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Experimental and in silico investigations of organic phosphates and phosphonates sorption on polymer-ceramic monolithic materials and hydroxyapatite

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ABSTRACT

A method based on experimental and in silico evaluations for investigating interactions of organic phosphates and phosphonates with hydroxyapatite was developed. This quick and easy method is used for determination of differences among organophosphorus compounds of various structures in their mineral binding affinities. Empirical sorption evaluation was carried out using liquid chromatography with tandem mass spectrometry or UV–VIS spectroscopy. Raman spectroscopy was used to confirm sorption of organic phosphates and phosphonates on hydroxyapatite. Polymer-ceramic monolithic material and bulk hydroxyapatite were applied as sorbent materials. Furthermore, a Polymer-ceramic Monolithic In-Needle Extraction device was used to investigate both sorption and desorption steps. Binding energies were computed from the fully optimised structures utilising Density Functional Theory (DFT) at B3LYP/6-31 + G(d,p) level. Potential pharmacologic and toxic effects of the tested compounds were estimated by the Prediction of the Activity Spectra of Substances using GeneXplain software.

1. Introduction

The pharmacological effect of bisphosphonates (BPs) is related to their binding to mineral bone and their biochemical effect on cells, predominantly osteoclasts. Preclinical studies with different BPs showed that these antiresorptive agents not only inhibit bone loss, but can also increase bone mass and its resistance to fracture. Various investigations have been performed to elucidate molecular interactions between BPs and bone or calcium phosphate to better understand their retention phenomena. Although some studies have reported the release of phosphate ions during adsorption of several molecules, including BPs, suggesting an ion exchange reaction, this phenomenon has rarely been quantified, and the adsorption process remains unclear (Ebetino et al., 2011; Errassifi et al., 2014; Graham and Russell, 2011; Zacharis and Tzanavaras, 2008).

The differences in mineral binding affinity might be expected to influence the length of the inhibition of bone resorption process to recover after bisphosphonate therapy. Accumulation of these drugs on bone may also influence crystal behaviour in a way that contributes to their pharmacologic actions (Nancollas et al., 2006). The differences among BPs in binding to hydroxyapatite (HA) are associated with the long duration of the action. It was proved that BPs can be found in plasma and urine many months after dosing. This means that BPs must be present in the circulation and available for reuptake into bone for prolonged periods (Graham and Russell, 2011).

The strong affinity of the BPs for HA can be explained by the presence of the P-C-P linkage combined with two side chains, one of which is usually the hydroxyl group (R^1) (Kos et al., 2011). Recent studies on mineral binding have shown that there are hitherto unexpected differences between BPs, indicating that not only the P-C-P structure, but also R^2 side chains must contribute to mineral binding (Graham and Russell, 2011). Nitrogen-containing bisphosphonates, e.g., alendronate and risedronate (structure see in Table 1), were found to be 10–100-fold more potent than those that did not have it (Zacharis and Tzanavaras, 2008). The physicochemical interactions of risedronate with synthetic nanocrystalline apatite as a model bone mineral were investigated by Errassifi (Errassifi et al., 2014). In these studies the authors suggested that risedronate adsorption on the apatite scaffold corresponds to an ion substitution reaction with phosphate ions at the crystal surface.

The proposed method of assessing the usefulness of the tested compounds as antiresorptive drugs was divided into three key steps as follows: *i*) the sorption examination on polymer-ceramic monolithic material and bulk HA; *ii*) the potential pharmacologic and toxic effects

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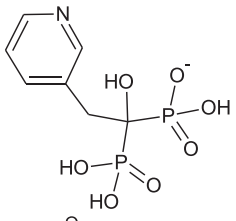
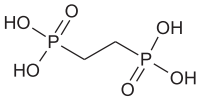
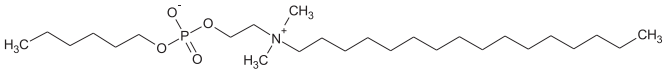
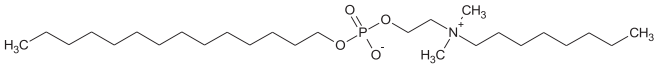
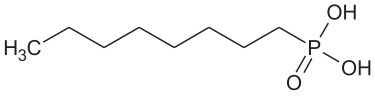
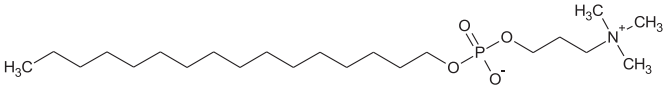
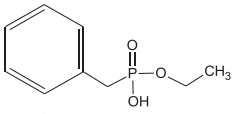
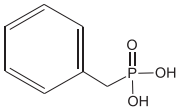
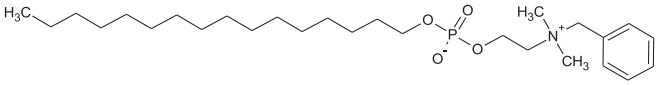
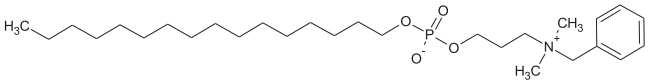
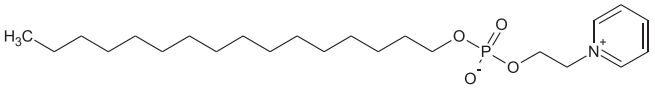
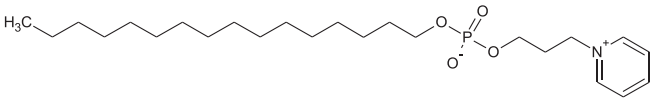
Table 1
Structures of organophosphates used in this study.

Comp.	Name	Structure
1	Risedronate	
2	Ethane-1,2-diphosphonic acid	
3	2-[Dimethyl-(hexyl)ammonio]ethyl hexadecyl phosphate	
4	2-[Dimethyl-(octyl)ammonio]ethyl tetradecyl phosphate	
5	Octylphosphonic acid	
6	Hexadecyl 3-(trimethylamminio)propyl phosphate	
7	Ethyl benzylphosphonate	
8	Benzylphosphonic acid	
9	2-[Benzyl-(dimethyl)ammonio)propyl hexadecyl phosphate	
10	3-[Benzyl-(dimethyl)ammonio)propyl hexadecyl phosphate	
11	Hexadecyl 2-(pyridinium-1-yl)propyl phosphate	
12	Hexadecyl 3-(pyridinium-1-yl)propyl phosphate	

of tested compounds estimated by Prediction of the Activity Spectra of Substances (PASS) program; *iii*) the binding energies computed from the structures fully optimised using B3LYP/6-31 + G(d,p) method with Gaussian 09.

In many cases, HA has been used as a model of bone surface. Sorption experiments on ceramic materials were conducted with a number of different chemicals. Adsorption experiments of risedronate were carried out by Errassifi et al. (Errassifi et al., 2014) at the temperature of the human body (37 °C). The adsorption of Sn(II) on HA as a model for the mineral phase of bone was studied in vitro in the presence of either 1-hydroxy-ethylidene-1,1-diphosphonate or methylenediphosphonate by Claessens and Kolar, (2000), (Nancollas et al., 2006). Sorption experiments were also conducted with Gd(III) and Tb(III) complexes using HA by Kubicek et al. (Kubıcek et al., 2005). Bulk HA was applied for the preparation of solid phase microextraction fiber (Feng et al., 2011). In this case, nanostructured HA was used as a coating by a process of polydopamine-assisted biomineralisation. Monolithic polymer-ceramic material has been used mainly as a stationary phase in HPLC, although it has been also used as a solid-phase sorbent by Pinto et al. (Pinto et al., 2010) for the selective enrichment of casein phosphoproteins/phosphopeptides (CPP) from complex mixtures. Krenkova et al. (Krenkova et al., 2010) prepared poly(2-hydroxyethyl methacrylate-*co*-ethylene dimethacrylate) monolithic stationary phases embedded with the commercially available HA nanoparticles. This type of monolithic material was used in this work as a sorbent material in a MINE device. In our previous work, the MINE device was presented (Pietrzyńska et al., 2013a; Pietrzyńska et al., 2013b; Pietrzyńska and Voelkel, 2014) as a tool used for analytes extraction directly from water samples. Incorporation of a polymer-ceramic monolithic material in the stainless steel needle should allow to obtain a device for investigation of the interactions between analytes (drugs) and HA.

PASS allows the evaluation of the general biological potential of small-molecule organic substances based on their 2D structural formulas. PharmaExpert analyses the relationships between biological activities, drug-drug interactions and multiple targeting of chemical