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Effect of textural properties on the drug delivery behaviour of nanoporous TiO_2 matrices

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Abstract

In this work several nanoporous titania powders have been considered as potential carriers for the sustained release of ibuprofen, used as model drug. The textural features and the physico-chemical nature of the surface carriers have been investigated by means of N_2 physisorption measurements and FT-IR analyses. The delivery profiles have been collected in vitro in physiological solution at pH 7.4, maintaining the temperature at 37°C. It has been possible to observe a close correlation between the drug release kinetic and the textural properties of the carriers, in particular for what concerns their pores dimension. The choice of the proper synthetic approach allows a high control of the properties of the final material and of its behaviour in the drug delivery process that can be controlled to a very high extent.

Keywords: TiO_2, pores dimension, drug delivery, ibuprofen

1. Introduction

In recent years controlled drug delivery applications have gained increasing attention and the rapid expansion in the advanced materials and technology has resulted in a remarkable progress in their development. The aim of controlled drug delivery is (i) to administer the requested amount of drug to the relevant sites in the human body and (ii) to regulate the drug delivery profile, in order to obtain the optimal therapeutic benefits as much as possible. The conventional metals, oxides and mixed materials used in the drug/medical devices are generally designed at the nano-scale level. In fact, nanoporous materials and coatings are characterized by large surface area and tuneable pores size;

moreover, their surface chemical properties can be manipulated ad hoc to suit the final applications.

In particular, many efforts have been (and are) devoted to the realization of nano-structured materials combining controlled drug delivery properties with the features required by tissue engineering (i.e., design of devices that replace or act as a fraction of the whole biological structure).

These studies deal with either polymeric materials and/or with inorganic oxides, such as nanoporous alumina, porous silicon, nanostructured ceramics and nanostructured TiO_2 [1-3]. Among these systems titanium and TiO_2 materials are well known in the biomedical applications since the 1970s for their use as orthopaedic implants. In fact, titanium, titanium based alloys and TiO_2 systems are among the most common implant materials (such as cardiovascular stents, joint replacements and dental implants) used in the human body because of their desirable mechanical strength, low density, excellent resistance to corrosion and lack of cytotoxic effects [3-5]. The addition of controlled drug delivery properties to the well known features of TiO_2 could expand its potential applications in the biomedical field, and this represents a very attractive field of research.

Several works concerning the use of TiO_2 nanotubes as drug carriers have been published [6-8]; in particular, Popat et al. [9] have studied and reported the effect of titania nanotubes templates as sustained drug release platforms for the treatment of acute infections arising after orthopaedic implant surgeries. These studies evidenced that titania nanotemplate carriers are not only effective against the bacterial infection but, parallel to this, they exhibit improved osteoblast cell adhesion and growth.

In addition to biocompatibility, another important issue must be considered, i. e. the textural properties of the material. A carrier possessing high surface area, large pore volume and proper pore size is fundamental to ensure the loading of the support with the desired amount of drug, thus increasing its adsorption capacity [10]. Moreover, among the several factors affecting the release profile (i. e. the nature of the carrier, the chemical interactions between the drug and the support, etc), the pores size dimension hardly affects the performance of a drug delivery system, because it influences the rate by which the drug is released from the matrix [11]. The possibility to tune the pores size distribution of the support then allows a better control of the drug release profile.

Titania nanoporous surfaces are usually prepared either using an anodization method [12] or by employing a block copolymer in combination with a titanium precursor ($TiCl_4$) [13]. Many studies are reported on the design of nanostructured titania or titania-silica biomedical ceramics obtained by the sol-gel method, which is a very attractive technique because it allows a high control of the textural properties of the final products by choosing the proper synthetic conditions; this fact becomes particularly important for the possible use of nanostructured carriers in the drug delivery process.

There are several examples of TiO_2, SiO_2 and TiO_2/SiO_2 carriers prepared by the sol-gel approach [14-17]. Lopez et al. [18] have investigated a sol-gel synthesized nanostructured TiO_2 matrix with different channel size as reservoirs for the controlled delivery of Temozolomide, an important drug for the treatment of tumors.

In the light of the remarkable potentialities of TiO_2 in the biomedical field, in the present work the attention was focused on several TiO_2 nanoporous matrices to sustain the release of ibuprofen, used as model drug. A series of commercial titania nano-

powders and a TiO_2 sample prepared by a sol-gel method were investigated in order to identify the correlation among the synthetic approach, the physico-chemical properties and the drug delivery behaviour.

2. Experimental

2.1 Materials

Ethanol (Fluka), Tris Buffered Saline (0.2 M TRIS HCl; 9.0% NaCl; pH 7.5±0.1) (Fluka), hydrochloric acid (Fluka), titanium tetraisopropoxide $Ti(OC_3H_7)_4$ (Fluka), Ibuprofen sodium salt (Aldrich), isopropyl alcohol (Fluka). All reagents have been used as received.

2.2 Synthesis

2.2.1 TiO_2 powders

Five matrices were selected as potential carriers: four commercial TiO_2 powders (P25, Millennium, Mirkat, PC105) and a TiO_2 matrix synthesized in our laboratory by a sol-gel approach as briefly described in the following. The $Ti(OC_3H_7)_4$ precursor (25 mL) was suspended in 2-PrOH (23 mL): the proper amount (80 mL) of H_2O was added dropwise to this suspension under vigorous stirring. The obtained sol was stirred for 90 minutes and then aged at room temperature in static condition for 20h. The aged gel was dried at 80°C for 12 h and finally calcined at 300°C in flowing air. The final material was labelled as TiO_2.

The drug was embedded on the carriers by incipient wetness impregnation as previously reported in ref. [19]. In a typical synthesis, a proper amount of ibuprofen sodium salt (in order to obtain a concentration of 80 mg of ibuprofen/g TiO_2) was dissolved in ethanol

and added to 1g of the titania support containing a pore volume equal to that of the added solution. Capillary action draws the solution into the pores. The drug/TiO_2 composite was then dried at 50°C for 12 hours to get off the volatile components within the solution. The obtained samples were conformed (pressure 2.5 Ton for 5 minutes) as capsules (diameter 1.2 cm; thickness: 0.5 cm).

2.2.2 Delivery release (in vitro study)

In vitro study of ibuprofen release from the supports was performed as follows.

In a typical experiment, a capsule was soaked in a proper volume (10 mL) of a saline solution at pH 7.4 and maintained at 37°C. Samples of 1 mL were removed from the solution at predetermined times and replaced by the same volume of fresh medium. The drug concentration in the liquid phase was evaluated by UV spectrometry at 272 nm (Perkin-Elmer λ40 instrument). Calibration curve of ibuprofen was determined by taking absorbance vs ibuprofen concentration between 0 and 2000 ppm as reference parameters. The effective drug concentration in solution was calculated on the basis of the following equation [20]:

$$C_{eff} = C_{app} + \frac{v}{V}\sum_{t}^{t-1} C_{app}$$

where C_{eff} is the corrected concentration at time t, C_{app} is the apparent concentration at time t, v is the volume of sample taken and V is the total volume of the dissolution medium.

In order to check the reliability of the collected data, a test was carried out in the conditions previously reported by taking a single sample from the dissolution medium at the end of the release experiment. We have obtained the same drug concentration

value of that calculated on the basis of the formula for a drug release test studied with multiple sampling.

In order to check for reproducibility, each release test has been carried out in triplicate by collecting, each time, the data analysis simultaneously from two identical tablets.

2.2.3 Characterization

Specific surface area and pores size distribution were obtained from N_2 adsorption-desorption isotherms at 77K (MICROMERITICS ASAP 2000 Analyser). Surface area was calculated by the BET equation [21], whereas the mesopores size distribution was determined by the BJH method [22], applied to the N_2 adsorption isotherm branch. Prior to the adsorption experiments all the analysed samples were outgassed in vacuum at room temperature (RT) for 12 h.

FTIR spectra were obtained on a BRUKER 113v spectrophotometer (2 cm^{-1} resolution, MCT detector). All materials were inspected in the form of self-supporting pellets (10 mg cm^{-2}). All samples were activated in controlled atmosphere at IR beam temperature (BT, namely 60°C) in quartz cells connected to a gas vacuum line, equipped with mechanical and turbo molecular pumps (residual pressure $p<10^{-5}$ Torr). Samples have been treated (i.e., evacuated) only at BT from 1 up to 60 min in order to get rid of all physisorbed species.

3. Results and discussion

In order to evaluate the possibility of using a TiO_2 matrix as carrier to sustain the release of a drug molecule and identify the key factors affecting the delivery behaviour, four commercial TiO_2 nano-powders have been selected and tested as carriers for the

controlled release of ibuprofen. The matrices were chosen on the basis of their textural properties, i.e. surface area and pores dimension.

The drug was introduced on the matrices by incipient wetness impregnation, an effective and reliable method for the preparation of porous oxide/drug composites, as reported in ref. [19].

The corresponding drug delivery profiles are reported in Figure 1.

First of all it is possible to evidence that, at the end of the delivery experiment, both shape and dimensions of the tablet are unchanged. This confirms that the release process is due to the drug diffusion out of the tablet and not to the dissolution of the titania matrix.

The four delivery profiles are quite different. For the P25 sample the release rate is very fast and almost all the drug embedded in the TiO_2 carrier is delivered in the first 4-6 hours. On the other hand, Mirkat and Millennium samples exhibit a very similar drug release profile: gradual and controlled to a high degree, but extremely slow. In fact at the end of the delivery experiment only a limited fraction (~ 30%) of the drug is released from these two matrices. Among the investigated carriers, PC105 exhibits the best performance: its release profile is rather controlled and most of the drug is released at the end of the delivery test.

In order to explain these results, FTIR and N_2 physisorption analyses were resorted to.

All systems have been characterized by means of FTIR spectroscopy in order to obtain information about: (i) all surface terminations (i.e., intrinsic and/or added functionalities); (ii) the nature of the interaction between the TiO_2 surface and the embedded ibuprofen.

Figure 2 reports the FTIR profiles collected after 1 hour evacuation at RT. The temperature of the thermal dehydrating treatment has been kept close to the physiological temperature (i.e. ~37°C), in order to avoid any decomposition/alteration of the drug itself.

FTIR spectra are very similar for all the investigated systems. As for the spectra relative to the plain TiO_2 systems (set b in each section of Figure 2), all of them exhibit the typical OH pattern of titania, i,e,:

(i) a complex band located in the 3600-3700 cm^{-1} range which can be ascribed, on the basis of its spectral behaviour and of literature data [23], to the stretching mode (□□□) of Ti-OH species free from hydrogen bonding interactions;

(ii) a broad envelope, located in the 3600-3000 cm^{-1} range, which can be ascribed to the □□□ of all H-bonded OH groups present at the surface of the solid [24]. This is not surprising, as an activation in vacuo at RT can only get rid of the physisorbed fraction of (associated/undissociated)water molecules present at the surface of the various TiO_2 systems;

(iii) a complex of bands (in some cases present in an envelope, in some other ones singled out in components) located in the 3100-2750 cm^{-1} range (somehow superimposed to the envelope described in (ii)) and ascribable to the stretching modes (□CH) due to hydro-carbonaceous species present at the surface of TiO_2. This is again not surprising, as after the calcinations step all powders were exposed to the laboratory atmosphere, in which contaminants, like hydrocarbons and CO_2, are present and can readily react with the oxide surface to give rise to surface species [25]. This reaction is very rapid and favoured if the nature of the

oxide is ionic: this is the case of alumina, titania and in general of all IVB group metal oxides [26];

(iv) as for the envelope located at □ < 1800 cm-1, it is mainly made up of a component centred at □ 1630 cm-1, ascribable to the □HOH mode of undissociated water molecules. At lower □, the bands can be ascribed to the spectral modes of surface carbonates/hydrogenocarbonates generated by the reaction of CO_2 with the surface species of the ionic oxide [27].

Curves a in each set of figure 2 refer to the spectra relative to the various model TiO_2 impregnated with Ibuprofen. It is possible to observe that in all cases the typical OH pattern of the titania matrix above described is strongly affected by the presence of the bioactive molecule. In fact, the envelope of bands ascribable to the "free" Ti-OH species (□□□ in the 3620-3700 cm-1 range) is totally absent in the case of all the titania+ibuprofen samples. Moreover, it is worth noting that the presence of additional bands on the profile of the titania/drug composite is due to the presence of ibuprofen. In fact, in the high□□ region (2750–3100 cm-1), new sharp bands appear: their spectral behaviour allows to assign them to either □C-H stretching modes (□~2800-3100 cm-1) of all CH-containing species of either aliphatic or aromatic nature or to the □N-H stretching vibration modes (□~3000-3400 cm-1) present in the ibuprofen molecule. At low frequency (□<1800 cm□1) intense and broad bands are also present: these represent either the spectral bending (□C-H, □N-H) counterparts of the above-described stretching modes of all CH- and NH-containing species or the □CO (~1695 cm-1) of the carboxylic residue present in the drug.

All these features confirm the presence of the bioactive molecule on the matrices and its interaction with the titania surface is likely to take place by hydrogen bond. This is confirmed by the differential curves (a)-(b) reported in the FTIR patterns, as signals relative to species that disappear (i.e. OH species) upon drug loading are pointing down, whereas bands relative to species that appear ($\delta_{CH,NH}$ and $\nu_{CH,NH}$) after ibuprofen loading are pointing up.

These results are significant but they cannot justify the very different delivery behaviour exhibited by the various samples. In order to shed some light on these differences, N_2 physisorption analyses were carried out. The adsorption/desorption isotherms and the pores size distributions of the TiO_2/ibuprofen pressed samples are reported in figure 3 and figure 4, respectively; surface area, pore volume and pores diameter values of both ibuprofen-free and unpressed TiO_2 samples and drug loaded and pressed samples are listed in Table 1.

In all cases, it is possible to observe a significant contraction of BET surface area and pore volume values and a slight reduction of the pores diameter in all the drug loaded and pressed samples compared to the plain TiO_2 systems.

Both effects can be plausibly attributed to the presence of the drug into the pores and this fact confirms the successful adsorption of the active molecule inside the porous network; another contribution could derive from the partial collapse of the structure, as a consequence of the tableting action. In any case, in all pressed samples the original texture of the carriers is preserved to a high degree, as the isotherms shapes are very similar for both the pressed and un-pressed systems. This is an important result, which indicates (i) the reliability of the synthetic method, but also (ii) the mechanical stability of the investigated TiO_2 systems.

Mirkat/Ibu and Millennium/Ibu samples exhibit a IV type adsorption-desorption isotherm which contains an H3 hysteresis loop (IUPAC definition) [28]. The hysteresis loop is extended in a wide range of relative pressure (from 0.4 to 0.9), suggesting a broad distribution of the pores dimension. In fact, these distributions are characterized, for both samples, by a bi-modal distribution with a large fraction of small pores (centered around 3.5 nm) and another fraction of bigger pores (between 10 and 70 nm). On the contrary, the isotherm relative to the P25/Ibu sample is that typical of a material characterized by large pores, as confirmed by the BJH distribution curve (see Figure 4): the small value of surface area (36 m_2/g) is in good agreement with these evidences. The isotherm of PC105/Ibu is similar in shape to that of the P25/Ibu sample, but the total volume adsorbed is higher and the hysteresis loop starts at lower pressure according to the presence of smaller pores [29]. It can be supposed that these significant differences in the textural properties exhibited by the different titania systems strongly affect their behaviour in the drug delivery process and provide a key role on directing the drug kinetic release.

A standard controlled drug release mechanism involves: (i) diffusion of the drug through the carrier matrix; (ii) carrier matrix erosion; (iii) combined erosion/diffusion process; (iv) interaction between matrix and drug molecules. In the case of the TiO_2 carriers the drug delivery process is mainly controlled by diffusion: the drug dissolves in the release medium and then diffuses from the matrix into the solution along the solvent-filled porous channels. The comparison between the drug delivery profiles and the pores size distributions (see Figure 4) suggests a close correlation between pores dimension and drug diffusion process. In the case of Mirkat/Ibu and Millennium/Ibu systems, which are characterized by both a very similar bi-modal pores size distribution

and a definite number of pores with relatively small dimensions (2±5 nm), the ibuprofen release out of the porous matrix is well controlled; but unfortunately a lot of the drug keeps trapped into these smaller pores (d~2 nm). On the other hand, the large pores of P25/Ibu sample are absolutely detrimental for the drug release kinetic, which is too fast and uncontrolled. A good compromise is achieved only in the case of the PC105/Ibu system that possesses pores of suitable dimensions (centred on a relatively extended range of size, 6-25 nm): this feature allows a fair control of the delivery process and ensures the release of almost all the loaded drug.

N_2 physisorption analyses were carried out on the samples Millennium/Ibu and PC105/Ibu at the end of the release process, in order to verify what happens to the systems after the desorption of the drug. We chose these two samples because their performance in the release process is quite different: the PC105/Ibu sample releases most of the loaded ibuprofen, while the Millennium matrix retains a great amount of the drug.

The shape of the isotherms of both samples remained unaltered, thus deducing that their structural integrity was preserved, but an increase of the surface area (compared to that of the samples before the release tests) was observed. The PC105/Ibu sample has a final surface area of 68 m_2/g, while that of the Millennium/Ibu sample is 137 m_2/g; the increase is then of 21% and 12% respectively. These results confirm that part of the drug loaded in the matrices desorbed setting the pores free. It is also possible to note that a strict correlation between the amount of ibuprofen released from the matrix and the increase of the surface area exists: in the case of the PC105 sample, which released ~90% of the ibuprofen loaded, the increase of the surface area is twice as that of the Millennium sample, which retains a lower amount (only ~50%) of the drug.

In order to further verify the role of the TiO_2 textural properties on the drug delivery process and to obtain a release profile controlled to a high extent, a TiO_2 matrix was synthesized employing a sol-gel approach (see section 2.2.1). The main target was the synthesis of a final material (TiO_2/Ibu) characterized by both high surface area and pores with dimension between that of Mirkat and Millennium systems (which exhibited slow and partial drug release) and that of PC105 sample (which on the contrary exhibited a drug release almost complete but quite fast). The first step of the study was then the check of both surface and textural properties of this system by means of FTIR spectroscopy and N_2 physisorption analysis, respectively.

Figure 5 reports the FTIR profiles collected after 1 hour evacuation at BT, i.e., in the same conditions experienced by all the other samples. It is again possible to evidence that the typical OH pattern of the titania matrix is strongly affected by the presence of the bioactive molecule. In fact, the band ascribable to the "free" Ti-OH species (□□□□~ 3655 cm^{-1}) [23] is totally absent in the case of ibuprofen-loaded samples. Moreover, the presence of ibuprofen is witnessed, as also reported in case of the commercial TiO_2+ibuprofen samples (see figure 2), by the spectral components located in:

- the 2750–3100 cm^{-1} range where sharp bands appear. On the basis of their spectral behaviour, they are assigned to (i) □C-H stretching modes (□~2800-3100 cm^{-1}) due to all CH-containing species of either aliphatic or aromatic nature and (ii) or the □N-H stretching vibration modes (□~3000-3400 cm^{-1}) present in the drug molecule;
- At low frequency (□<1800 cm□1) intense and broad bands are also present, representing the same features reported in the case of the commercial drug loaded titania samples.

The isotherms and the pores size distributions of the as-synthesized TiO_2 and of the ibuprofen loaded and pressed carrier are reported in figure 6.

The adsorption-desorption isotherms are typical of mesoporous systems with relatively high surface area (189 and 146 m_2/g respectively, for plain TiO_2 and TiO_2/Ibu) and unimodal pores size distribution. As expected, the addition of the drug and the tableting action lead to a decrease of both surface area and pores volume, even if the original texture of the TiO_2 sample is preserved, as confirmed by the unchanged shape of the isotherm. In figure 6(b) it can be observed that pores size (3-7 nm) of the TiO_2/Ibu sample is effectively consistent with what expected in the case of the different commercial samples (see Figure 4): the TiO_2/Ibu system possesses pores exhibiting diameters with dimensions between those of the PC105/Ibu (6-25 nm) and of the Millennium/Ibu samples (3-4/15-60 nm). This result confirms that the sol-gel approach allows to control to a high degree the textural properties of the final material. In particular, we observed that through the optimization of the synthesis parameters (Ti precursor:water ratio, solvent amount, rate of water addition, aging modality) a modulation of the pores size distribution can be achieved.

Figure 7(a) reports the drug release from the TiO_2/Ibu sample. The delivery profile is gradual and well controlled: at the end of the experiment ~ 67% of the total ibuprofen initially loaded has been released from the tablet (this value is definitely higher than that obtained in the case of the Millennium/Ibu and Mirkat/Ibu samples). Despite the partial drug release, the behaviour of this sample can be considered suitable for the realization of a controlled drug delivery system. This result is very significant as confirms the close correlation between the pores dimension of the carriers and the drug release process. This feature affects to a high extent the release trend, that is slower and more controlled

than that exhibited by the PC105/Ibu system, with a final released drug amount higher than that obtained for the Millennium/Ibu sample. An important role in directing the drug delivery process is probably played by the pores dimension of the TiO_2/Ibu system, and also by the unimodal nature of its pores distribution. This kind of distribution favours a more controlled and uniform drug release than that exhibited by a bi-modal distribution.

4. Conclusions

In this work we have studied a series of nanoporous titania systems as possible carriers to sustain the release of ibuprofen, a well known anti-inflammatory drug.

By a sol-gel approach it is possible to modulate the physico-chemical properties of the matrix as a function of the dimension of the drug, thus controlling the rate of its release. In particular, we have observed a close correlation between the pores dimension of the matrix and the release rate of the embedded drug: it is then possible to design a drug delivery device as a function of the final application (i. e. dimension of the drug, therapeutic action duration, …).

A further improvement here reported could be then gained by the synthesis of a matrix possessing pores dimension slightly shifted towards higher values, in order to achieve the total release of the embedded drug, as well as a gradual and well controlled delivery profile.

This work shows the possibility of combining the well known biocompatibility of TiO_2 with drug delivery properties, thus increasing the number of potential applications of this inorganic material in the biomedical field.

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Table 1

Sample	Ibuprofen amount (mg)	BET surface area (m_2/g)	Total Pore Volume (mL/g)	Pore diameter (nm)
P25	0	52	0.3	>10
P25/Ibu	80	36	0.2	15-40
PC105	0	84	0.4	7-40
PC105/Ibu	80	56	0.2	6-25
Mirkat	0	329	0.5	4-5/15-70*
Mirkat/Ibu	80	131	0.3	3-4/10-70*
Millennium	0	339	0.5	4-5/5-45*
Millennium/Ibu	80	121	0.3	3-4/15-60*
TiO2	0	189	0.3	2.5-7
TiO_2/Ibu	80	146	0.2	3-7

*bi-modal pores size distribution

Figure captions

Figure 1. a) Ibuprofen (%) release as a function of the immersion time in the release medium (n=3, mean±sd); b) release profiles in the first 360 min of analysis.

Figure 2. Absorbance FTIR spectra in the 4000-1250 cm^{-1} range for the plain (b) and ibuprofen loaded (a) TiO_2 matrices. (a)-(b) Differential curves obtained subtracting the spectrum of the plain TiO_2 material to the spectrum of the drug loaded corresponding system.

Figure 3. N_2 adsorption/desorption isotherms of the drug loaded and pressed TiO_2 commercial samples.

Figure 4. Molecular model of ibuprofen (a) and BJH pores size distribution of the ibuprofen loaded TiO_2 commercial samples (b).

Figure 5. Absorbance FTIR spectra in the 4000-1250 cm^{-1} range for the plain (b) and ibuprofen loaded (a) TiO_2 home-made matrix. (a)-(b) Differential curves obtained subtracting the spectrum of the plain TiO_2 material to the spectrum of the drug loaded corresponding system.

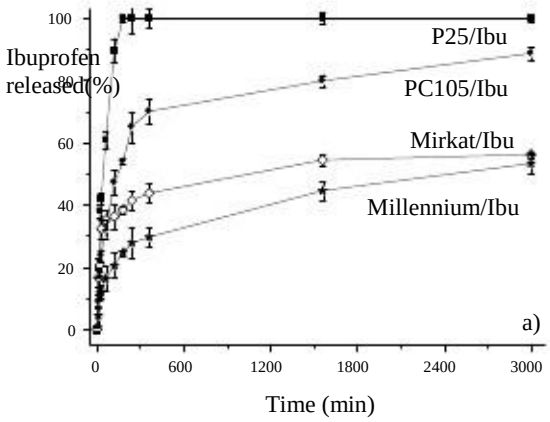
Figure 6. N_2 adsorption/desorption isotherms (a) and BJH pores size distributions (b) of the plain TiO_2 home-made system and of the drug loaded and pressed sample.

Figure 7. Drug delivery profiles (a) and BJH pores size distribution (b) of PC105/Ibu, TiO_2/Ibu and Millennium/Ibu samples.

Table captions

Table 1. Surface area, pore volume and pores diameter values of the ibuprofen-free and unpressed TiO_2 samples and of the drug loaded and pressed samples

Figure 1


Ibuprofen released(%)
P25/Ibu
PC105/Ibu
Mirkat/Ibu
Millennium/Ibu
a)
Time (min)

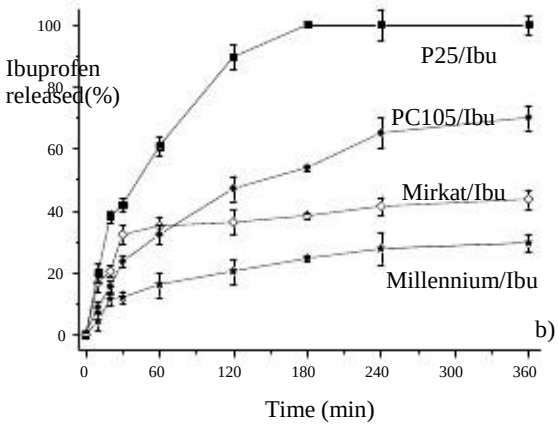

Ibuprofen released(%)
P25/Ibu
PC105/Ibu
Mirkat/Ibu
Millennium/Ibu
b)
Time (min)

Figure 2

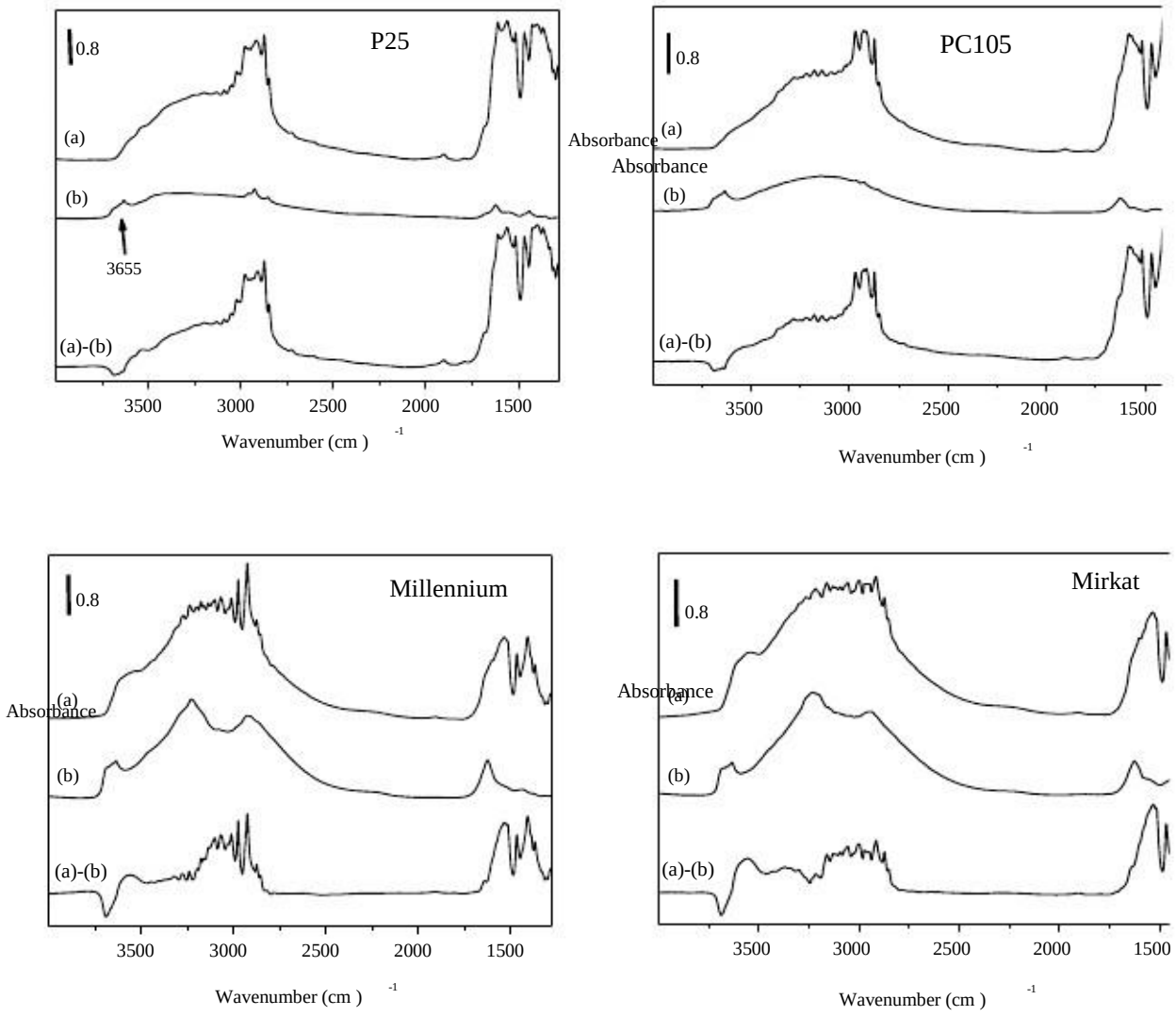

P25
0.8
(a)
(b)
3655
(a)-(b)
3500
3000
2500
2000
1500
Wavenumber (cm)
-1
PC105
0.8
Absorbance
(a)
Absorbance
(b)
(a)-(b)
3500
3000
2500
2000
1500
Wavenumber (cm)
-1
Millennium
0.8
Absorbance
(a)
(b)
(a)-(b)
3500
3000
2500
2000
1500
Wavenumber (cm)
-1
Mirkat
0.8
Absorbance
(a)
(b)
(a)-(b)
3500
3000
2500
2000
1500
Wavenumber (cm)
-1

Figure 3

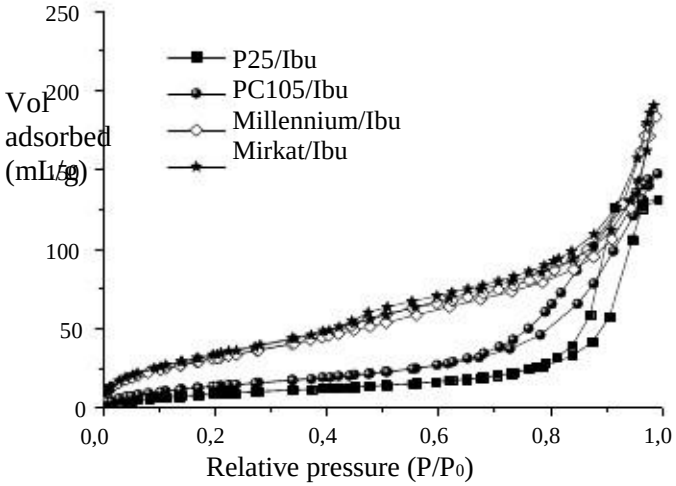

250
200
150
100
50
0
Vol adsorbed (mL/g)
P25/Ibu
PC105/Ibu
Millennium/Ibu
Mirkat/Ibu
0,0
0,2
0,4
0,6
0,8
1,0
Relative pressure (P/P0)

Figure 4

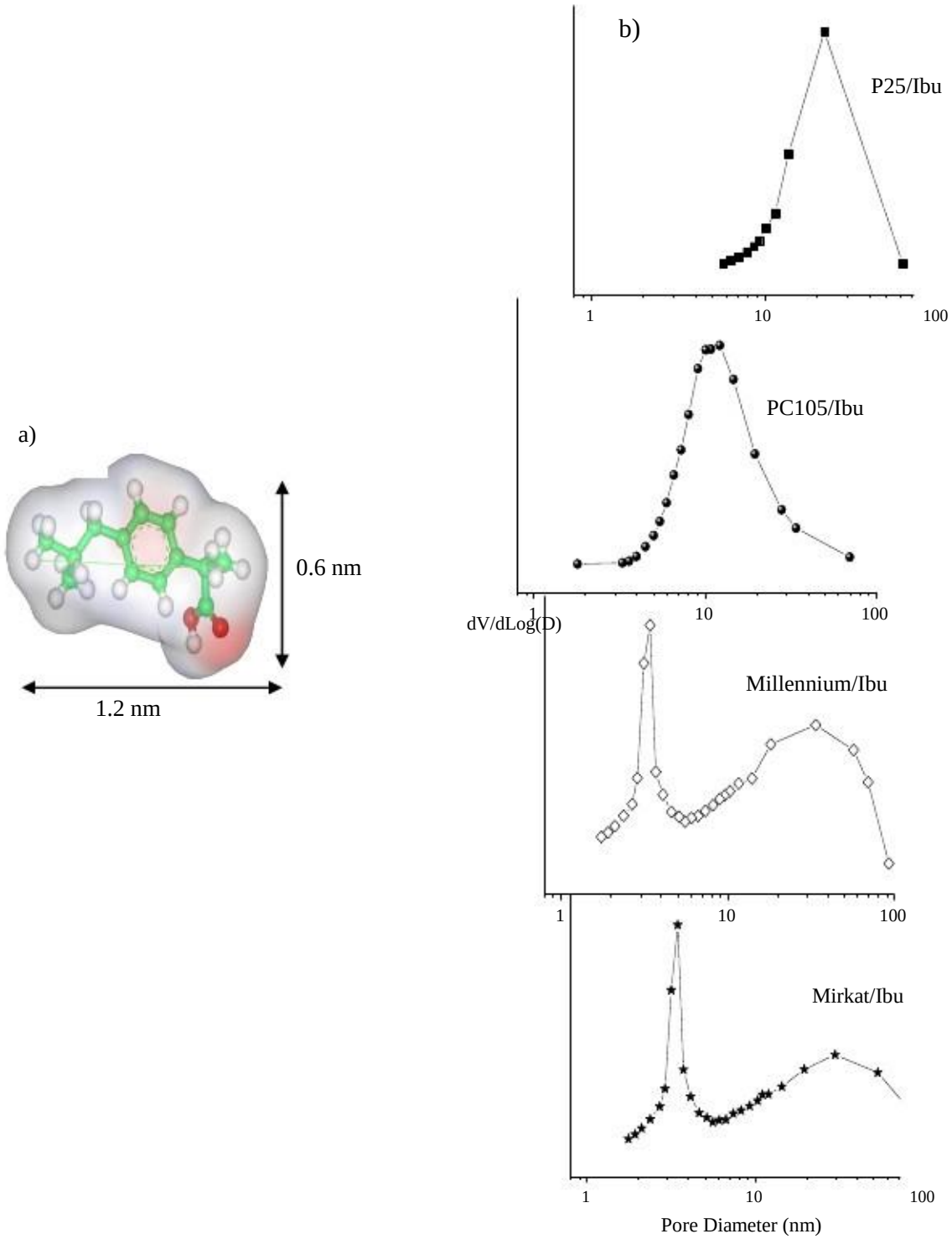

a)
0.6 nm
1.2 nm
b)
P25/Ibu
PC105/Ibu
Millennium/Ibu
Mirkat/Ibu
1
10
100
dV/dLog(D)
Pore Diameter (nm)

Figure 5

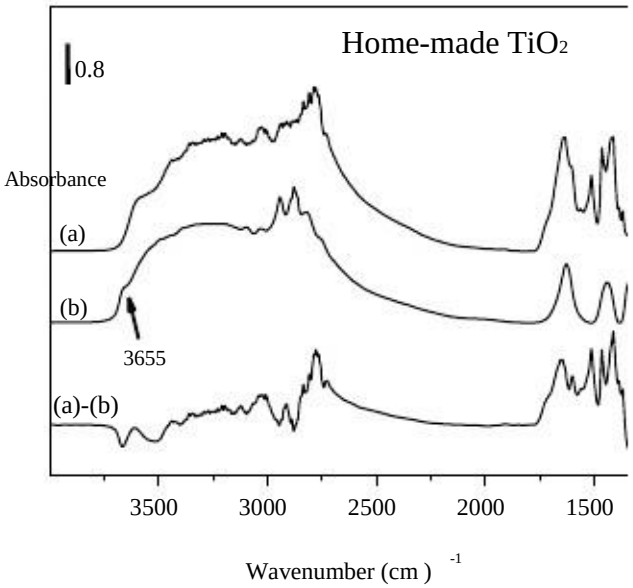

Home-made TiO2
0.8
Absorbance
(a)
(b)
3655
(a)-(b)
3500
3000
2500
2000
1500
Wavenumber (cm)
-1

Figure 6

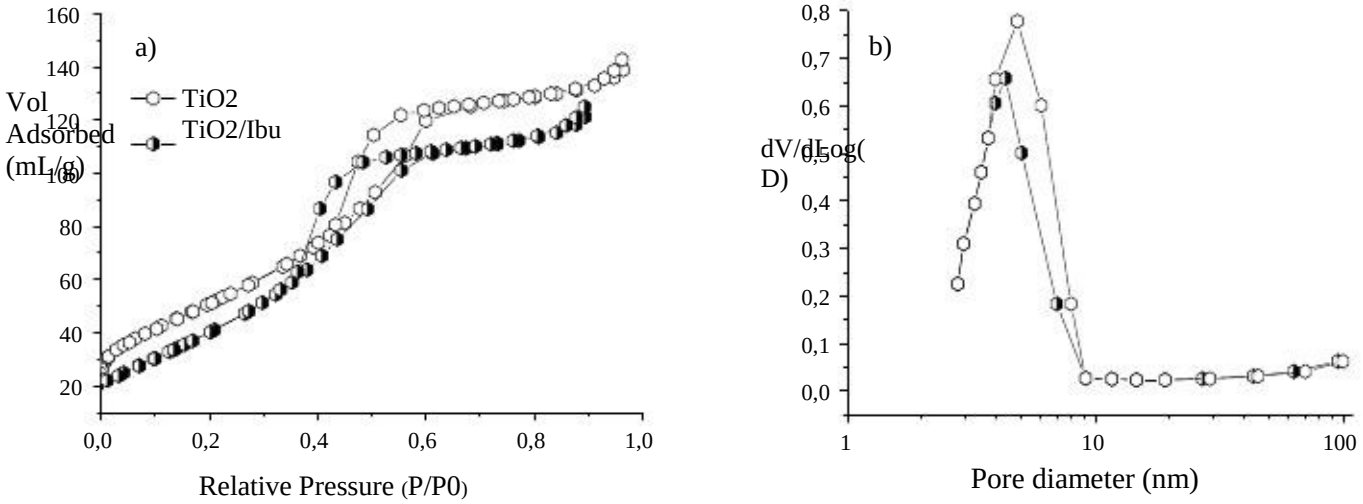
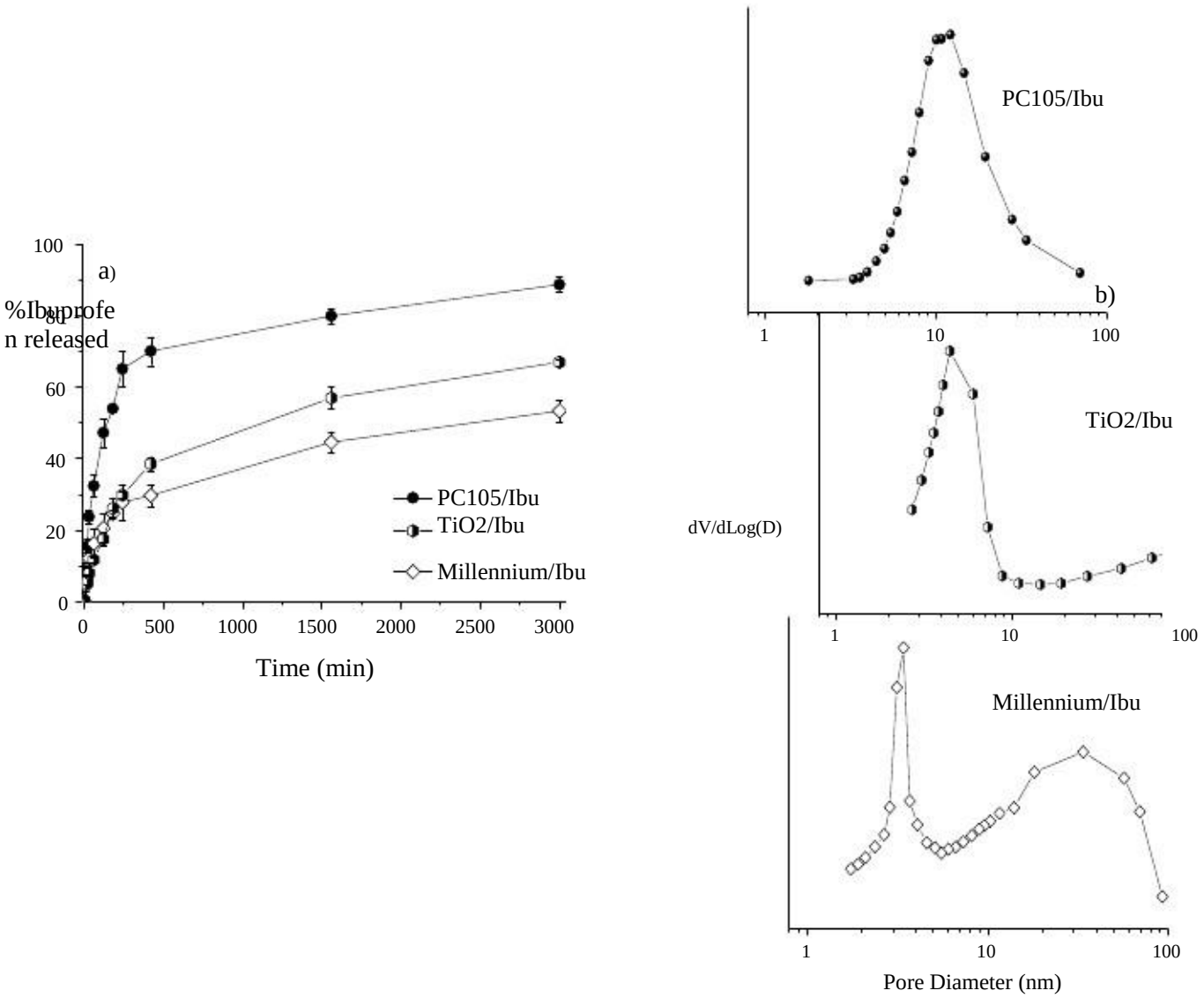

a)
TiO2
TiO2/Ibu
Vol Adsorbed (mL/g)
Relative Pressure (P/P0)
b)
dV/dLog(D)
Pore diameter (nm)

Figure 7


a)
%Ibuprofen released
100
80
60
40
20
0
0
500
1000
1500
2000
2500
3000
Time (min)
PC105/Ibu
TiO2/Ibu
Millennium/Ibu
b)
dV/dLog(D)
1
10
100
Pore Diameter (nm)