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Structure directing agent for the synthesis of TiO_2-based Drug Delivery Systems

Elena Ghedini[a], Valentina Nichele[a], Michela Signoretto[a]*, G. Cerrato[b]

Abstract: A series of titanium oxides was prepared by a surfactant template method (STM) and used as carrier to sustain the release of ibuprofen, chosen as model drug. The STM procedure provides an efficient method to prepare TiO_2 matrices with both high surface area (if compared with those obtained with the traditional synthetic approach) and a well defined mesoporous texture. Some parameters of the synthetic procedure were varied: pH, surfactant and thermal treatment. The physico-chemical nature of the surface carriers were investigated by means of N_2 physisorption measurements and FT-IR analyses. The effect of the drug amount on the release kinetic was also investigated. The drug delivery was evaluated *in vitro* in four different physiological solutions (simulating the gastro-intestinal tract) in order to analyze the behaviour of the TiO_2-based systems if formulated as oral DDS. The optimized approach turns out to be a good alternative to the classical methods employed to prepare efficient TiO_2-based drug delivery systems.

Keywords: Titanium oxide • Surface texture • Porosity • Drug delivery • *In vitro* test

Introduction

One of the main goals in material design is the optimization of a preparation method that can be easily modulated as a function of the final application. This is a key point in the development of materials devoted to be used as reservoirs in the drug delivery process, in particular when a strict control of the release rate of the drug is required. In this field it is fundamental to identify the correlations between the features of the carriers and the control on the drug release. In general, a substrate must have the ability to incorporate the required amount of drug, preserve it and delivery it gradually as the time goes by and eventually address it to a specific target site. High surface area, large pore volume and proper pore size are fundamental prerequisites for a matrix to be able to ensure loading of the support with the desired amount of the molecule guest, thus increasing its adsorption capacity [1-3]. Moreover, by varying surface area, dimensions and distribution of the pore size and surface properties (hydrophilic-hydrophobic groups, acid-basic functions, etc), both drug loading and drug release can be opportunely modulated [2-5]. In the light of these considerations, it is clear that a wise choice of the material and of the procedure adopted for its synthesis is necessary. The investigations reported in literature deal with either polymeric materials [6] and/or inorganic oxides, such as nanoporous alumina, porous silica, nanostructured ceramics [7-9] and many synthetic approaches are available, among which: template method [10,11] and sol-gel [12,13].

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In particular, the use of ordered mesoporous silica as carrier (MCM-41, MCM-48, SBA-15) provides an effective way for the realisation of controlled delivery systems: the key factors for the modulation of the release are both pores dimension and ordered structure [14-16]. At the same time, the sol-gel synthesis is very attractive, as its major advantage is that the matrix can be simultaneously generated in the presence of the drug molecule in a one-step process. Moreover, the physico-chemical features of silica can be suitably modulated by both control and opportune variation of the process parameters (such as composition of precursor mixture, catalysts, pH, aging). In particular, by a one-pot sol-gel process it is possible to obtain hybrid inorganic-organic matrices [9]: in fact, the introduction of the proper functional groups allows a high control of the drug delivery process. Increasing attention has been recently devoted to titanium-based drug delivery systems (DDS) [17]. Titanium is well known for its biomedical applications since the 1970s in the field of 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 [18,19]. The addition of controlled drug delivery properties to the well known features of titanium-based materials could expand its potential applications in the biomedical field, and this represents a very attractive research outcome.

Many studies can be found in literature about the preparation of nanostructured titanium-based DDS. The research is focused, in particular, on either the use of titania nanotubes or on sol-gel derived matrices to sustain the release of antibiotic, anti-inflammatory or anti-tumoral drugs [20-23]. In a recent work [24] we have investigated the ability of a series of commercial TiO_2 matrices to control the release of ibuprofen. 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, etc). In order to achieve this goal, in the present work we have studied a series of

TiO_2 matrices prepared by using a surfactants-template method. The possibility of using a supramolecular aggregate of surfactants for the preparation of ordered mesoporous titania samples is a topical subject and many efforts have been made to develop an effective synthetic way [25,26]. Unfortunately, these approaches, that are successful for the preparation of mesoporous silica usually, fail for TiO_2: in fact, it is quite difficult to obtain thermally stable mesoporous titania carriers.

So, in this work we have pursued a double goal: the development of a reliable procedure for the synthesis of mesoporous titania materials and its application in the design of titania-based drug delivery systems. In particular we focused our attention on the feasibility of this system as oral DDS. Despite of the growing interest in using these materials as biomedical devices, there are a few studies concerning lab-made titania used for the controlled release of drugs, in particular if formulated for an oral administration.

For this purpose we have carried out a preliminary study on the release behaviour in a simulated gastro-intestinal environment. We think that these experimental results could be useful to the scientific community in consideration of the few data available on this topic.

With the aim to control the textural features of the carriers and, in particular, pores size dimension and organization and surface area, we have investigated the effect of some parameters (surfactant type, pH, calcination temperature, drug amount) on the final properties of the materials, in order to single out the optimal synthetic conditions and the best drug delivery performance.

Results and Discussion

Effect of the template agent

In a recent work [24] we have demonstrated the close correlation between the porous structure and the surface properties of a series of nanoporous commercial titania carriers and their performance as DDS. In the light of these results, the first aim of this work has been the synthesis of titania carriers with well controlled physico-chemical (surface and textural) features by a reliable synthetic method. The use of a supramolecular aggregate of surfactants as directing agents allows a strict control of the textural features of the final oxide by the opportune choice of the operative parameters. The application of this method to the synthesis of nanoporous titania carriers is actually of great interest, but the process variables and their influence have not been clearly explained yet. In order to detect the optimal synthetic parameters we have compared, at first, the delivery behaviour of two TiO_2 carriers prepared by using either a cationic (CTA-Br) or a polymeric neutral (P-123) surfactant, respectively. For the preparation of the matrix, using CTA-Br, we have partly followed the procedure optimized for the synthesis of the MCM-41 [27] by the opportune modification of some synthetic parameters. On the other hand, in the case of P-123, we have adapted the synthesis, recently reported in literature [28]. The use of a cationic or a neutral surfactant implies the choice of different operative conditions, among which: molar ratio of the reagents, aging time, pH. In particular, the use of CTA-Br requires an alkaline environment (pH~11), whereas with P-123 we have operated in drastic acidic conditions. The pH plays a key role in directing the final features of the TiO_2 carriers. In fact, as reported by Bradley et al. [29], the hydrolysis rate of $Ti(OBu)_4$ is lower in basic environment than in either acidic or neutral conditions and the condensation kinetics are systematically enhanced under basic conditions. The base-catalyzed condensation should be directed toward the middle rather than the end of chains, leading to more compact, highly branched species. 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 previously reported [15].

In a typical experiment, the corresponding drug delivery profiles are reported in Figure 1. The two delivery profiles are quite different. For the TPi6 systems, at the end of the delivery experiment, only a limited fraction (~ 30%) of the initially embedded drug is released from the tablet; the delivery profile shows an increasing and gradual trend only in the first 3 h. On the other hand, in the case of the TCi6 sample, the release is rather controlled and almost all the drug is released at the end of the delivery test.

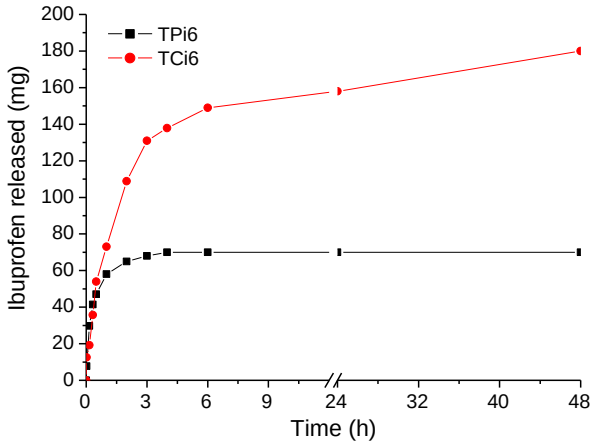

Figure 1. Drug delivery profile for TCi6 and TPi6 systems

In order to explain these results, FTIR analyses were resorted to in order to shed some light on the physico-chemical features of the various TiO_2 materials.

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 possible nature of the interaction between the TiO_2 surface and the embedded ibuprofen drug.

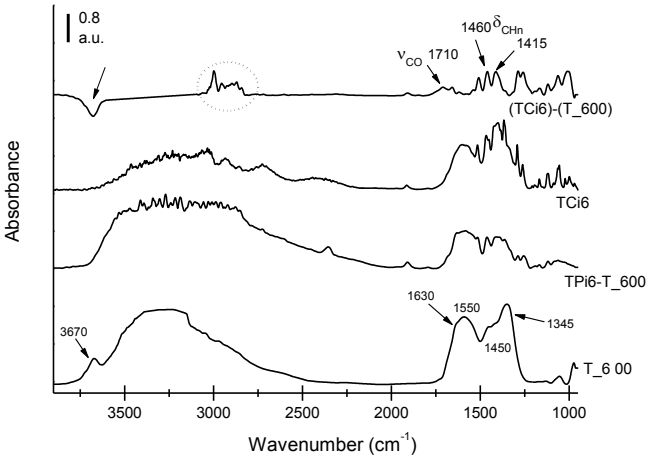

Figure 2. FTIR spectra relative to the various TiO_2 materials before and after IBU addition. All spectra have been recorded after a plain activation in vacuo at IR beam T.

FTIR spectra are very similar for all the investigated systems. As for the spectra relative to the plain TiO_2 systems (T-600), 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 (νOH) 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 νOH 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.

As for the envelope located at $\nu < 1800$ cm^{-1}, it is mainly made up of a component centred at ~ 1630 cm^{-1}, ascribable to the δHOH mode of undissociated water molecules. At lower ν, the different components can be ascribed to the spectral modes of surface carbonate/hydrogen-carbonate species generated by the reaction of CO_2 with the surface species of an ionic oxide like TiO_2 [25].

When Ibuprofen (IBU) is added to the TiO_2 matrix, it is possible to observe that in all cases the above described typical OH pattern of titania is strongly affected by the presence of the bioactive molecule: see curves TCi6 and TPi6 in Figure 2. In fact, the envelope of bands ascribable to the "free" Ti-OH species (νOH in the 3620-3700 cm^{-1} range) is totally absent in the case of all the titania+IBU samples, as confirmed by the differential spectrum (see curve TCi6 – TC6 in Figure 2). 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 IBU. In fact, in the high ν region (2750-3100 cm^{-1}), new sharp bands appear: their spectral behaviour allows to assign them to the νC-H stretching modes (ν~2800-3100 cm^{-1}) of all CH-containing species of either aliphatic or aromatic nature [30] present in the ibuprofen molecule. At low frequency (ν<1800 cm^{-1}), intense and broad bands are also present: these represent either the spectral bending δC-H counterparts of the above-described stretching modes of either all CH-containing species or the νCO (~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 (bands relative to OH species upon drug loading disappear whereas bands relative to CH and/or CO species appear after IBU loading).

HR-TEM analyses of the TiO_2 powders before and after IBU addition have been carried out: the corresponding images are reported in Figure 3, respectively referred to the plain TC6 (left-hand section) and to the TCi6 (right-hand section) materials.

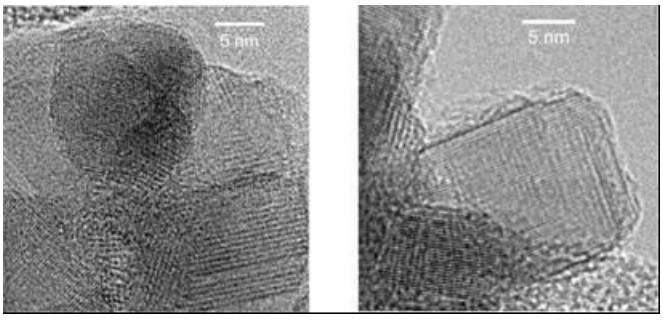

Figure 3. HR-TEM images. TC6 (left-hand section) and to the TCi6 (right-hand section).

The plain TiO_2 material exhibits particles of 20-30 nm average size, characterized by very smooth edges: these particles exhibit also a highly crystalline nature, as witnessed by the very high incidence of either fringe patterns, due to low indexes crystal planes, or Moirè's fringe patterns. The detailed inspection of the fringes distances indicates that the most frequently exposed planes belong to the (101) anatase polymorph [ICCD card File No. 21-1272]. When IBU is present, the general morphological features seem to be a little different: TiO_2 particles are still both highly crystalline and belong to the same phase, but their edges are either more disordered or present amorphous nature, most likely due to the effect of IBU addition.

These results are significant but they cannot justify the very different delivery profiles. In order to shed some light on these differences physisorption analyses were carried out and the obtained results are reported in Table 1 and the corresponding curves are shown in Figure 4.

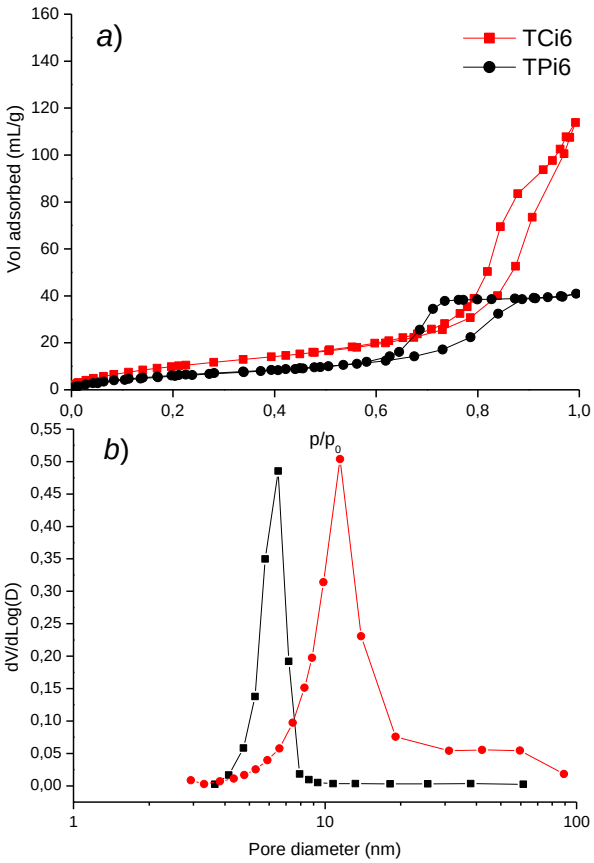

Figure 4. Adsorption /desorption isotherms (a) and pore diameter distribution (b) for TCi6 and TPi6 samples.

Sample	Ibuprofen amount (mg)	BET surface area (m^2/g)	Total Pore Volume (mL/g)	Pore diameter (nm)
TC4		130	0.3	3-8
TCi4	**200**	**57**	**0.2**	**3-10**
TC5		108	0.3	3-30
TCi5	**200**	**67**	**0.2**	**3-30**
TC6		49	0.2	6-20
TCi6	**200**	**34**	**0.2**	**5-20**
TP6		160	0.4	2-5
TPi6	**200**	64	0.2	**3-8**
TCi5/ibu100	**100**	**70**	**0.2**	**3-30**
TCi5/ibu400	**400**	**64**	**0.2**	**3-30**
TCi5 (after release, pH1.2)	**200**	**65**	**0.2**	**3-30**

Table 1. Physisorption data for the samples wit and without ibuprofen.

Upon nitrogen adsorption, both materials exhibit a type IV isotherm typical of a mesoporous system but some differences concerning the isotherm shape are evident. The CTA-Br derived sample presents a clear type-H1 hysteresis loop that is typical of materials with cylindrical mesopores characterized by a uniform distribution of the dimensions. The pores size distribution, calculated on the adsorption branch by the BJH method, is unimodal and centred at 15 nm. The hysteresis loop of the TPi6 sample is shifted towards lower partial pressures, indicating the presence of smaller pores as confirmed by the BJH curve, that shows a unimodal pore size distribution with dimension between 4 and 10 nm. The comparison between the drug delivery profiles and the pores size distribution suggests a close correlation between pores dimension and drug diffusion process. The relative smaller pores of the Pluronic-derived sample can explain, in fact, its partial release: most of the drug remains trapped into its relatively small pores (d < 8 nm).
On the basis of these results, the work was continued by focusing the investigation only on the matrices prepared with CTA-Br. We have investigated, in particular, the effect of two parameters: the calcination temperature and the drug amount.

Effect of the thermal treatment

It is well known that the thermal treatment directly influences the textural properties of a material: in order to investigate the effect of this variable the as-synthesized matrix has been calcined at 450 °C (TC4) and 550 °C (TC5) and compared with the carrier treated at the highest temperature (TC6). In order to evaluate if the thermal treatment can affect the surface features of the these samples, also in this case FTIR analyses were carried out; unfortunately, no relevant differences have been detected among them and the TCi6 materials and consequently no spectra have been here reported for the sake of brevity.

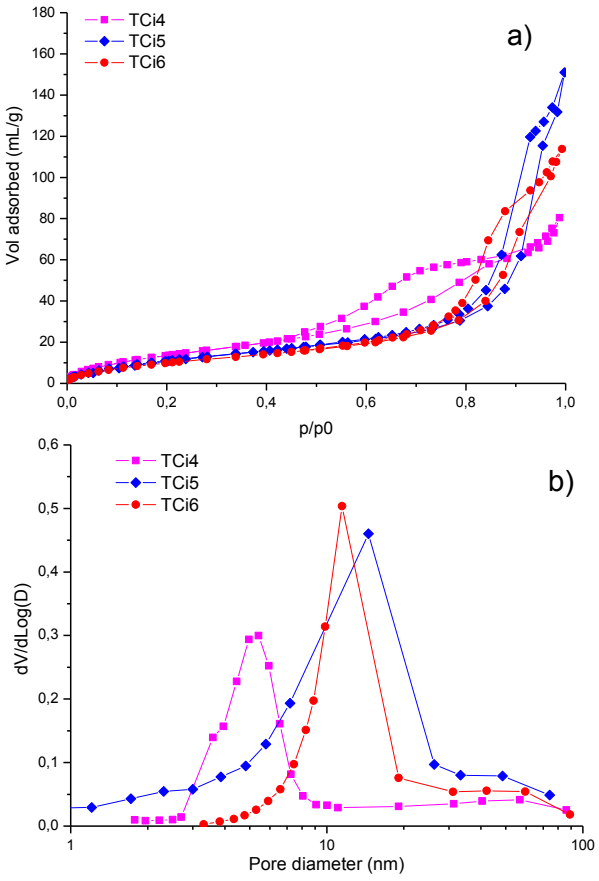

Figure 5. Adsorption/desorption isotherms (a) and pore diameter distribution (b) for TCi4, TCi5 and TCi6 samples.

On the contrary, physisorption analysis revealed significant differences: the corresponding adsorption-desorption isotherms and the pore size distribution curves for the ibuprofen-loaded matrices are shown in Figure 5, whereas the relevant data are reported in Table 1.
All the samples exhibit a type IV isotherm. The hysteresis loop of the TCi4 sample is broad and located in a p/p_0 range between 0.5 and 0.9; the corresponding BJH pore size distribution, in the adsorption branch, indicates the presence of relatively small pores with a mean dimension in the 3-8 nm interval. The TiO_2 carriers treated at higher temperatures show a very similar isotherm shifted toward highest p/p_0 values suggesting the presence of larger pores. In fact, the pores size distribution curves are respectively centred at 10 nm for the TCi6 material and at 15 nm for the TCi5 carrier. The distribution of the sample calcined at 550 °C is rather wide, as it is comprised in the 3-30 nm range. The BET surface area of the drug loaded and pressed carriers are relatively low (between 45 and 70 m^2/g); on the contrary the surface area values of the corresponding supports are about 100 m^2/g, higher than that obtained by the traditional synthetic method (*i.e.*, precipitation) [31] or by other template assisted sol-gel preparations [26,32]. This evidence indicates the efficiency of the adopted synthetic procedure.
The effects of the different textural properties on the drug delivery behaviour is shown in Figure 6.

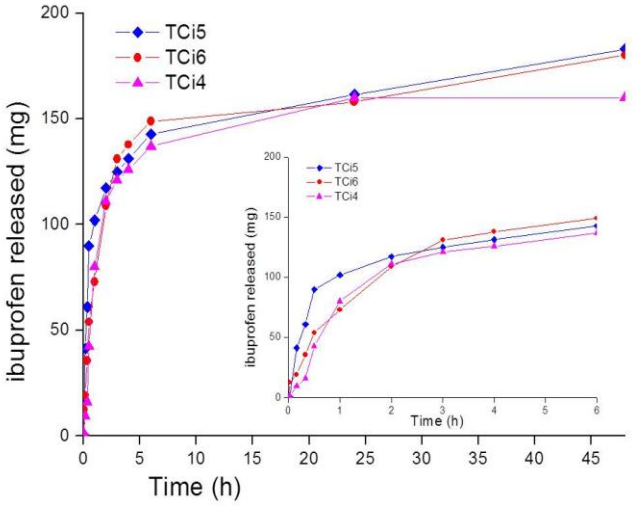

Figure 6. Drug delivery profile for TCi4, TCi5, TCi6 matrices.

The drug delivery is almost complete for both the carriers treated at high temperatures, whereas only 70% of the ibuprofen loaded is released from the TCi4 matrix at the end of the release test. The latter carrier reaches the maximum drug delivered amount after 24 h, whereas in the case of both the other matrices the delivery process continues gradually and well controlled up to 48 h. A careful analysis of the delivery profiles of TCi5 and TCi6 samples in the first two hours of analysis indicates another interesting difference: it is evident that the slope of the release curve of the TCi5 carrier is much more marked. This behaviour could be more suitable for an efficient DDS, in fact it ensures the rapid achievement of the minimal therapeutic concentration which is essential for the correct management of the drug. Once again, this behaviour can be ascribed to the pores organization of the samples: in particular, the presence in the carriers calcined at the highest temperature of a significant fraction of pores of relatively high dimension (~ 10 nm) ensures the complete release of the drug amount adsorbed with a profile very similar to that expected for an ideal DDS. Moreover, an optimal pores size distribution, allowing a fair control of the delivery process, is likely to exist in the case the TCi5 carrier: in particular, it ensures an expected fast release in the first 2 h of analysis and a good control of the delivery rate up to 48 h.

Drug amount and delivery behaviour

In order to evaluate the effect of the drug amount on the delivery behaviour, a last test has been carried considering only the TC5 carrier. Considering the drug concentrations in the different commercial formulations, we have investigated a concentration range between 100 and 400 mg. The delivery profiles are reported in Figure 7.

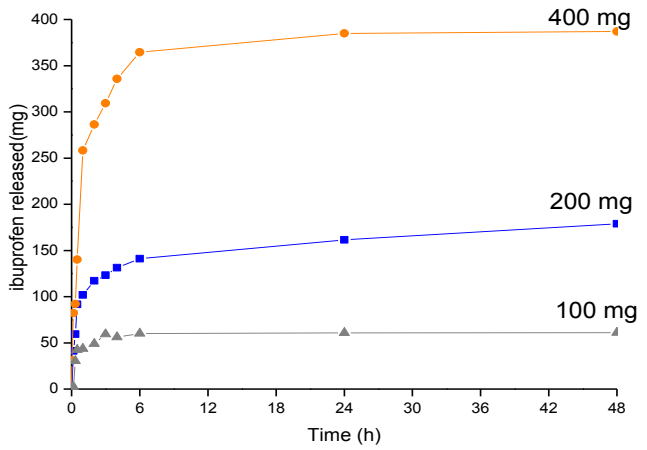

Figure 7. Effect of drug amount on the drug delivery behaviour.

The matrix containing the lowest concentration of drug (100 mg ibuprofen) exhibits a partial release, accounting for 50% of the total. The desorption profile shows a gradual release only within the first interval of analysis, as it already stabilizes after 6 hours, indicating that the drug is no longer released. This is in contrast with what obtained for the sample with the highest drug content (400 mg ibuprofen), for which the desorption is very fast. The corresponding curve shows a pronounced slope within the first 100 min and after only 6 hours most of the active principle is desorbed (98%).
The sample containing 200 mg of ibuprofen exhibits the best release profile: the drug is released almost completely (the percentage of ibuprofen released is 90% of the loaded amount) and the trend is gradual and continuous even after 48 hours.
In the case of the investigated 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. This process is governed by both physical (steric effect) and chemical interactions between drug and carrier. We have demonstrated that for matrices with different textural properties the key factor in directing the drug delivery is played by the pore organization (pore size and pores size distribution). The matrices loaded with different drug amount possess the same pores size dimension and specific surface area (see Table 1) and, in this case, the drug delivery process is evidently controlled not only from physical factors, but also from chemical interactions with the matrix surface.
In an attempt to justify and explain the experimental results we reported in graphical form (see Fig. 8) the way by which the active molecule may be distributed in the matrix and then released.
As shown in Figure 8, in the case of the sample in which 400 mg of drug were loaded, the ibuprofen molecules are, plausibly, distributed inside the pores and on the surface of the material. The drug on the surface is the first to be released with no real control of the rate of desorption; on the contrary, for the drug contained within the porous structure, the rate of desorption is controlled by both shape and size of the pores of the support, thus resulting more gradual. In the case of the sample with the lowest concentration of active molecule (100 mg ibuprofen) only a small fraction of this is found at the surface, as the majority remains within the channels of the support interacting with it through weak chemical interaction (i.e., H-bonding, see FTIR data section).

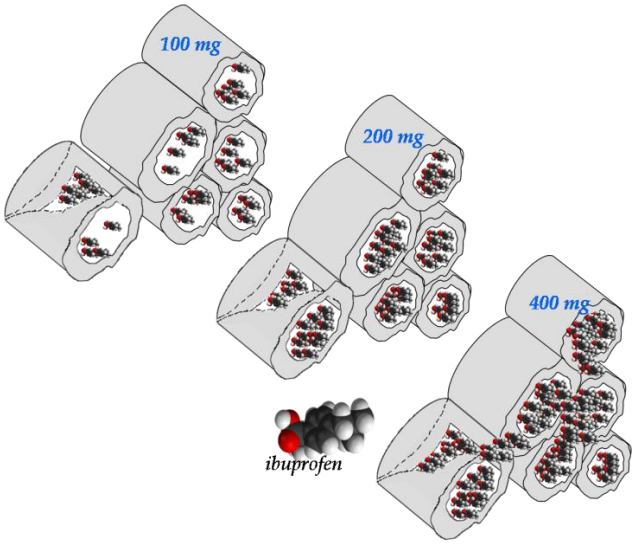

Figure 8. Ibuprofen distribution in the TiO_2 porous channels as function of drug amount.

In this case the "steric" effect (due to the porous structure) adds even more direct chemical effect because of the interaction of ibuprofen molecules with the hydroxyl groups of the matrix. In other words, in the case of the matrix containing only 100 mg of ibuprofen each molecule is affected by a greater number of interactions with the surface than in the case of the matrix loaded with a higher content; consequently, ibuprofen is more strongly bonded to the titania surface and the diffusion process is hindered. All these factors could explain the partial release exhibited by this system.
In the case of the sample at intermediate concentration (200 mg), an almost optimal situation has been reached. The percentage of drug present on the surface allows to achieve in a short time the minimum effective therapeutic concentration, while the percentage of drug in the porous channels is responsible for a gradual release.
Probably by modifying the matrix through the introduction of proper functional groups at the surface and/or through the modulation of its textural properties, it could be possible to obtain a controlled release regardless of the total amount of drug loaded.

Delivery behaviour along the gastro-intestinal tract

The last part of the work was devoted to the study of the *in vitro* behavior of the TiO_2-based drug delivery systems in the gastro-intestinal tract, in order to simulate the conditions that the formulate would experience when designed for oral administration. ~~To this end,~~ For this purpose, the release by ~~from~~ the best sample (TCi5, 200 mg of ibuprofen) has been studied in solutions reproducing the physiological environment of the stomach and small intestine.
The first solution simulates the gastric fluid (pH 1.2); in this medium, drug release has not been observed. In order to explain this experimental evidence we have first evaluated, the effect of the strong acid environment on the TiO_2 matrix. For this purpose nitrogen physisorption has been resorted to. Fig. 9 reports the adsorption-desorption isotherms of the matrix before and after the release test in gastric solution (24 h).
It ~~may~~ can be noted that the isotherm remains substantially unaltered, indicating that the texture of the material has been preserved (also surface area and pore diameter remain unchanged; see Table 1). The carrier suffered no stress associated with the environment and it is plausible to think that it kept inside all the drug initially loaded (in the case of drug desorption a partial texture modification is

expected). In order to check this last hypothesis, the tablet used for the test was consistently washed with a buffered solution at pH 7.4. In the solution, 200 mg of ibuprofen have been detected by means of HPLC analysis: it corresponds the amount initially loaded into the matrix. Another factor to consider is that ibuprofen in acidic aqueous solutions has a very low solubility [36]. This may have inhibited the desorption of the active agent from the matrix. In any case, the tests carried out have demonstrate that the TiO_2 matrix is stable in gastric solution and is able to preserve the integrity of the active principle.

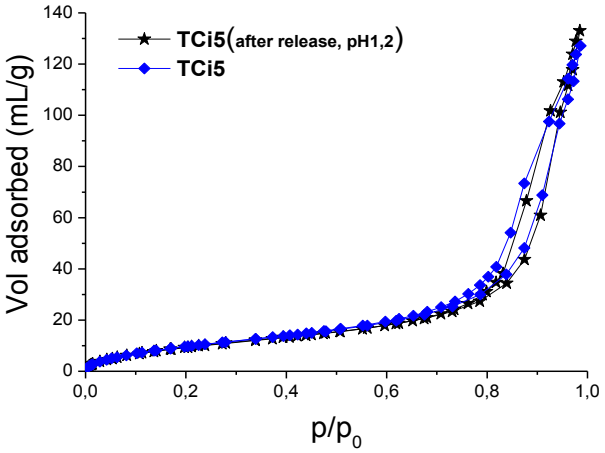

Figure 9. Adsorption/desorption isotherms for TCi5 sample: as prepared and after the release test in the gastric solution.

Thereafter we analyzed the behavior of the DDS in the intestinal fluid; it is at the level of small intestine that the active molecule is adsorbed, and it is here that the drug should perform its therapeutic action. In order to realistically simulate the intestinal environment, a pH 6.8 buffered solution containing pancreatin was prepared. The pancreatin is constituted by a mixture of enzymes (amylase, lipase, and protease) produced by exocrine glands present in the intestinal mucosa of mammals. ~~In~~ Fig. 10 reports the desorption profiles for the TCi5 sample studied in two pH 6.8 buffered solutions with and without pancreatin, respectively. The observed behaviors are very different. In the solution prepared without the addition of enzymes, the desorption profile recovers ~~to~~ that observed at pH 7.4; on the contrary, the presence of pancreatin, significantly changes the release kinetics. The drug diffusion rate from the matrix to the solution has considerably slowed down, indicating a much more gradual release. The amount of drug delivered after 48 hours is slightly lower than that desorbed at pH 6.8 in the absence of pancreatin, but the release profile is growing and longer times would allow the release of almost all the loaded ibuprofen.

The obtained results are useful because, to the best of our knowledge, they represent the first example of a study of a TiO_2-based DDS in a gastro-intestinal environment.

Moreover, we can state that not only TiO_2-based DDS act very well in a medium that simulates the intestinal environment but it seems to have improved to some extent its performance (more gradual and controlled release).

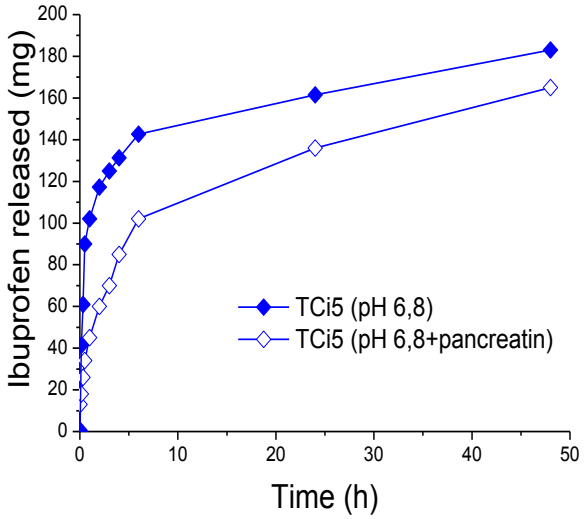

Figure 10. Drug delivery profiles for TCi5 in intestinal solution with and without pancreatin.

Conclusion

The study demonstrated the actual potential of the titanium dioxide as a carrier for the development of drug delivery systems. In particular we have optimized a synthetic approach that allows an effective modulation of both the morphological and structural properties (porous organization) of the matrix and the drug release. Moreover we have observed that the features of the carrier should be properly designed taking into account the final amount of drug and the administration form. The study has provided a series of useful information to the development of a TiO_2-based drug delivery device that can be specifically formulated for a particular therapeutic application. In particular we have demonstrated the feasibility of the TiO_2 carrier for the formulation of an oral DDS.

Experimental Section

TiO_2 powders by CTA-Br

These matrices were prepared by using the CTA-Br as structure directing agent. A given amount of cetyltrimethylammonium bromide (CTABr, ALDRICH) was added to a NaOH aqueous solution. The mixture was stirred slowly at room temperature for 40 min. The resulting solution was combined with a suspension of $Ti(OBu)_4$ (ALDRICH) in $Bu(OH)_4$ as source of titania and the reaction mixture was stirred at room temperature for 3 h. The molar composition of the resultant gel was: 1: TiO_2, 0.12: CTABr, 0.53: NaOH, 590: H_2O. The gel was crystallized in static condition at 75 °C for 40 h. The solid product was filtered, washed with deionized water, dried at room temperature and then calcined at three different temperatures (450 °C, 550 °C and 600 °C). The final material was labelled: TCx (T=titanium; C=CTA-Br; x=calcination temperature).

TiO_2 powders by P-123

In this synthesis we have used non-ionic surfactants. In a typical preparation, the surfactant P-123, $EO_{20}PO_{70}EO_{20}$, (3.6 g) (Aldrich) was dissolved in a solution of water (5.4 mL), ethanol (47 mL) and HCl (4 mL) with stirring. Then, the titania precursor, $Ti(OBu)_4$, (21 mL) was slowly added to the homogeneous solution with stirring at room temperature. The obtained gel was transferred in a crystallizer and dried at 35 °C for 24 h. The solid product was recovered and crushed. The resulting powder was then calcined at 600 °C in order to remove the template. The obtained sample was labelled: TPx (T=titanium; P=P-123; x=calcination temperature)

Synthesis of TiO_2/ibu samples

The drug was embedded on the carriers by incipient wetness impregnation as previously reported in ref. [15]. In a typical synthesis, a proper amount of ibuprofen sodium salt (in order to obtain a concentration of 100, 200 and 400 mg of ibuprofen/g of 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 35 °C for 12 hours to get off the volatile components within the solution. The obtained samples were conformed (pressure 2.5 Ton/cm^2 for 5 minutes) as capsules (diameter 1.2 cm; thickness: 0.5 cm). The final samples were labelled TCix and TPix (i=ibuprofen).

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 physiological solution 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).

The release was studied in four physiological solutions:

1. Commercial pH 7.4 buffered saline solution (TRIS BUFFERED SALINE SOLUTION, FLUKA)
2. Acid buffered solution (pH 1.2). This solution was prepared by dissolving 2.0 g of NaCl (Fluka) in 7.0 mL of HCl and making up to volume (1 L) with ultra-pure water. (U.S. PHARMACOPEIA)
3. Buffered solution (pH 6.8). This solution was prepared by dissolving 6.8 g of potassium phosphate monobasic (FLUKA) in 250 mL of water into a flask of 1 L. 77 mL of a solution 0.2 N NaOH (FLUKA) and 500 mL of ultra pure water were added. Then a solution 0.2 N NaOH was added until the desired pH (6.8). (U.S. PHARMACOPEIA)
4. Intestinal Simulated Fluid (pH 6.8). This solution was prepared by adding 10.0 g of pancreatine (ALDRICH) to the pH 6.8 buffered solution. (U.S. PHARMACOPEIA)

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 [33]:

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

where Ceff is the corrected concentration at time t, Capp 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 duplicate by collecting, each time, the data analysis simultaneously from two identical tablets.

Characterization

Specific surface area and pores size distribution were obtained from N_2 adsorption-desorption isotherms at 77 K (MICROMERITICS ASAP 2000 Analyser). Surface area was calculated by the BET equation [34], whereas the mesopores size distribution was determined by the BJH method [35], 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.

HR-TEM images were collected with a JEOL JEM 3010UHR (300 kV) transmission electron microscope fitted with a single crystal LaB6 filament and an Oxford INCA Energy TEM 200 energy dispersive X-ray (EDX) detector. All samples were dry deposited on Cu "holey" (200 mesh) carbon grids.

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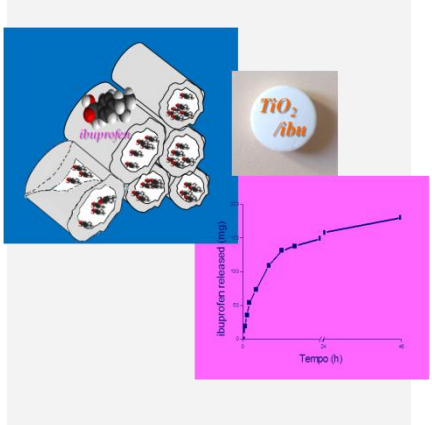
Structure directing agent for the synthesis of TiO_2-based Drug Delivery Systems



A series of titanium oxides was prepared by a surfactant template method (STM) and used as carrier to sustain the release of ibuprofen, chosen as model drug. The study has provided a series of useful information to the development of a TiO_2-based drug delivery device that can be specifically formulated for a particular therapeutic application.