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Ion exchanges in apatites for biomedical applications

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The modification of the composition of apatite materials can be made by several processes corresponding to ion exchange reactions which can conveniently be adapted to current coatings and ceramics and are an alternative to setting up of new synthesis methods. In addition to high temperature thermal treatments, which can partly or almost totally replace the monovalent OH^- anion of stoichiometric hydroxyapatite by any halogen ion or carbonate, aqueous processes corresponding to dissolution-reprecipitation reactions have also been proposed and used. However, the most interesting possibilities are provided by aqueous ion exchange reactions involving nanocrystalline apatites. These apatites are characterised by the existence on the crystal surface of a hydrated layer of loosely bound mineral ions which can be easily exchanged in solution. This layer offers a possibility to trap mineral ions and possibly active molecules which can modify the apatite properties. Such processes are involved in mineralised tissues and could be used in biomaterials for the release of active mineral species.

1. Introduction

One of the most interesting properties of apatites is their ability to accept ionic substituents and vacancies. Although living creatures have fully used these abilities to adapt mineralised tissues to their physiology and functional needs [1, 2], substituted apatites are only starting to be developed in elaborate tailored biomaterials and some of them have been shown to exhibit improved biological properties compared to stoichiometric hydroxyapatite (HA) [3–7]. Most substituted apatites are obtained by synthesis and, in addition to bulk composition alterations, modifications of crystal size, morphology, surface composition, physical-chemical properties (zeta potential, surface energy, solubility) and materials properties (microstructure, texture, porosity) may also occur which prevent the clear identification of the factors involved in the biological behaviour of these materials [6]. Ion exchange processes have been the subject of various studies and are an interesting alternative to synthesis to fully or partly modify the composition of apatite and their properties in a controlled way. Considering the generic chemical formula of apatites:

$$Me_{10}(XO_4)_6(Y)_2,$$

where Me are bivalent cations, XO_4 trivalent anions and Y monovalent anions, high temperature reactions allow the exchange of Y ions and in a few cases, removal of some cations. However, most exchange reactions involved in living beings concern nanocrystalline apatites and are related to the exchange of surface ions. These ionic exchanges play a significant role in homeostasis and in intoxication (and sometimes detoxification) by mineral ions, but at a very different time scale they also seem to participate in slower phenomena resulting in diagenetic alterations of geologic sediments and fossils. Such exchanges are made possible because of the very high specific surface area of the nanocrystals but also, essentially, because of the existence of a metastable hydrated layer on the crystal surface containing loosely bound ions [8]. The aim of this report is to review and describe some of the ion exchange processes in apatites and their related effects on materials properties and biological behaviour.

2. Types of ion exchange

2.1. High-temperature exchange reactions

High-temperature exchange reactions were the first to be used to change apatite composition. Thus Elliott and Young [9] prepared the first synthetic HA monocrystals from Chlorapatite monocrystals obtained by a flux method, and solved the crystal structure of HA [10]:

$$Ca_{10}(PO_4)_6Cl_2 + 2H_2O \leftrightarrow Ca_{10}(PO_4)_6(OH)_2 + 2HCl \quad (I)$$

The exchange reaction involved only ion diffusion at temperature close to 1300 °C and kept the monocrystals unchanged. Several other reactions were then done

using this principle and it is now possible to replace virtually any Y ion from the apatite structure using an adequate gaseous atmosphere. Thus, the reverse of reaction (I) can also be used to prepare chlorapatite from HA crystals and similar reactions may be carried out to prepare fluorapatite, bromapatite or carbonate apatite (type A, where two OH^- ions are replaced by one CO_3^{2-} ions) [11]:

$$Ca_{10}(PO_4)_6(OH)_2 + 2HX \leftrightarrow Ca_{10}(PO_4)_6X_2 + 2H_2O \quad (X = Cl, F, Br) \quad (II)$$

$$Ca_{10}(PO_4)_6(OH)_2 + CO_2 \leftrightarrow Ca_{10}(PO_4)_6CO_3 + H_2O \quad (III)$$

Although fluorapatite is among the most stable apatites it is also possible to replace F^- ions at high temperatures by Cl^- ions using several chlorinated compounds (SO_2Cl_2, PCl_5, $POCl_3$, or even Cl_2):

$$Ca_{10}(PO_4)_6F_2 + 2Cl_2 \leftrightarrow Ca_{10}(PO_4)_6Cl_2 + 2ClF$$

The advantage of these processes is that they can be easily performed from existing HA (or FA) syntheses and they do not generally disturb, the ceramic microstructure (crystal size, porosity) provided the exchange temperature is lower than 1000 °C. All these reactions involve ion diffusion in apatites and in some cases restructuring. Of course, the reaction rates depend on the temperature, on the size of ions and crystals, and on the porosity of the ceramics. Thus fluoridation and chloridation of HA are relatively fast reactions and crystals of a few hundred of microns can be totally exchanged in a few hours at 1000 °C. Conversely, carbonation appears much slower.

These processes have been applied to study the effect of carbonation in type A position on biological properties [12, 13]. The surface of a dense HA ceramic could be totally transformed into type A carbonate apatites. The carbonation induced a decrease in the dipolar component of the surface energy and resulted in a lower initial adhesion and spreading of osteoblast compared to HA associated with a lower production of collagen [12]. The same samples showed a poor adhesion of osteoclasts and a low resorption ability [13].

High-temperature solid-gas reactions, using chlorinated gas, may also be used to remove volatile metal chlorides. These reactions have been applied to the recovery of uranium and rare earth elements from apatitic ores as well as elements like V and Mn. They could be used for the purification of HA ceramics and the removal of trace elements [14].

2.2. Low-temperature aqueous ion exchange reactions involving well crystallised apatites

Although low-temperature exchange reactions have also been described [15], they generally occur in aqueous media and they in most instances involve a dissolution-reprecipitation mechanism. This type of reaction may be used to partly or totally alter the surface composition of ceramics or coatings. In order to use this process the resulting apatite may be less soluble than the starting compounds in the solution conditions. This is the case, for example, of fluoride uptake by HA. Due to the existence of solid solution and epitaxial growth however surface equilibration often occurs limiting the extent of the pseudo-exchange phenomenon especially at low temperatures. However these reactions are useful and they have been proposed for the transformation of coatings and ceramic surfaces. They essentially lead to more stable and less absorbable coatings with an increased surface area, nucleation ability and adsorption properties.

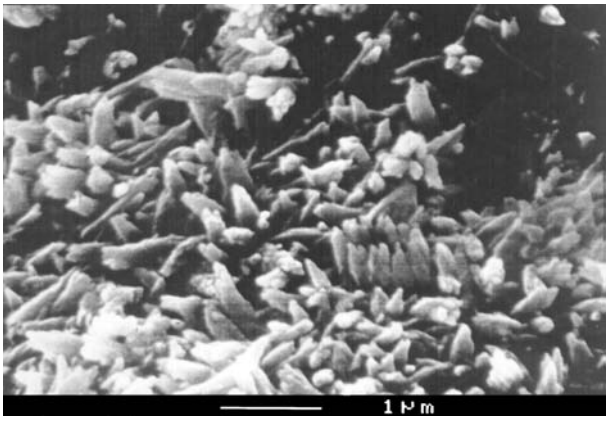

Figure 1 SEM micrograph of a vacuum plasma sprayed HA coating after treatment in a fluoridating solution (KF: 0.05 M; KH_2PO_4: 0.15 M; pH: 7, temperature: 100 °C, 10 h). The layer is made up of thin needle-like crystals (0.5 to 3 μm long, 0.1–0.3 μm width). The fluoridation rate was close to 80%.

As an example, aqueous fluoridation of plasma-sprayed HA coatings can be obtained by treatment of the raw coating in a fluoride-containing solution (KF: 0.05 M at 100 °C). The addition of phosphate ($F/P = 1/3$) to the solution and the neutral pH, prevents the formation of calcium fluoride [16]. The treatment is completed after 10 h and results in the formation of fluoridated apatite crystals on the surface of the coating (Fig. 1) essentially at the expense of the amorphous fraction of the plasma sprayed coating. The modified surfaces were tested in cell culture with human osteoblasts, although cell adhesion was found to be about equivalent on treated and raw surfaces, cell proliferation greatly improved, after 10 days, on the fluorinated surface (Figs. 2 and 3). In addition, the fluoridation treatment considerably reduced the degradation of the coating.

The two processes described lead to well crystallised apatites very different from nanocrystalline bone apatites. In addition to simple ionic substitution in the apatitic lattice, nanocrystals offer enhanced possibilities of reactivity and ion substitution due to their remarkable surface properties.

2.3. Ion exchange reactions involving nanocrystalline apatites

Nanocrystalline apatites offer faster and improved capabilities for ion exchange compared to well crystallized apatites. This phenomenon was described several decades ago, for the first time by Neuman [17], but the

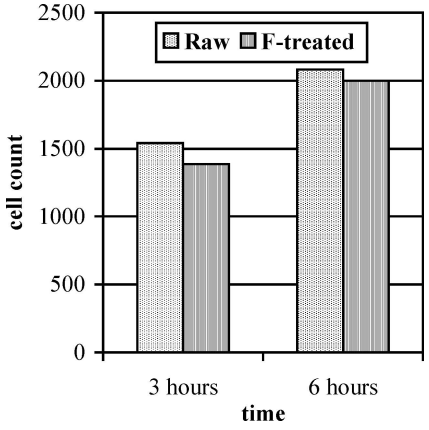

Figure 2 Human osteoblast cells adhesion to the raw (vacuum plasma-sprayed HA) and the fluoridated surface after 3 and 6 h.

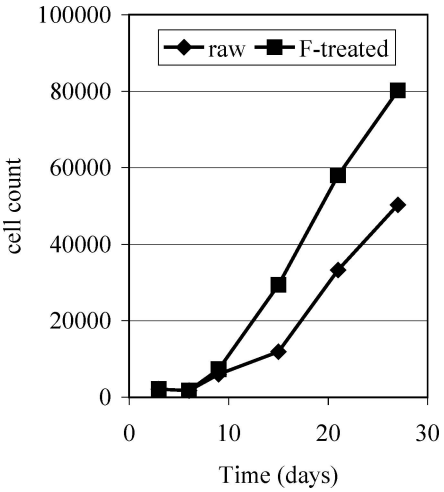

Figure 3 Human osteoblast cell proliferation to the raw (vacuum plasma-sprayed) and fluoridated surface.

interpretation was not clear. Since then several spectroscopic studies have consistently confirmed the existence in apatite nanocrystals of non-apatitic environments of the mineral ions. Solid state NMR data have indicated that these environments correspond to a hydrated layer probably located at the crystal surface [18, 19].

Very recently it has been shown that the hydrated surface layer is structured in aqueous media, but is very fragile and that it was destroyed by drying the samples [20]. However, even in aqueous media, the hydrated layer is metastable, compared to an apatite structure, and it is irreversibly transformed into apatite on ageing in aqueous media [8]. It has been suggested that the hydrated layer could lower the surface energy of the nanocrystals and thus favour their nucleation in aqueous media [21]. With its loosely bound mineral ions, this layer seems to be involved in homeostasis and in other interactions of bone mineral crystals with their surrounding media. It might also play a role in the mechanical properties of mineralised tissues, related to the hydration level, and also possibly in biological regulation processes involving specific bone proteins and organic constituents [22]. The interactions of the nanocrystal surface with its aqueous environment are summarised in Fig. 4.

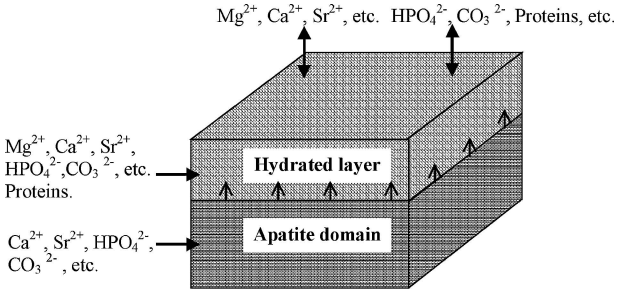

Figure 4 Nanocrystalline apatite model. The hydrated surface layer may trap and release several ions from solution. Due to ion mobility and disturbances related to substitutions, charged protein moieties may also be attached to the surface layer. Some of the mineral ions may be included in the regular, non-stoichiometric apatite domains during their growth.

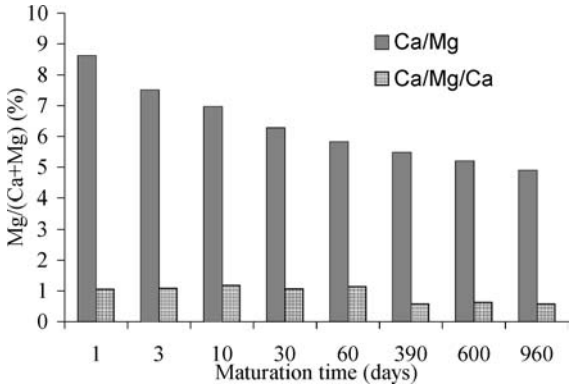

Figure 5 Example of Ca-Mg exchange in apatite at different maturation stages. The exchange rate (Ca/Mg) decreases as the maturation time increases. The exchange is almost totally reversible (Ca/Mg/Ca).

The exchange reactions involving the surface layer are fast and facile. Concerning Ca-Mg exchange, for example, the equilibrium is reached in a few minutes and the reaction can be made at room temperature. The amount of ions exchanged always seems related to the maturation stage of the crystals: it decreases considerably in matured crystals (Fig. 5) due to the reduction of the surface hydrated layer. The exchange level also depends on the nature of the mineral ions. For example for identical solution concentrations the exchange rate of Sr appears always higher than that of Mg at any maturation stage [23]. When the foreign mineral ions remain located in the hydrated surface layer they are available for reverse exchange. Like the direct ion exchange reaction, the reverse reactions are fast although incomplete: a foreign ion residue always remains in the nanocrystals.

TABLE I Sr^{2+} ions released after primary exchange and increasing ageing time before the reverse exchange reaction (in 1 M Calcium nitrate solution, at room temperature and neutral pH)

Maturation time (days)	Sr ions released (% of original content)
No maturation	90
1	39
3	23
10	23
30	20

TABLE II Mg^{2+} ions released from coprecipitated ($Ca^{2+} + Mg^{2+}$) nanocrystalline apatites after different maturation times (exchange in 1 M calcium nitrate solution, at room temperature and neutral pH)

Maturation time (days)	Mg ions released (% of original content)
1	84
3	84
10	87
30	82

However, the foreign mineral ion behaviour can be very different when ageing (maturation) is involved. When the foreign mineral ion can enter the apatitic lattice and substitute for calcium, phosphate or OH^- ions, they do not disturb the maturation process and, as they enter the growing apatitic domains, their concentration in the hydrated layer progressively decreases and fewer remain available for reverse exchange reactions. On the contrary, if the foreign mineral ions cannot enter, or enter the apatitic domains with difficulty, they remain exchangeable and may possibly stabilise the hydrated layer [23]. These different behaviours are illustrated by Sr and Mg ion exchanges. In the case of Sr, which can form continuous solid solutions with calcium phosphate apatites, the exchange rate decreases as the maturation time increases after a primary exchange reaction (Table I). This behaviour indicates the incorporation of the ion in the growing apatitic domain during maturation. On the contrary Mg^{2+} ions, which can only partly substitute for Ca in the apatitic lattice, remain exchangeable even in coprecipitated (Ca and Mg) apatites for any maturation time (Table II). The reverse exchange reaction supports the availability of the Mg^{2+} ions and their preference for the hydrated layer. Carbonate shows an intermediate behaviour. Part of the ions can be incorporated in apatitic sites but some may remain in the hydrated layer depending on the maturation stage. These ions (Mg^{2+} and carbonate) disturb the growth of the apatite lattice and they may delay the maturation process. Living beings have learned to control and use these specificities to regulate their homeostasis. So, fresh mineral crystals with a well developed hydrated layer are a living necessity and this is one of the reasons why energy is spent, in mammals, for bone renewal and remodelling.

An example of use of these possibilities is given by strontium uptake and release from bone mineral. Sr^{2+} ions have been shown to have a direct effect on bone cells and they are proposed for the treatment of osteoporosis [24]. In animals fed with a strontium-rich diet, Sr^{2+} has been shown to be taken up, like many other bone seeking elements, preferably by recent mineral deposits, for example the amount of Sr^{2+} was found to be twice higher in cancellous bone which has a high turn-over rate, than in compact bone which has a low turn over rate [23]. This preference can be due to several causes : a better blood supply and contact with the mineral, a faster remodelling, but also a higher amount of labile hydrated environment in cancellous bone than in compact bone. In fact the hydrated layer appears as a reservoir for the storage and regulation of circulating Sr^{2+}.

Several mineral ions act directly on cells when they are in solution (Sr^{2+}, Mg^{2+}, Mn^{2+}, Zn^{2+}) and nanocrystalline apatites can be used as ion reservoirs for the slow release of these mineral ions. The release could be determined by two processes : spontaneous release by reverse ion exchange with calcium ions from body fluids, depending on local equilibrium conditions, and cell-mediated release resulting from the complete dissolution of the crystals by osteoclast cells. The first process could play a role in the local stimulation of stem cells or osteoblasts on a nanocrystalline Ca-P material. The second would have a long term effect, requiring a remodelling stage to be activated, and involving both osteoblast and osteoclast cells. It is worthwhile noting that the hydrated layer offers a wider range of ion substitution and uptake than the apatite lattice itself.

3. Conclusion

Ion exchange can be used at different levels to modify the properties of apatite ceramics. Nanocrystalline apatites especially offer different levels of ionic susbitution which are used in certain living creatures but which have not yet been utilised in biomaterials. The main difficulties are the very high reactivity and the instability of these compounds which raise problems of accurate characterisation, reproducibility, stability and materials preparation. In order to take advantage of these properties, new processes for the low temperature preparation of ceramic should be now investigated and developed.

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