INTERACTION OF BISPHOSPHONATE (RISEDRONATE) WITH HYDROXYAPATITE NANOCRYSTALS MODIFIED WITH POLYETHILENIMINE (PEI).

Sodium risedronate, (1-hydroxy-2-(3- pyridinyl) ethylidene) bisphosphonic acid monosodium salt (Fig. 1), is a member of the drugs called nitrogen-containing bisphosphonates (N-BPs).

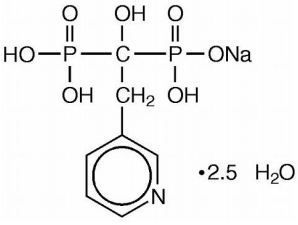


Figure 1 chemical structure of Risedronate monosodium salt

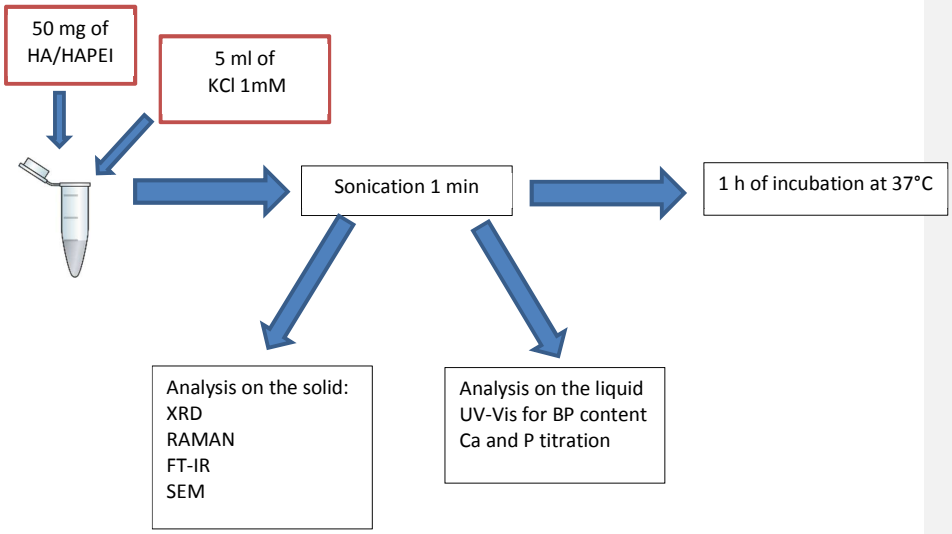
Bisphosphonates (BPs) are synthetic pyrophosphate analogs, in which the P-O-P group is replaced by the P-C-P bridge. Like pyrophosphatse, BPs present a high affinity to adsorb onto apatite crystals, and they have been shown to prevent mineral dissolution. Moreover these molecules inhibit bone resorption by controlling osteoclast cells activity and are widely used for the treatment of osteoporosis and other metabolic bone diseases such as Paget's disease, osteogenesis imperfecta and bone metastases. BPs with nitrogen containing R2 sidechains (N-BPs) display a dramatic inhibition of osteoclast mediated bone resorption, due to their action on the enzymes within the mevalonic acid pathway. [1]

On this basis, the objective of this project is to synthesize and characterize hydroxyapatite nanocrystals (HA) at different BP contents and at tailored drug release kinetics. To this aim, the processes of adsorption / desorption of BPs onto HA has been investigated in details. The study has also been performed on HA functionalized with polyethyleneimine (PEI), HAPEI, prepared according to two different routes: direct synthesis of HA in aqueous solution containing different amount of PEI and adsorption of PEI on pre-formed HA nanocrystals. The presence of PEI, which is a polycationic polymer, should increase the number of positive charges on HA nanocrystals, and thereby promote the adsorption of bisphosphonate from solution and control its release. In fact, the planned research activities produce new calcium phosphate based materials with modulable bioactivity, bioresorption and osteogenecity, able to provide a tailored local release of the antiresorptive drugs.

The study on adsorption / desorption of BPs on apatite materials and the characterization of these samples were performed in the CIRIMAT Laboratory in Toulouse (France), in the research group of Prof. Christèle Combes. The techniques used for the characterization of the powder samples are the following: X-ray diffraction, FT-IR and Raman spectroscopies, Scanning electron microscopy (SEM) and specific surface area measurement by Brunauer–Emmett–Teller method (BET). Complementarily, the analyses of BPs and PEI concentrations released in solution were performed by UV spectrophotometry and chemical analysis.

The characterisation by FTIR and Raman spectroscopies of the HA and HAPEI powders after adsorption confirm the presence of BPs on the solids. No additional crystalline phase was observed by XRD and SEM observations.

In the following scheme is illustrated the procedure for the preparation of the sample to obtain the point for the construction of the Langmuir model.



The adsorption isotherms were obtained by plotting the quantity adsorbed of BPs on the solids (Qads expressed in mg of BPs / m^2 of HA or µmol / m^2) in function of the concentration of BPs in the solution at equilibrium (Ceq expressed in mol / L). The isotherm of BPs on HA was Langmuirian in shape, in accordance with the literature [3]. The Langmuir model is based on the following key assumptions:

• adsorption is localized and reversible;

• adsorption sites are energetically equivalent

These assumptions imply that each site can adsorb a maximum of one molecule of solute, and that the probability of adsorption is the same for each site. The formula of the Langmuir isotherm is:

$$Qads = N * \frac{(K * Ceq)}{1 + (K * Ceq)}$$

Where:

N is the amount of BPs adsorbed at saturation, expressed in µmol of BPs / m^2 of HA

K is the affinity Langmuir constant of BPs for the surface of HA, expressed in L / mol

This work is aimed to clarify the interaction of risedronate with two different apatitic supports, a well-crystallized hydroxyapatite (HA) and HA with PEI. The results show that model obtained for isotherm of adsorption of the BP on HAPEI powder seem to be different from HA, putting in evidence the influence of PEI on BP adsorption on apatitic surface. Further experiments have to be performed to understand such mechanism of adsorption.

[1] R.G.G. Russell. Bone, 2011, 49, 2–19.

[2] C.T Leu, E. Luegmayr, L.P. Freedman, G. A. Rodan and Reszka. Bone, 2006, 38, 628–36

[3] P. Pascaud, P. Gras, Y. Coppel, C. Rey, S Sarda. Langmuir,2013,29,2224-2232

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