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Cyclodextrin-grafted Barium Titanate Nanoparticles for improved dispersion and stabilization in water-based systems.

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ABSTRACT

Ceramic nanoparticles with piezoelectric properties, as BaTiO₃ (BT), constitute a promising approach in the fields of nanocomposite materials and biomaterials. In the latter case, the drawback of their fast aggregation and practically null stability in water has to be overcome to succeed in their preparation. The objective of this investigation has been the surface functionalization of BaTiO₃ nanoparticles with cyclodextrins (CDs) as a way to break the aggregation and improve the stability of the nanoparticles in water solution, preventing and minimizing the fast precipitation. As a secondary goal, we are able to achieve extra-functionality, bestowed from the hydrophobic cavity of the macrocycle, which is able to lodge guest molecules that can form inclusion complexes with the oligosaccharide. The nanoparticle functionalization has been fully tracked and characterized, and the cytotoxicity of the modified nanoparticles with fibroblasts and pre-osteoblasts cell lines assessed with excellent results in a wide range of

concentrations. The modified nanoparticles resulted suitable for the easy preparation of nanocomposite hydrogels, by dispersion in hydrophilic polymers of typical use in biomedical applications (PEG, Pluronics and PEO), and further processed in the form of films by water casting, showing very good results in terms of homogeneity in the dispersion of the filler. Likewise, as examples of application and with the aim of exploring a different range of nanocomposites, Rhodamine B was included in the macrocycles as a model molecule, and films prepared from a thermoplastic matrix (EVA) by high energy ball milling have been tested by impedance spectroscopy to discuss their dielectric properties, which indicated that even little modifications in the surface of the nanoparticles involve a different kind of interaction with the polymeric matrix. The CD-modified nanoparticles are thus suitable for easy preparation either of water-based nanocomposites as hydrogels or nanocomposites based on thermoplastic matrices.

1. INTRODUCTION

Nanocomposite materials, composed of polymers and nanostructures, lay behind most of the biomaterials being developed at the moment, as a small amount of nanoparticles can dramatically modify the properties of the matrix, empowering tailored compositions for different uses (**Gaharwar** et al. 2011). Recently, a wide range of inorganic materials as barium titanate (BaTiO_3 , BT), hydroxyapatite or synthetic silicates such as laponites have started to gain consideration for their prospective use in bioengineering due to their unique mechanical and chemical properties (**Wang** et al. 2013; **Gaharwar** et al. 2013; **Mamana** et al. 2015). Specifically, biocompatible nanocomposites have a key role in important fields of medicinal, chemical and biological research, arousing important innovations for bone regeneration, tissue engineering, implants or drug delivery systems

(**Shi** et al. 2010). BT is a perovskite-type ceramic, ferroelectric in all its crystalline phases except the cubic one. It possesses a high dielectric constant with piezoelectric properties on its tetragonal, orthorhombic and rhombohedral crystalline phases. These properties make BT useful for applications other than bioengineering, such as in electronics as printed circuits, piezoelectric sensors for ultrasonic transducers, capacitors and random access memories as some examples (**Ring** et al. 2003; **Yu** et al. 2011). However, BT has been replaced in some of these applications by multiceramic materials as lead zirconate titanates, or PZTs (**Park** et al.1997). On the other hand, the high processing temperature of these ceramic materials makes them unsuitable for many practical uses where polymeric materials are involved as in printed circuit boards (PCBs). This problem may be overcome by its preparation in form of polymeric nanocomposites, which are easily processable and with tuneable properties, and in order to do that, the first and most important requisite is to ensure a uniform dispersion of the filler, since the formation of particles agglomerates may lead to the unwanted discontinuity or deterioration of their properties. In some previous works we have described an easy, inexpensive and solvent-free way of achieving a good dispersion of the filler in thermoplastic-matrix nanocomposites, based on solid state methods as high-energy ball milling (HEBM) (**Serra-Gómez** et al. 2012). Nonetheless, biocompatible nanocomposites mostly require that their components are soluble in water, or at least stable in suspension in order to achieve an adequate dispersion of the filler. As PZTs are not suitable materials for most biomedical applications, due to the high toxicity of the lead components (**Sakai** et al. 2006; **Tsuchiya** et al. 2011), BT has been pointed as a good alternative provided that the stability issue is overcome; some examples are as second harmonic generators for imaging (**Dempsey** et al. 2013; **Hsieh** et al. 2010), as drug and gene delivery carriers

(**Ciofani** et al. 2010; **Jeong** et al. 2013), or as ceramic fillers in bone defects to promote its regeneration (**Feng** et al. 1997; **Baxter** et al. 2009). All the more, these nanomaterials have often been used as fillers in polymers and hydrogels that do not present the desired mechanical properties for the use they were intended for (**Huang** et al. 2007; **Schexnailder** et al. 2008; **Knauert** et al. 2007). Yet, the main difficulty to use BT in biocomposites is to achieve a uniform and stable dispersion in aqueous media since the nanoparticles tend to aggregate as a result of their high area-to-volume ratio (**Blanco-López** et al. 1997; **Paik** et al. 2002). These aggregates can reach sizes of a few micrometres (**Serra-Gómez** et al. 2012; **Gao** et al. 2015) and are a main drawback because of their high tendency to precipitate. The modification of the surface of the nanoparticles is a possible approach to improve the stability of the dispersions, either by adsorption on the surface of different substances like polyethylene glycol, PEG (**Čulić-Viskota** et al. 2012), polyacrylic acid ammonium salts, PAA-ammonium (**Jean** et al. 2005) and polyalcohols or by covalent bonding by first generating either amine (**FarrokhTakin** et al. 2012), phosphonic (**Kim** et al. 2007) or hydroxyl (**Chang** et al; 2009) groups on the surface for further grafting of molecules of interest.

Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6, 7 or 8 D-glucopyranose rings termed α , β and γ -CD respectively. Their sizes (ca. 1 nm) fall within the low limit of the nanometric scale so they can be considered as a limiting type of nanofiller. CDs are shaped like truncated cones, with a hydrophobic cavity and a hydrophilic exterior. The definite number of hydroxyl groups, according to the number of glucose units, makes it possible to establish strong interactions with certain polymeric matrices. One of the few applications of CDs with ceramic nanoparticles as TiO_2 and BT has to do with the stabilization of nanocrystals and nanoparticles in their hydrothermal-synthesis steps to

provide a shell for the nanocrystals to grow, allowing the sizes to be precisely controlled (2-10 nm) and therefore a better stabilization as the aggregation is suppressed (Li et al. 2006; Sun et al. 2008; Shiraishi et al. 2015).

In this paper we report on a novel method of disaggregation and water stabilization of commercially available BT nanoparticles of different sizes (50, 100 and 200 nm in diameter) by coating them with β -CD attached by hydrogen bonding forces to the previously generated –OH groups via the hydroxylation of the surface through reaction with H_2O_2 (**Choudhury** et al. 2012; **Hiroki** et al. 2005). As a consequence of that, the addition of the macrocycles on the surface opens the possibility of adding extra-functionality to the nanoparticles, as they can include different types of molecules and drugs of interest in their cavity (**Städe** et al. 2015). Another type of covalent modification via conjugation with oleate (SOA) as proposed by Chang et al. to improve the dispersion in organic solvents has been used, followed by the addition of α -cyclodextrin (α -CD), which is known to form supramolecular complexes via the inclusion of the hydrocarbon tail of the surfactant (**González-Gaitano** et al. 2000) proving by this method that the water stability is also enhanced when incorporating the CD to the surface of the nanoparticle.

With the modified nanoparticles, and as examples of possible applications, various types of nanocomposites have been prepared by changing the polymeric matrix and have been tested for their use in solid and in solution, confirming that the modified surface is able to endure both solid-state methods of dispersion (high energy ball milling, HEBM) as well as water casting methods. The cytotoxicity of the modified nanoparticles has been evaluated in different concentrations and cell lines and films have been casted in different polymeric matrices as poly (ethylene-co-vinylacetate), EVA, polyethylene oxide (PEO),

PEG and Pluronic® F127 (an amphiphilic PEO-PPO-PEO block copolymer) to show the ability of the nanoparticles to form stable suspensions and hydrogels to use in biomedical applications. The samples have been fully characterized by means of FTIR-ATR spectroscopy, thermogravimetric analysis, dynamic light scattering, X-ray diffraction and electron microscopy. The dielectric response of the films has also been evaluated to study the influence of the filler modification on the dielectric properties of the nanocomposites, showing that the individual properties of the components are maintained after the solid-state treatments.

2. MATERIALS AND METHODS

2.1. Materials.

Inorganic submicrometric particles of barium titanate (BT), with an average diameter size of 200 nm (99.9% purity, $\rho=6.02 \text{ g}\cdot\text{cm}^{-3}$ and tetragonal crystalline structure) and nanoparticles of 100nm (99.9% purity, $\rho=5.85 \text{ g}\cdot\text{cm}^{-3}$ and cubic crystalline structure) were supplied by Nanostructured and Amorphous Materials Inc. BT of 50nm in diameter was supplied by Sigma-Aldrich (99.9% purity, $\rho=6.08 \text{ g}\cdot\text{cm}^{-3}$ and cubic crystalline structure). Sodium oleate ($\geq 82\%$ fatty acids, as oleic acid) was supplied by Aldrich and α CD and β CD were supplied by Wacker as Cavamax®, W6 and W7, respectively. PEO with $4\times 10^6 \text{ g}\cdot\text{mol}^{-1}$ from Aldrich, polyethylene glycol, PEG, Mw of $10.000 \text{ g}\cdot\text{mol}^{-1}$ from Fluka, and Pluronic® F127 with an average Mw. of $12600 \text{ g}\cdot\text{mol}^{-1}$, have been used for the preparation and casting of water based composites. Poly (ethylene-co-vinyl acetate), EVA (12% w/w in vinyl acetate, density $0.933 \text{ g}\cdot\text{cm}^{-3}$ at 25°C , Vicat temperature of 65°C and melting point of 95°C) was supplied by Sigma Aldrich.

2.2 Sample preparation

i) Surface Modification. The process used for the modification of the nanoparticles consisted of three steps: a) Hydroxylation of BT by oxidation with H_2O_2 in a reflux setup for 4 h at 106 °C; b) Covalent bonding of SOA to the hydroxyl groups generated in the previous step by stirring a suspension of nanoparticles (2 wt%) in a SOA aqueous solution (0.5 wt%) for 3 h at 90 °C. c) Reaction with α -CD for 3 h at room temperature under vigorous stirring. Three washing and rinsing cycles were done in each step. In the case of the modification only with CD, the second step was skipped and the reaction with α -CD and β -CD was directly done on the hydroxylated surface. The resulting modified nanoparticles were freeze-dried and characterized.

ii) Cryo-HEBM. In order to make easier the subsequent blending process with the particles, EVA pellets were firstly ground in a MF 10 Basic IKA WERKE grinder at a rotation speed of 4500 rpm. A mixture of BT with EVA (20 wt%) was subjected to cryo-HEBM as described in our previous work (**Serra-Gómez** et al. 2012), followed by the film preparation as described by **Olmos** et al. (2011).

The nomenclature used for the samples during the synthesis and characterization is as follows: *BT* plus a number depending on the diameter size of the nanoparticles (1 for 100 nm and 2 for 200 nm) plus the coating applied; *-OH* for the hydroxyl generation, *-SOA* for the oleate, *-SOA- α CD* for the oleate plus cyclodextrin and *- α CD* and *- β CD* for the alpha and beta cyclodextrins, respectively.

2.3 Techniques

Attenuated total reflectance was used for the IR characterisation, using an FTIR-ATR Nicolette Avatar 360 spectrometer, with a resolution of 2 cm^{-1} and 32 scans per spectrum. Thermogravimetric analysis, TGA, was carried out in a TGA-SDTA 851 Mettler Toledo with a heating program from 25 °C to 600 °C at 10 °C/min under a N_2 atmosphere.

Fluorescence studies on the modified nanoparticles tagged with Rhodamine B (RhB) were done using an Edinburgh Instruments FLS920 spectrofluorimeter. Samples in a quartz cuvette of 10 mm of path length were excited at 553 nm and the emission recorded from 560 to 700 nm under constant stirring, averaging 5 scans with a 1 nm step and 0.1 s dwell time. Excitation and emission slits were set at 2 nm. 30 mg of CD-modified nanoparticles were put in contact with a $4 \cdot 10^{-6}$ M RhB solution and stirred for 1h. Then they were centrifuged at 8000 rpm for 30 min and the nanoparticles were separated from the supernatant and dried at 80 °C for 24 h.

The size distribution of the different particles was determined by dynamic light scattering (DLS) using a DynaPro photon correlation spectrometer. The particles were dispersed in deionized water by sonication and diluted before the measurements without further filtration. The intensity size distributions, expressed in terms of the hydrodynamic radius, R_h , were calculated by the method of regularization with DynaLS 1.0 software.

For the Zeta potential measurements, an electroacoustic-based zeta potential analyser (ZetaProbe of Colloidal Dynamics), specifically for the study of concentrated suspensions, was used. Alkaline pH was reached by addition of NaOH 0.1M and the titration from pH=12 to pH=3 was conducted with HCl 0.1M. For the Transmission Electron Microscopy (TEM) images the samples were treated with osmium tetroxide 1% and were kept at 4 °C for 1 h. Then a drop of the suspension was placed in a copper grid and phosphotungstic acid 2% as a negative contrast agent was applied. Samples were analyzed using a LIBRA 120 energy-filtering TEM (Zeiss) operated at 80 KV.

The cytotoxicity of the modified BT nanoparticles was tested on the fibroblast cell line NIH3T3 and MC3T3-E1 pre-osteoblasts. The Tetrazolium assay (MTT) was used to assess the viability of the cells, and therefore the cytotoxicity established by the loss of viable

cells upon treatment with the compounds of interest. The cells were incubated in Dulbecco's modified eagle medium from Life's Technologies, supplemented with 10% of fetal bovine serum and 0.1% of penicillin/streptomycin at 37 °C and 5% CO₂. Cells were seeded into 96-well plates at a concentration of 5x10⁴ cells/mL and 24 hours later the nanoparticles at different concentrations were added. MTT tests were conducted on day 3 and day 7 by addition of MTT 1 mg/ml and incubation of 3 h. The formazan absorbance at 540 nm was measured with a Thermo Scientific Multiscan EX microplate reader. DMSO was used as a positive control, and the appropriate negative controls were performed.

Impedance measurements in the frequency range 1 Hz–1 MHz were carried out at room temperature using an impedance analyzer SOLARTRON 1260A. A 3 V sinusoidal voltage signal was applied, measuring the current to finally obtain the complex impedance with its amplitude and phase over a range of frequencies (20 points per decade). Zview[®] software (Scribner Associates, Inc.) was used for the numerical fitting to the impedance data by considering a specific equivalent circuit. The measurements were performed on capacitors made by a dielectric film consisting on each sample in between two plate electrodes with circular surfaces of 1.25 cm in diameter. The thicknesses of the dielectrics were measured with a thickness meter Easy-Check FN of NEURTEK Instruments with an accuracy of ± 1 µm.

3. – RESULTS AND DISCUSSION

3.1. - Characterization of the surface modification of the BT nanoparticles.

The surface modification consists of a three-step process that can be easily followed by FTIR-ATR spectroscopy. Fig. 1a shows the spectra of the as received nanoparticles (BT, black trace) where the Ti-O stretching band can be seen in the fingerprint region starting

at 600 cm^{-1} ; the C-O band at 1452 cm^{-1} corresponds to vibrations coming from residual BaCO_3 from the synthesis method, usually deposited on the surface (**Chaudhary** et al. 2011). After the H_2O_2 treatment (BT-OH, red trace) the particles start showing the typical broad band of hydroxyl groups around 3300 cm^{-1} . On the other hand, when incorporating hydrophobic chains after the SOA reaction (BT-SOA, green trace), the characteristic bands at $2850\text{-}2910\text{ cm}^{-1}$ that relate respectively to the antisymmetric and symmetric stretching of the C-H bonds, together with their bending modes at $1510\text{-}1430\text{ cm}^{-1}$, are clearly seen. The spectrum of BT-SOA- α CD (navy blue trace) shows the inclusion complex of the α CD, as seen by the growth of the -OH band due to the CD hydroxyl groups and the 1154 cm^{-1} bands of the C-O-C vibrations. From 1700 to 1300 cm^{-1} the skeletal C-C vibrations appear, along with the stretching vibrations of C-H and C-O bonds at 1082 cm^{-1} . Lastly, the BT- β CD trace (light blue), shows how the -OH band and vibrations of the CD groups appear at the same wavenumbers than the previous one, but with considerable lower intensities, as expected due to the different proportions between the bulk nanoparticle and the CD on the surface.

Fig. 1a FTIR spectra of the BT nanoparticles along the different surface modification steps. BT as received (black), BT-OH (red), BT-SOA (green), BT-SOA- α CD (navy blue) and BT- β CD (light blue). **1b** TGA of the modified nanoparticles 100 nm (top) and 200 nm (bottom) with SOA and α CD (Left) and modified with α CD and β CD (right)

Due to the proportions between the nanoparticle and amount of modifier bound to the surface it can be challenging to fully characterize the three different steps of the modification process. In order to facilitate that, an estimation of the -OH groups that are

generated on the surface can be calculated from the weight loss of the samples analyzed by thermogravimetry. As the stoichiometry of the reaction between SOA and the OH is 1:1, we can estimate the maximum number of bound SOA molecules per nanoparticle, and compare it to the experimental results to assess the extent of the functionalization. On the other hand, considering the size of the α CD (4.7-5.3 Å), its height (7.1 Å) (Saenger et al. 1998) and the length of the SOA chains ($\approx$ 2 nm) (Lingley et al. 2013), it is expected that each SOA molecule can host a maximum of 3 α CD molecules; however, steric effects as the bending of the oleate due to the double bond and the proximity of other chains already including CDs might reduce that number. The composition of the coating can be followed by TGA as SOA and the CD decompose around 300 °C, while the ceramic nanoparticles remain intact; therefore the weight loss should indicate the weight percentage of the coating. Table 1 shows the results of the calculations as well as the experimental values obtained by TGA on the different nanoparticles for the SOA modification. As expected, the weight percentage of the decreases as the nanoparticle diameter increases, but always within the limits of the theoretical estimations.

Table 1: Theoretical and experimental values estimated by TGA of the wt.% of –OH and oleate groups upon modification of BT 50 nm nanoparticles (BT50), BT 100 nm nanoparticles (BT100) and BT 200 nm nanoparticles (BT200).

Sample	-OH (TGA loss)	Theoretical Maximum SOA (1:1)	Experimental SOA
BT50	3.4%	55%	14%
BT100	3.4%	53%	3.0%
BT200	2.2%	37%	1.8%

The decomposition of the CD can be attributed to the weight loss occurring between 315 °C and 350 °C, being the lower end of the range for the decomposition of CDs adsorbed in the surface and the higher value for the CDs with oleate chains included in them. The oleate loss takes place from approximately 368 °C to 507 °C, which corresponds to the

oleate chains that are covalently bonded to the surface; when free or weakly attached chains are considered, decomposition occurs at lower temperatures around 290 °C, as described **Ozel et al. (2013)**. As expected, the amount of SOA on the surface varies due to the variation on the surface-volume relation between the three sizes of nanoparticles. Fig. 1b shows the TGA thermograms of the BT100 and BT200 samples, exhibiting a coating well within the limits of the estimation done before for the SOA treatment. The weight loss values of the CDs and oleate thermal degradation are shown in Table 2.

Table 2: Weight loss percentage calculated from TGA of the modified BT nanoparticles in the temperature region of the CDs and oleate degradation.

BT Samples	α CD	SOA	BT Samples	α CD	β CD	CDs monolayer estimation
BT0.5+SOA		13.1%	BT0.5+ α CD	0.56%		0.23%
BT0.5+SOA+ α CD	21.1%	3.73%	BT0.5+ β CD		0.59%	0.21%
BT1+SOA		5.21 %	BT1+ α CD	0.75%		0.12%
BT1+SOA+ α CD	11.0 %	2.88 %	BT1+ β CD		1.31%	0.11%
BT2+SOA		1.84 %	BT2+ α CD	0.58%		0.06%
BT2+SOA+ α CD	14.2 %	1.31 %	BT2+ β CD		1.20%	0.05%

In the case of the modification only with CD the values are considerably higher than the ones expected from the previous estimation, so it is clear that there is not only a monolayer on the surface of the nanoparticle. It is known that CDs self-aggregate in water, both in native form or when forming complexes (**González-Gaitano et al. 2002**), so it is likely that a multilayer of CDs is formed on the surface of the nanoparticles, especially when the treatment involves having the precursors in solution at relatively high concentration and after further drying. In both cases, BT100 and BT200, the adhesion of CDs to the surface of the nanoparticles is larger when β CD is the one involved, which confirms the stated above since the β CD self-aggregation tendency is much higher than that of α CD (**González-Gaitano et al. 2002**).

However, the thermogravimetry results of the CD modified samples fall in the sensitivity range of the technique (1 wt%), and in order to confirm the presence of the CD layer, given that the values from TGA are relatively low and that the amount of CD is scarce for a reliable FTIR quantification, an alternative procedure was used, taking advantage of the inclusion complex formation between Rhodamine B (RhB) and β CD (Serra-Gómez et al. 2012). The modified nanoparticles were mixed with a RhB solution and both the fluorescence signal emitted by the solid samples as well as the fluorescence loss in the solution were measured.

After putting the nanoparticles together with the RhB solution an extensive adsorption of the RhB in the surface takes place, appreciated by the pinkish color acquired by the samples. Fluorescence measurements on the supernatant of the modified nanoparticles (Fig. 2) show a decrease in the emission of a 6% in relation to the untreated BT as well as an increase in the fluorescence of the solid (not shown), evidencing the formation of the inclusion complex between the RhB and the adsorbed CDs. It is also remarkable the decrease of the fluorescence yield of the BT-SOA modification, being a 35% loss over the native BT. In the case of the BT-SOA- α CD the long oleate chains are capped with the CDs and the fluorescence values show that, as the oleate chains are included in the CDs, the RhB molecules are hindered towards the long alkyl chains, with the subsequent reduction in the amount of RhB attached to the nanoparticle and its concentration increase in the supernatant. The last result is not only important because it provides evidence of the attachment of the CDs to the surface, but it opens a wide array of possible molecules that can be successfully carried and released from the CDs, using the BT as a nanocarrier in the body.

Fig. 2 Fluorescence emission of the supernatant of RhB $1.25 \cdot 10^{-7}$ M aqueous solution containing modified nanoparticles. The inset shows the fluorescence signal loss of the samples in relation to RhB

The aggregation behavior of all the samples has been tested by DLS. Figure 3 shows the intensity size distributions for the 50 nm nanoparticles (the corresponding peak analyses are shown in SI Table 1). A strong aggregation of the native nanoparticles (black trace) can be perceived, with an important contribution of agglomerates of around 300nm and >1000nm in diameter. However, with the SOA-αCD complex (green trace in Figure 3 left), as well as with βCD (blue trace in Figure 3 left), the disaggregation is notably improved (50-80 nm). This corroborates that the first step to achieve a proper dispersion for an improved suspension in water is to break up the aggregates. The stability in suspension of these samples was tested with a Z-potential analyzer on a pH range from 3 to 12. Figure 3 (right) shows a significant change in the modified samples reaching potentials -200 mV for

the BT50- β CD (green trace upper graph) and -100 mV for the BT200- β CD (green trace bottom graph) when pH is in the physiological range between 7 and 11.

Fig. 3a Intensity size distributions of as received and modified BT 50 nm nanoparticles. **3b** Z-potential measurements of 1 wt%. suspension of native and modified BT samples

These Z potential values, together with the above presented data suggest that the modified samples with oleate and CDs as well as the ones with β CD present a stability

improvement in the mentioned pH range, as the modifications involve enough change in the surface charge to prevent aggregation, in contrast to the untreated nanoparticles, as a result of the presence of the high density of hydroxyl groups on the β CD. The difference in Z-potential values is in accordance with **Paik et al. (1998)** where they state the direct dependence on the percentage of BT surface covered with the solution stability. As stated previously, the modification with CDs alone yields a multilayer due to the CD self-aggregation and therefore a higher percentage of surface coverage than when the SOA treatment is applied. An example of the improved dispersion of the nanoparticles in water can be seen in the supplementary data photographs of samples after 4 h (SI, fig 1). TEM microscopy was performed upon selected samples, to show the difference in the nanostructure upon functionalization. The untreated nanoparticles (Fig 4 left) present a homogeneous surface, while the –SOA- α CD modified ones (Fig 4 right), display a surface with a variation of dark tonalities resulting from the osmium oxide reaction with the SOA unsaturation, which proves the presence of the functionalization all over the surface.

Fig. 4 TEM image of the commercial BT 100nm (left) and the BT-SOA- α CD modified nanoparticles (right)

3.2 Cytotoxicity.

The cytotoxicity of the CDs modified BT has been assessed in a wide range of concentrations from 0 to 200 $\mu\text{g/ml}$. By reviewing the literature on BT cytotoxicity, mainly the studies of **Dempsey** et al. (2013) and **Ciofani** et al. (2010), it seems clear that the coating plays a crucial role as it can noticeably change the way the cells interact with the BT, and represent the main contribution to the cytotoxicity. In our case, the CD coating seems to allow higher concentrations of nanoparticles without any negative effect in the cell viability. Figure 5 shows the MTT assay results for the BT-CD, which show excellent viability of the cells even up to concentrations of 200 $\mu\text{g/mL}$ after a week of treatment with significant improvements in the cell proliferation at concentrations of 100 $\mu\text{g/mL}$ and 200 $\mu\text{g/mL}$ according to the ANOVA and Student's T test ($p < 0.01$; $n = 12$).

Fig. 5 MTT results for NIH3T3 cells and Barium Titanate nanoparticles modified with βCD . 50nm nanoparticles are represented in the blank bars and 200nm nanoparticles in the patterned bars (Left). Notes: ** denotes $p < 0.01$ by ANOVA variance test and Student's T Test. The confocal image (Right) shows the MC3T3-E1 cells after 14 days of culture. Cell nuclei are stained blue, actin in green and the BT- βCD appears in red

The same nanoparticles were tested against the MC3T3-E1 cell line and phase contrast (SI Fig 2, 3) and confocal images were taken at days 3, 7 and 14 after treatment. The confocal image shows how, after 14 days of treatment the nanoparticles (200 $\mu\text{g/ml}$, red) are internalized in the tissue formed by the cells that grew normally. Other images of the sequence are presented in the SI (fig. 2 and 3). The βCD modification, as opposed to other

coatings used to disperse BT, does not present a cytotoxic effect in the concentrations studied.

3.3 Examples of Application

As examples of the improvement achieved by the surface modifications, two cases will be shown in which the nanoparticles have been used to prepare different types of nanocomposites: one by water casting with EO based -polymers to obtain a nanocomposite hydrogel, and another one by cryo-HEBM as the processing method from a thermoplastic matrix. Lastly, the outcomes of these two examples of application will be tested by impedance spectroscopy to study the effect of the BT modification on some electrical properties of the composites. This is a common technique to study the capacitance and the relaxation behavior of the nanocomposite films, particularly in those containing nanofillers with ferroelectric or piezoelectric properties, for their use as capacitors or as sensors and actuators (Beier et al., 2010).

a) Interaction of the modified nanoparticles with water-soluble hydrogel matrices.

Firstly, in order to test the preparations based on the modified NP with polymers, 15 wt%. solutions of PEG and Pluronic® F127 were prepared and mixed with 10 wt%. of commercial and modified nanoparticles. These two polymers have been chosen as they are commonly used as hydrogel substrates and have a similar average molecular weight. Therefore the different interactions with the surface should be mainly derived from their structures and the modifications applied. Based on the coating of the nanoparticles (type of modification) by the polymers, it can be seen in Figure 6 how the Pluronic® F127 presents a higher interaction than the PEG chains as seen by the weight loss in the 300-400 °C range. The effect is even bigger when α CD is on the surface, as it is known to form an inclusion complex with the PEO chains of the F127, opposed to the β CD that due to its

size is able to enter the chain and for the complex with the inner PPO chain (Larrañeta et al. 2012). As a result, the interaction of the particles with the hydrogel matrix can be tailored to some extent by the type of CDs attached to the surface.

Fig. 6 Coating of PEG and Pluronic® F127 on the BT nanoparticles before and after the different surface treatment.

Interaction of the modified nanoparticles with thermoplastic polymers and solid state dispersion methods.

On a second step we mixed by cryo-HEBM the modified BT with EVA at a 20 wt%. proportion to ensure the surface modifications applied are kept and contribute to achieve a good dispersion in solid state preparations. The powders were processed into films and characterized by FTIR-ATR and TGA to evaluate the effect the HEBM produces on the nanoparticles and its surface modifications. The main bands of the EVA polymer are in the same positions as the SOA ones (SI Fig. 4), as they mainly consist of -CH₂- groups.

However in the samples where α CD is added an absorbance increase of the -OH band over 3000 cm^{-1} as well as that of the characteristic bands of the CD at 1000 , 1078 and 1150 cm^{-1} can be observed. In the samples where only the CDs are attached to the nanoparticles their characteristics bands in FTIR cannot be seen well (SI Fig. 5), being hidden under the EVA ones due to the low amount of oligosaccharide (the CDs represent just 1% of the filler in this case, which corresponds the 20 wt% of the composite with EVA, accounting for the small contribution of the small band from the CDs OH groups above 3000 cm^{-1}).

Similar conclusions can be extracted from the TGA analysis (SI Fig. 6). The EVA thermodegradation occurs within the same temperature range than the SOA and CD. The degradation process for the thermoplastic takes place in two stages. In the first one, deacylation with the loss of acetic acid and the formation of double bonds occurs between 300 and $400\text{ }^{\circ}\text{C}$, with a maximum rate of degradation at around $370\text{ }^{\circ}\text{C}$. In the second step the olefin degradation between 450 and $520\text{ }^{\circ}\text{C}$ takes place (**Zattera et al. 2005**). Both processes overlap the SOA and CD ones, so only the proportion between the total amount of filler and the polymeric matrix can be deduced from the thermal analysis. Lastly, as another example of the dispersion from water casting, the nanoparticles were dispersed in a 1% (w/v) polyethylene oxide aqueous solution. As a result thin films were obtained as shown in Fig. 7 (right), where the uniform dispersion achieved is comparable to that obtained by solid-state methods (Fig. 7 left).

Fig. 7 Films casted from EVA samples prepared by HEBM (left) and PEO samples prepared by water suspension (right)

Impedance Spectroscopy tests on films prepared from solid and water based precursors.

In the frequency response analysis (FRA, impedance spectroscopy) the magnitude being measured is the complex impedance of the samples. The dielectric parameter as a function of frequency is described by the complex impedance in the form of (Tripathi et al. 2012):

$$[1] \quad Z = Z' + iZ''$$

where Z' and Z'' are real and imaginary part of the complex impedance.

$$[2] \quad Z(\omega) = \frac{U(\omega)}{I(\omega)} = \frac{1}{i\omega C(\omega)} \quad [3] \quad C(\omega) = \frac{A}{d} \epsilon(\omega)$$

The capacitance is defined by [3]. A being the area of the dielectric and d the thickness of the sample. The polarization phenomenon exerted by the oscillatory electric field applied during the FRA measurement can be modeled in many dielectric materials using a series RC circuit connected in parallel with another capacitor, which has been the model to fit the experimental (SI Fig 7). From this equivalent circuit and taking into account the Debye model (Scaife 1998) the following parameters can be deduced (Jonscher 1983):

$$[4] \quad \epsilon_s = \frac{C_1 + C_2}{\frac{A}{d}} \quad [5] \quad \epsilon_\infty = \frac{C_2}{\frac{A}{d}} \quad [6] \quad \tau = R_1 C_1$$

Where C_1 and C_2 are the capacities values associated to the bulk and the interphase respectively as C_1 relates to the atomic polarization and C_2 to the fastest dipoles, and from

them, the real and imaginary parts of the permittivity as well as the loss factor can be obtained. The values thus calculated have been gathered in Table 3, where the low error values indicate the goodness of fit.

Table 3: C1, C2 and R-values calculated from Impedance Spectroscopy on selected samples.

Sample	C1 (nF)	R1 (M Ω)	τ (x10 ² s)	C2 (pF)
EVA	9.3 $\pm$ 0.2	9.01 $\pm$ 0.09	8.4 $\pm$ 0.1	54.1 $\pm$ 0.4
EVA + BT100	9.3 $\pm$ 0.2	8.92 $\pm$ 0.08	8.3 $\pm$ 0.1	52.4 $\pm$ 0.4
EVA + BT1-SOA-αCD	9.3 $\pm$ 0.2	8.92 $\pm$ 0.08	8.3 $\pm$ 0.1	66.3 $\pm$ 0.5
EVA + BT2-SOA-αCD	9.3 $\pm$ 0.2	9.00 $\pm$ 0.09	8.3 $\pm$ 0.1	65.3 $\pm$ 0.5
EVA + BT1-αCD	9.3 $\pm$ 0.2	8.94 $\pm$ 0.08	8.3 $\pm$ 0.1	47.0 $\pm$ 0.4
EVA + BT2-αCD	9.3 $\pm$ 0.2	8.93 $\pm$ 0.08	8.3 $\pm$ 0.1	58.6 $\pm$ 0.5
EVA + BT1-βCD	9.3 $\pm$ 0.2	8.92 $\pm$ 0.08	8.3 $\pm$ 0.1	47.5 $\pm$ 0.4
EVA + BT2-βCD	9.3 $\pm$ 0.2	8.93 $\pm$ 0.08	8.3 $\pm$ 0.1	52.4 $\pm$ 0.4
PEO	26 $\pm$ 2	2.65 $\pm$ 0.07	6.8 $\pm$ 0.1	113 $\pm$ 3
PEO + BT-αCD	11.6 $\pm$ 0.4	6.40 $\pm$ 0.09	7.4 $\pm$ 0.1	119 $\pm$ 2

The two sets of samples present significant differences. In the case of the samples prepared by HEBM there is no difference in the capacity of the bulk (C1) in the EVA alone or with the BT nanoparticles, which is also expected due to the low relative amount of filler. However, in the case of the capacity associated to the interphase there are differences that can be attributed solely to the different modifications of the nanoparticles since they are higher than the defined errors. While EVA and EVA+BT100 (without modification) present the same values, in the case of the nanoparticles have been modified with oleate and CD there is a 20% increase. For the samples modified only with CDs the difference appears for the samples of BT 100 nm with higher changes than

those obtained for BT 200 nm, regardless the type of CD probably because a higher polar surface area is facilitating the polarization. In the case of the water casted PEO the opposite trend is seen, with a dramatic decrease in the C1 contribution when the nanoparticles are dispersed in the polymer and a two-fold increment of the resistance, while the interphase contribution remains practically the same. In this case, the contribution of the nanoparticles to the PEO system is by far more important than to the EVA one, as they intercalate in the PEO chains and therefore change their structure, crystallization and rearrangement capacity in the system, similar to what Scrosati et al. mention in their study of PEO nanocomposites (**Scrosati et al. 2000**).

Fig. 8 Impedance spectroscopy loss factor measurements on selected samples with BT: EVA samples (left) and PEO samples (right)

These different behaviors can be better visualized in the loss tangent plots (Figure 8) showing a decrease in the height of the peaks as well as a shift to lower frequencies upon addition of the BT. As the relaxation behavior in polymeric nanocomposites depends on the interaction of the filler with the polymeric matrix, it can be concluded that the observed shifts are the result of the modifications made to the BT leading to slightly different interactions between the matrix and the nanoparticles surface. The differences

also show that the modifications produced on the nanoparticles are kept despite the high-energy conditions of the HEBM or the milder ones of the water casting process.

4. CONCLUSIONS

A novel way of modification of barium titanate nanoparticles has been achieved by the incorporation of cyclodextrins to their surface, for their potential use as nanofillers in nanocomposites. While oleate-modified particles also present some degree of aggregation in water, due to the hydrophobicity of the chains, once the hydrocarbon tails have been included in the cavity of the α CDs the stability of the suspension over time is increased. However, when incorporating α CD and β CD directly on the surface the disaggregation takes place much faster and is maintained through the same period of time, becoming an easier, faster and cleaner way of modification. Moreover, the addition of CDs bestows the nanoparticles extra-functionality due to the wide array of host-guest interactions that can be formed within the CD cavity, as tested by analyzing the fluorescence of rhodamine B that is included in the macrocycles, attached to the nanospheres surface. This opens a whole range of potential uses for these nanoparticles by their combination with drugs and molecules that could be transported and released in a controlled way, particularly in the case of biocomposites. The cytotoxicity of the modified nanoparticles with fibroblasts and pre-osteoblasts cell lines has been assessed with excellent results in a wide range of concentrations. The surface modification with CDs allows the nanoparticles to be suspended in aqueous solutions of different polymers (PEO, PEG and Pluronic F-127) and the further casting of films, with very good results of homogeneity. The same conclusion is reached with the films obtained from the solid mixtures produced by HEBM with a thermoplastic polymer (EVA). In the latter case, the

data obtained by impedance spectroscopy suggest that even little modifications in the surface of the nanoparticles involve a different kind of interaction with the polymeric matrix, as seen by the changes in the dielectric behavior. The modified nanoparticles are thus suitable for easy preparation either of water-based nanocomposites as hydrogels or nanocomposites of thermoplastic matrices.

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