescence, coarsening, sintering, and syneresis (network densification) leading to surface decrease [12,13,14,15].

The amount of water exerts in aerogels a clear influence on the micropores formation, as deduced from the decrease produced in the S_{BET} values when the amount of water is increased.

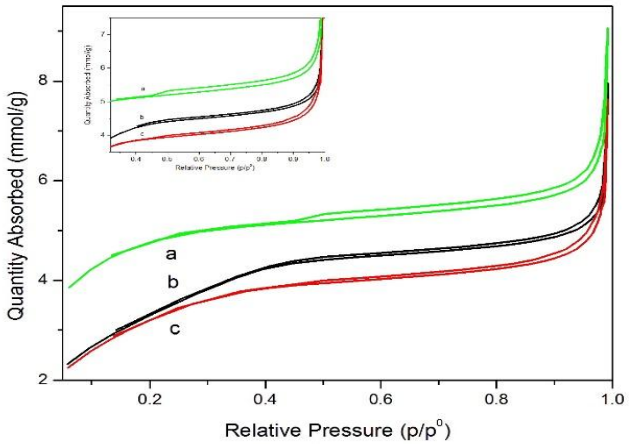

Fig 2 Adsorption-desorption isotherms of nitrogen of TiO_2OH-IBU with different water ratio, a) 1:8:8 b) 1:16:8 c) 1:24:8

For the analysis of this behavior the shape of the isotherms should be considered in detail. In principle it could be considered that all isotherms resemble each other, but with moderate hysteresis loops indicating the presence of mesoporosity. Furthermore hysteresis is more relevant for the matrix without ibuprofen (TiO_2OH-Ref)with an alkoxide/water ratio1:24:8 that is in correspondence with the pore diameter and its broader distribution [16].(see Fig 3).

Besides all the isotherms presented adsorption at the very beginning or lower pressure. This is an indication for adsorption in the more energetic sites or micropores [16-18]. The turning point to a more horizontal behavior where the monolayer is formed occurs at a pressure ratio of about 0.4-0.5, suggesting that a higher pressure is required to form the monolayer because pore sites are energetically weaker. A something similar isotherm has been obtained in the system TiO_2-valproic acid [19].

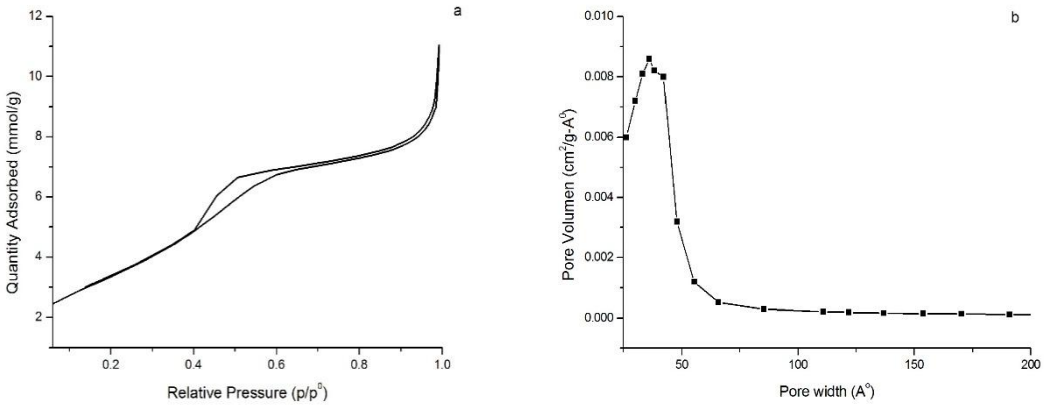

Fig 3 a)Adsorption-desorption isotherms of nitrogen b) BJH Pore diameter distribution of TiO_2OH Ref (1:24:8)

The chemical structure of Ibuprofen (Fig 4a) and the composites TiO_2OH-IBU obtained at three different alkoxide/water molar ratios were studied by FTIR analysis. The hydroxyl stretchingaround 3360 cm^{-1} and the deformation vibration of water at 1630 cm^{-1} appear in all composites (see Fig 4b). The latter signal is an evidence of the presence of a large amount of water in the systems [20].

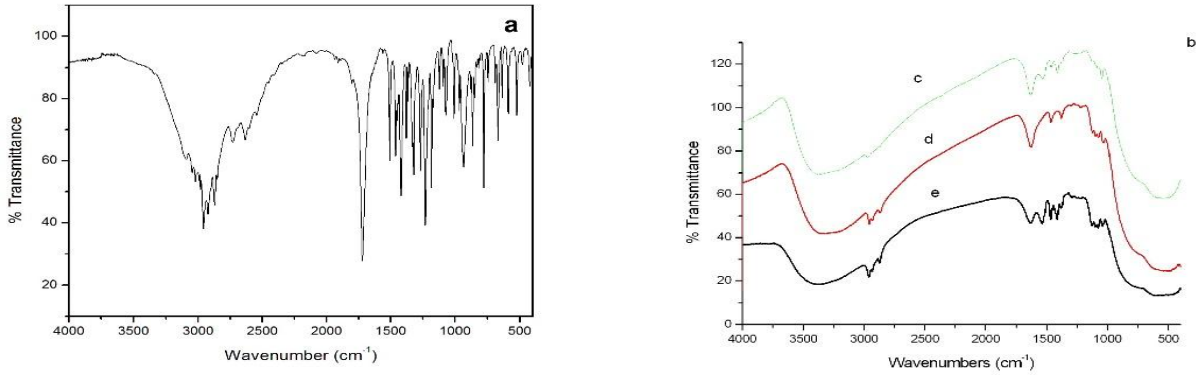

Fig 4 Fourier transforms infrared spectroscopy (FTIR) spectra of a)Ibuprofen (IBU), b) TiO_2OH-Ibuprofen with different water ratioc)1:24:8d)1:16:8 e)1:8:8

On the other hand, the sharp IBU signal at 1721 cm^{-1} is not present in any of the spectra, indicating that the IBU is confined inside the TiO_2OH particles. Then, other signals around 2800-2900 cm^{-1} could be attributed to the stretching modes of hydro-carbonaceous species, such as alkoxide residues. Thus, for the composite obtained with lower amount of water the amount of alkoxide residue is much greater than for the other composites.
The main reason for that is the incomplete hydrolysis of alkoxide molecules at low content of water during the sol-gel process [21]. It is confirmed by the TGA because appears a new loss weight (see Fig 5).
The sequence of surface dehydration begins with the removal of physically adsorbed water and hydrogen bonded hydroxyls at low temperature followed by progressive elimination of IBU for the composite. Furthermore it renders for the composite a much greater weight loss (about 32%) than for the matrix as expected.
The amount of water (OH and H_2O) of this material could be characterized by several types of hydroxyl groups (geminal, vicinal and isolated) [14] that give rise to weak and strong sites of adsorption, the latter associated to

isolated OH group [12] but FT-IR of this material did not reveal such stretching. Thus dehydration and dehydroxylation of the weakest bounded hydroxyls are taking place simultaneously.
Thermogravimetric analysis (TGA)also enabled to estimate the amount of ibuprofen incorporated to the composites (TiO_2OH-Ibuprofen) that is nearly 7% for all water/alkoxide ratios studied. The theoretical amount ofencapsulated drugwas 10%.
The nanostructured material is shown in Fig.6.The main features indicate a heterogeneous morphology with clusters of different sizes (~ 450-500 nm) and rough surface. There is no a sharp difference in morphology between the composites.

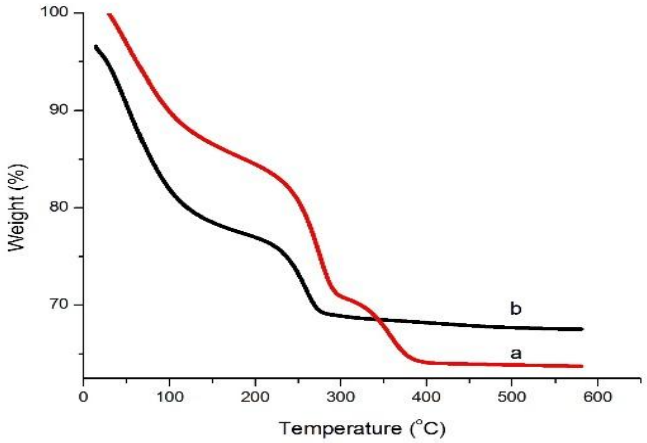

Fig5 Thermogravimetric analysis (TGA) a) TiO_2OH-Ibuprofen (1:8:8) b)TiO_2OH-Ref. (1:8:8).

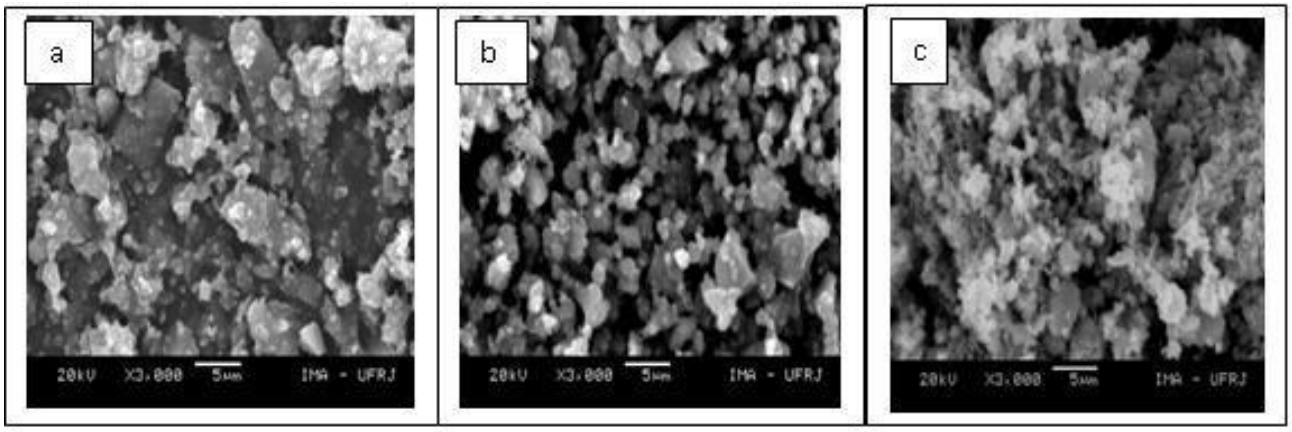

Fig 6 Scanning electron micrographs (SEM) of TiO_2OH-Ibuprofen, a) 1:8 b) 1:16, c) 1:24.

Diffraction patterns (XRD) up to 300°C were recorded for the reference matrix (TiO_2-Ref)as well as the composites (TiO_2-IBU) with increasing water in the alkoxide/water ratio in their preparations (Fig 7). These results show that anatase phase (2θ=25.35°), the most stable phase of crystalline titanium oxide, has been formed during the matrix preparation for the matrix alone even at room temperature. Also, it was observed that the increasing alkoxide/water ratio helps to anatase formation in particular at a ratio of 1:24:8, suggesting that water seems to act as a controlling factor. Thus, it is not necessary to heat the sample to obtain the anatasephase when alkoxide/water ratios 1:16:8 and 1:24:8 are used. Many researchers have reported the preparation of TiO_2 at low temperature giving anatase phase without the need for high temperature heat treatment [22].
However, unlike other studies that have reported the production of a mixture of the three forms of crystalline titania under acidic conditions at room temperature [21]. In the present work was obtained a crystalline TiO2OH without use of acid when it was used a higher water/alkoxide ratio.
In Fig7it can also be observed that the introduction of IBU in the matrix becomes the composites amorphous. It suggests that IBU can hinder the anatase phase formation in a certain degree because anatase phase signals have

considerable decreased for the ratio 1:8 or are masked for the ratio 1:24. This behavior could be ascribed to the hydrogen bridges Ti-O****HOOC- R or other type of carboxylic interaction such as chelating carboxylate ligands as has been demonstrated for acetic acid or acrylic polymer [22].

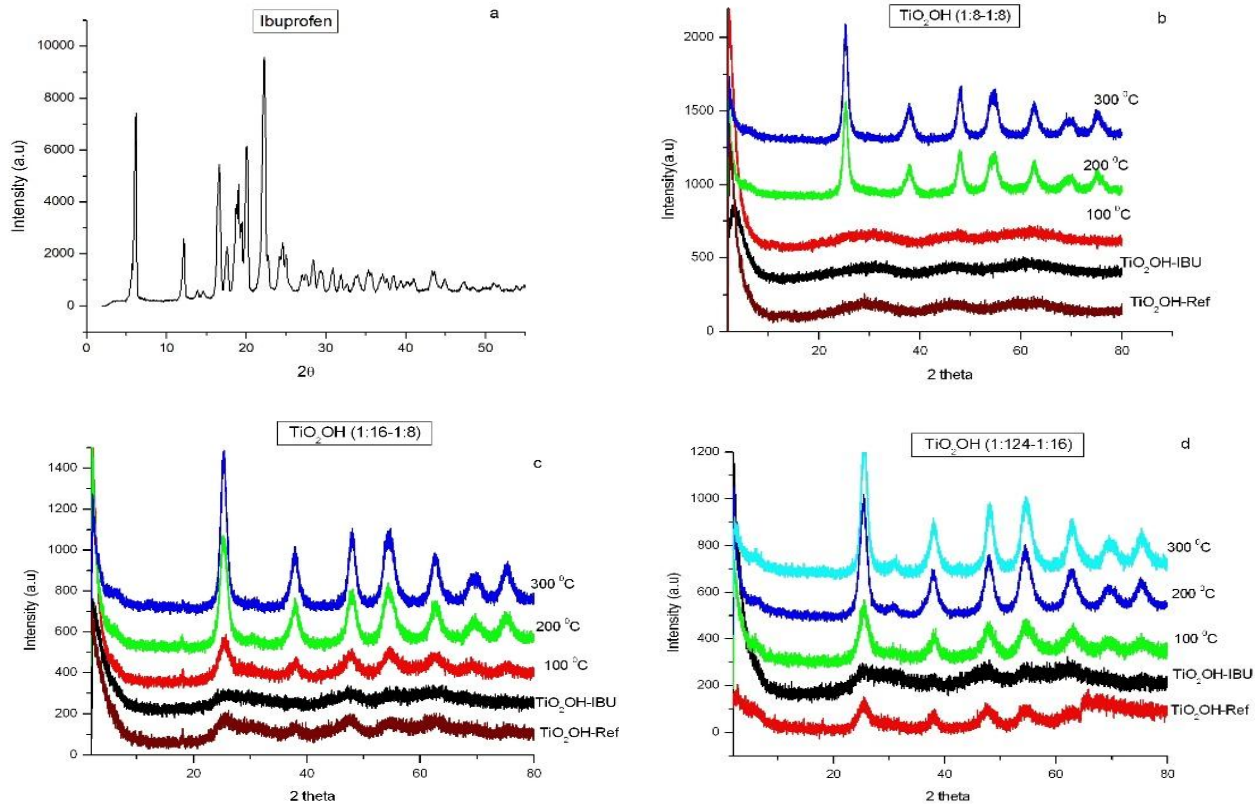

Fig. 7. Diffraction patterns (XRD) a) pure Ibuprofen, b)TiO_2OH-Ref and TiO_2OH-IBUcompositesat various temperatures

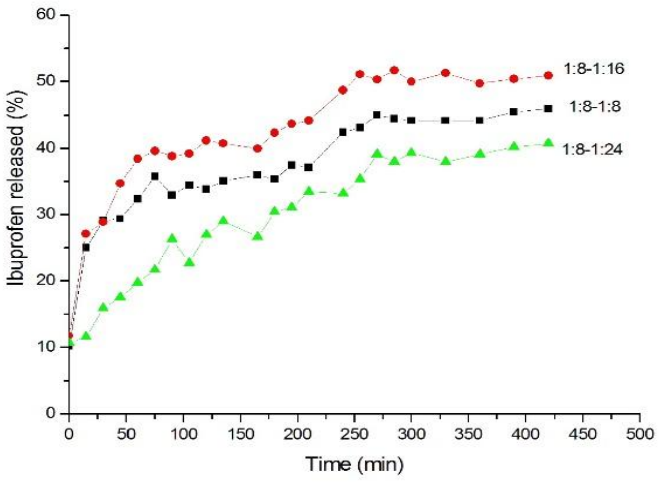

Fig. 8. Cumulative release profiles of TiO2OH-Ibuprofen related to E.E, a) 1:8 b) 1:16, c) 1:24.

The dissolution profiles(Fig. 8) show in all casestypicalcontrolled release behaviour. Cumulative drug release from samples starts with an initial burst effect, followed by a slower release rate, reaching a plateauat not greater than 50%. It seems that a high portion of the drug is occluded due to interactions drug-wall. Furthermore the sample that releases much drug is TiO2OH-IBU (1:16:8), which could be attributed tothe synthesis conditionsused. This is precisely the composite with less surface and higher encapsulation efficiency (E.E=58.3).

Conclusions

FTIR and TGA results have shown that a higher water amount leads the formation of materials with less or negligible non-hydrolyzed alkoxides. Also, it was observed that the materials presents 7%w of ibuprofen incorporated.The matrix (TiO_2OH-IBU) and their references (TiO_2OH-Ref) were characterized by N_2 adsorption isotherm and showed a decreasing specific surface and increasing pore diameter with the water content in the sol-gel procedure. Furthermore the presence of IBU seems to suggest that some occlusion pore or mouth blocking pore is present.The effect of IBU on the hydroxylated titanium matrix was also studied by DRX. The diffactograms indicates that it hinders in some extent the crystallinity of the anatase phase. The anatase phase is formed in the prepared matrix without ibuprofen (TiO_2OH-Ref) mainly at an alkoxide:water ratio 1:24:8. These materials are able to encapsulate ibuprofen giving a controlled release profile. They could be evaluated for it use in implants near the affected area or in topical forms.

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