THERMODYNAMICS STUDY OF SIMPLIFIED SBF SOLUTIONS

Ivan Napoleão Bastos[1]
Gustavo Mendes Platt[2]
Instituto Politécnico, Universidade do Estado do Rio de Janeiro, Caixa Postal 97282, CEP 28601-970, Nova Friburgo RJ
[1]inbastos@iprj.uerj.br, [2]gmplatt@iprj.uerj.br

Glória Dulce de Almeida Soares[3]
PEMM/COPPE, Universidade Federal do Rio de Janeiro, Caixa Postal 68505, CEP 21941-972, Rio de Janeiro, RJ
[3]gloria@metalmat.ufrj.br

Abstract. *This work is an attempt to study under thermodynamics approach some similar body fluids (SBF) with a simplified number of reagents in order to allow the homogeneous precipitation of hydroxyapatite. The Debye-Hückel's model of activity coefficient was used as well as chemical equilibrium and mass balance equations to model the multi-electrolyte system at 298K. Initially were considered ten reagents that are usually employed as raw material to produce SBF. Subsequently some reagents were selectively eliminated, that is their concentrations are equaled to zero. Then, equilibrium calculations were performed with a computational program based on multi-variable Newton-Raphson method, where the concentration and activity of each chemical specimen present in solution is considered. Besides, some modified chemical formulations were simulated in respect to free Gibbs energy change, Ca/P ratio and supersaturation.*

Keywords: *similar body solutions, computational modeling, thermodynamics, biomaterials*

1. Introduction

The artificial materials considered for implants are tested by *in vivo* and *in vitro* methods. The tests are focused on physical, chemical and mechanical properties that provide data for implanting into human organism to be assessed. Since the work of Branemark et al. (1969), the study of how implants interact with tissue is subject of great interest in biomedical and materials science fields. According to Kokubo et al. (2000), an essential requirement for *in vivo* bone growth on a synthetic material is the formation of a calcium phosphate layer on the materials surface, usually called bone-like apatite. This bone-like apatite seems to act signaling proteins and cells to start the cascade of events that result in bone formation. In other words, the *in vivo* behavior can be predicted by using *in vitro* tests such as immersion of synthetic materials into simulated body fluid (SBF) solution (Andrade et al., 1999).

The possibility of formulate different simulated body fluids have originated many published papers (Andrade et al., 2002; Habibovic et al., 2004). Few works in the literature consider the thermodynamics of solution applied to similar body fluids (Lin and Lee, 2003; Dorozhkina et al., 2003; Glinkina et al., 2004). Helebrant et al. (2002) investigated the effects of chloride and carbonate ions on precipitation, and their conclusion is that the initial supersaturation plays important role in apatite layer creation. They evaluate the relative supersaturation of different types of phosphates. A way to estimate the supersaturation index S_R uses the following formula, (Marques, 2003),

$$\sigma = \sqrt[n]{\frac{IAP}{K}} - 1$$

where IAP stands for ion activity product and K is the solubility product and n is the number of ions in precipitation formula. As bigger than one, more probable is the occurrence of precipitation. Negative values, on the other hand, imply that a precipitation will not take place.

The use of solutions to coat metals with calcium phosphate is important in biomedical and dental fields due to the possibility to improve the interaction implant/tissue. In this sense several solutions have been suggested to produce this type of coating (Andrade et al, 2000). One of them was even accepted as ISO standard (2005) draft. However, the solutions are complex from the point of view of preparation, and taken almost ten reagents to be prepared. We believe that, for in vitro coating, some of reagents are not necessary. Therefore, in this work some theoretical investigation is performed to confirm the possibility of homogeneous precipitation within a thermodynamics approach. The phosphates studied here were hydroxyapatite (HA), brushite (B) and octacalcium phosphate (OCP).

2. The thermodynamics modeling

In this work, the activity coefficients for the charged particles are calculated by Eq. (1)

$$log(\gamma_i) = -\frac{z_i^2 A I^{1/2}}{1 + BaI^{1/2}} \quad (1)$$

where a is the ionic radius, z_i is the charge of ion *i* and

$$A = \frac{1}{3}\left(2\pi L d_w\right)^{1/2}\left(\frac{e^2}{4\pi\varepsilon_0\varepsilon_e kT}\right)^{3/2} \quad (2)$$

In Eq. (2), *L* is the Avogadro number, e is the unit charge, ε_0 is the permittivity in vacuum, *k* is the Boltzmann constant, d_w is the density of water at 298.15 K (in kg/m^3) and ε_r is the dielectric constant of water at 298.15 K.

In Eq. (1), we used $Ba \cong 1.5$, following the recommendation of Glinkina et al. (2003), allowing us to describe activity coefficients up to 0.2 M concentrations. Finally, I is the ionic strength of the solution, calculated by:

$$I = \frac{1}{2}\sum_i z_i^2 C_i \quad (3)$$

Thus, if all ionic concentrations in the solution are know, one can easily evaluate activities for all chemical species. However, the determination of concentrations (and, therefore, activity coefficients) is a nonlinear algebraic problem, characterized by material balances equations and chemical equilibrium equations.

We consider the following chemical equilibria in solution:

(1) Water dissociation

$$H^+ + OH^- \xrightleftharpoons{K_w} H_2O \quad (4)$$

(2) Sequential dissociation of phosphoric acid

$$H^+ + PO_4^{3-} \xrightleftharpoons{K_1} HPO_4^{2-} \quad (5)$$

$$H^+ + HPO_4^{2-} \xrightleftharpoons{K_2} H_2PO_4^- \quad (6)$$

$$H^+ + H_2PO_4^- \xrightleftharpoons{K_3} H_3PO_4 \quad (7)$$

(3) Equilibrium with calcium phosphates

$$Ca^{2+} + HPO_4^{2-} \xrightleftharpoons{K_4} CaHPO_4 \quad (8)$$

$$Ca^{2+} + H_2PO_4^- \xrightleftharpoons{K_5} CaH_2PO_4^+ \quad (9)$$

$$Ca^{2+} + OH^- \xrightleftharpoons{K_6} CaOH^+ \quad (10)$$

(4) Carbonate/Bicarbonate Equilibrium

$$HCO_3^- \xrightleftharpoons{K_7} H^+ + CO_3^{2-} \quad (11)$$

Besides the chemical equilibrium relationships, we also include the following material balances

(1) Material Balance for Phosphorous

$$[P] = \left[PO_4^{3-}\right] + \left[HPO_4^{2-}\right] + \left[H_2PO_4^-\right] + \left[H_3PO_4\right] \quad (12)$$

(2) Material Balance for Carbon

$$[C] = \left[CO_3^{2-}\right] + \left[HCO_3^-\right] \quad (13)$$

(3) Material Balance for Calcium

$$[Ca] = \left[CaHPO_4\right] + \left[CaH_2PO_4^+\right] + \left[CaOH^+\right] \quad (14)$$

Analysis of the Degrees of Freedom

The system of equations which is solved in order to obtain all concentrations and activity coefficients for the chemical species in solution has eleven equations (Eqs (4)-(14)), and we need to know the concentrations for twelve species: $\left[PO_4^{3-}\right]$, $\left[HPO_4^{2-}\right]$, $\left[H_2PO_4^-\right]$, $\left[H_3PO_4\right]$, $\left[CO_3^{2-}\right]$, $\left[HCO_3^-\right]$, $\left[CaHPO_4\right]$, $\left[CaH_2PO_4^+\right]$, $\left[CaOH^+\right]$, $\left[H^+\right]$, $\left[OH^-\right]$, $\left[Ca^{2+}\right]$. Thus, the system apparently has one degree of freedom; but this degree of freedom is satisfied by a pH specification and inclusion of the definition of pH in the nonlinear algebraic system.

One can observe that the concentrations and activity coefficients for inert ions (i.e., chemical species not participating of chemical reactions), are not considered here; however, the activities for these species are easily calculated by Eq. (1) (see results section).

To estimate the supersaturation index Sr, we use the previous equations, and here it is written for HA. The product of solubility are: HA - $2.34x10^{-59}$; OCP - $2x10^{-49}$ and B - $2.32x10^{-7}$ (McDowell et al., 1977; Moreno et al., 1974). For example, for HA, this index is calculated using:

$$S_{R-HA} = \sqrt[8]{\frac{(\gamma_{Ca^+})^5(\gamma_{Ca^+})^3(\gamma_{OH^-})^4[Ca^+]^5[PO_4^{2-}]^3[OH^-]^4}{2.34x10^{-59}}} - 1 \qquad (15)$$

2.1 Numerical solution of the problem

The nonlinear system formed by Eqs. (4)-(14) and the definition of pH is solved by a Newton procedure (Ortega and Rheinboldt, 1970), i.e., the Jacobian matrix is numerically evaluated by forward finite-differences. The following figure illustrates the algorithm used.

An initial solution is necessary ($\underline{\theta}^{(0)}$), and the tolerance for stopping the algorithm (ε). The Jacobian matrix – $\underline{\underline{J}} = \underline{\nabla}^t \underline{F}$ – is calculated numerically by finite-differences. The vector of functions $\underline{F}$ represents the system of equations to be solved in the form: $\underline{F}(\underline{\theta}) = \underline{0}$, where $\underline{\theta}$ is the vector of variables. The algorithm is stopped when the norm of the differences of two consecutive approximations for $\underline{\theta}$ is less than the specified tolerance (in our simulation we specified $\varepsilon = 1\times10^{-7}$). Then, the algorithm was converged and the concentrations of all chemical species were determined. Finally, the activity coefficients as well as other parameters can be calculated by a simple substitution in Eq. (1).

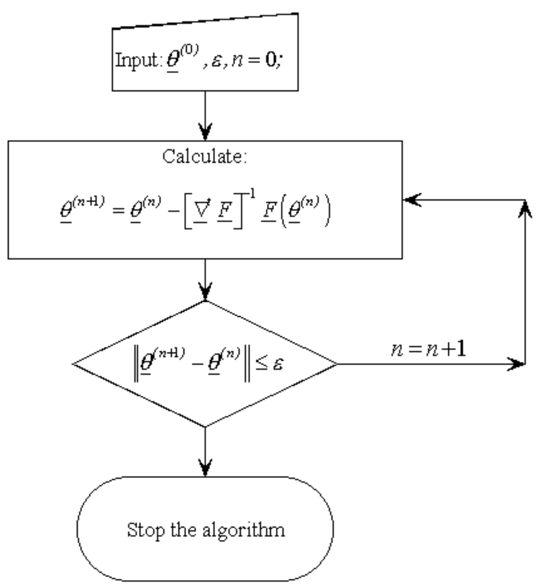

Figure 1– Newton algorithm.

3. Results and discussion

Two solutions were considered for this work. One is the classic described in ISO Draft (2005) and the other is a modified one. The Table 1 gives the ionic concentrations of both solutions.

Table 1– Ionic concentrations of solutions employed in thermodynamics analysis, 10^{-3} molar.

ion	Standard	Modified
Na^{+}	142.0	4.2
K^{+}	5.0	2.0
Ca^{2+}	2.5	2.5
Cl^{-}	147.8	5.0
HCO_3^{-}	4.2	4.2
HPO_4^{2-}	1.0	1.0

To obtain the standard SBF solution the necessary chemical reagents are NaCl, $NaHCO_3$, KCl, $K_2HPO_4.3H_2O$, $MgCl_2$, HCl, $CaCl_2$ and Na_2CO_3. We proposed an alternative set of reagents using only three reagents that are $NaHCO_3$, $K_2HPO_4.3H_2O$ and $CaCl_2$. This new formulation is named hereafter as modified SBF.

Figure 2 shows the Gibbs free energy change for the precipitation reaction of hydroxyapatite, brushite and octacalcium phosphate formed in standard SBF. All of them are dependent of pH, but the energy change of brushite is a positive value in this pH range. Therefore, it is impossible to precipitate in this condition. In principle, the phases with negative values are prone to occur spontaneously, and the more stable phase is that with more negative values. Thus, hydroxyapatite is the phosphate more stable; moreover, above pH 7 HA splits from octacalcium in a stead manner. The values of ΔG were calculated using the classical equation for supersatured solutions (see Lu and Leng, 2005).

The same objects are plotted in Fig. 3 for the modified SBF proposed in this work. Some scatterings observed at low pH region were consequences of numerical instabilities, but not enough to alter the average values of ΔG.

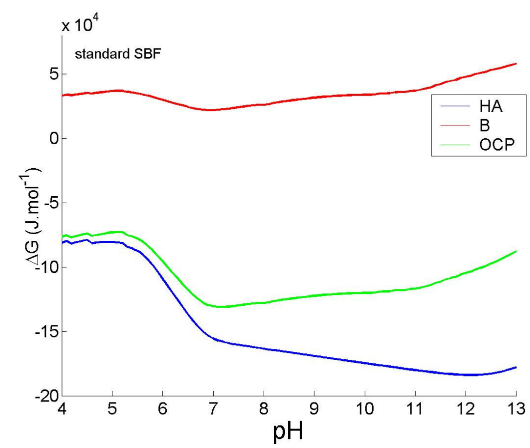

Figure 2 – Gibbs free energy change for the precipitation reactions of hydroxyapatite (HA), octacalcium phosphate (OCP) and brushite (B). Standard SBF.

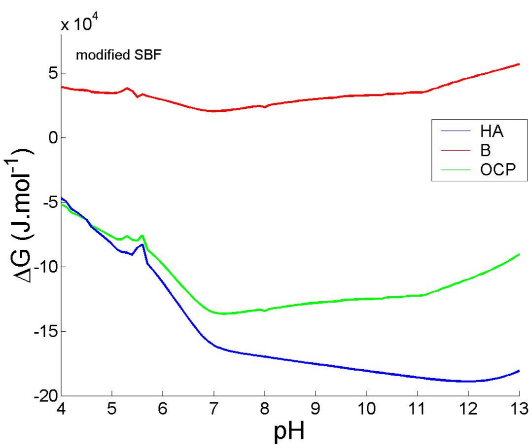

Figure 3 – Gibbs free energy change for the precipitation reactions of hydroxyapatite (HA), octacalcium phosphate (OCP) and brushite (B). Modified SBF.

Figures 4 and 5 present the supersaturation index (Sr) for the standard and modified SBFs, respectively. The brushite curve (plotted in red line) has negative values of Sr, which indicates the difficulties of precipitation. The other curves (HA and OCP) have positive values for Sr, and they present a strongly nonlinear behavior with pH variation. One can observe that at pH = 7.0 the OCP shows a maximum value for Sr. In this pH, the Sr for OCP is higher than that of HA. Above pH 8.0, the Sr of HA increases and the Sr of OCP decreases. Therefore, for high pH values, precipitation of HA is more favorable than OCP. Besides, the Sr for HA and OCP in the modified SBF presents a maximum value superior than that of standard SBF. Probably this is a consequence of the ionic strength of the medium, since chemical species (Na^+, K^+ and Cl^-) are inert ions in this chemical system, but modifies the ionic strength.

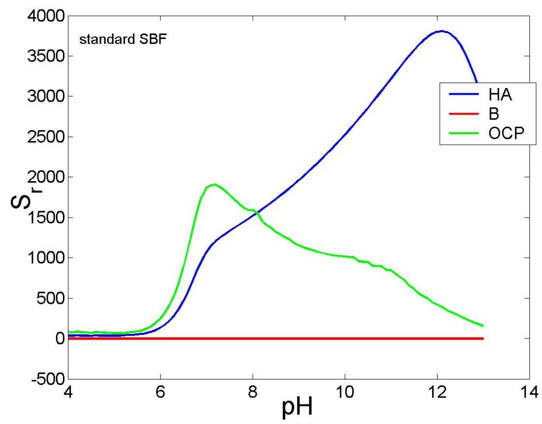

Figure 4 – Supersaturation index for standard SBF.

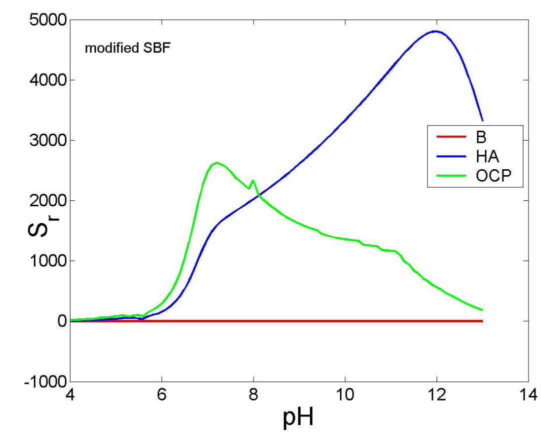

Figure 5 – Supersaturation index for modified SBF.

Finally, Figs. 6 and 7 show the ratios of total Ca/P (concentrations and activities) for standard and modified SBF. The concentration ratios maintain constant (2.5), for both solutions in the pH range from 4 to 13 (as a consequence of the conservation of chemical species in the electrolyte). On the other hand, the prediction of precipitation reactions is conducted by an analysis using activities instead of concentrations (Walas, 1985). There is a plateau in the range 7-11 for the standard and modified SBFs. This plateau occurs at a ratio [Ca]/[P] equals to 4 in the standard SBF and approximately 3 for the modified SBF. This [Ca]/[P] ratio affects the dissolution of phosphates and is an important aspect of apatites (Mavropoulos et al., 2003).

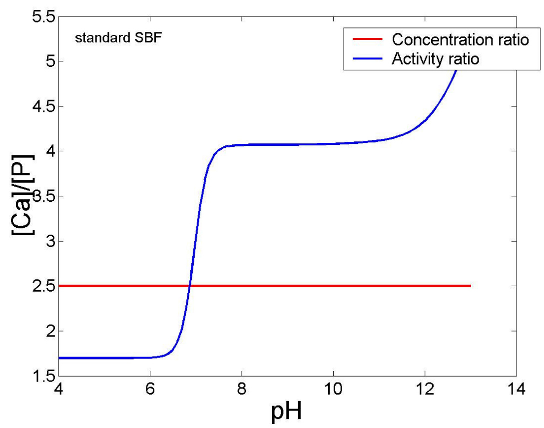

Figure 6 – Ratio of total Ca/P for standard SBF.

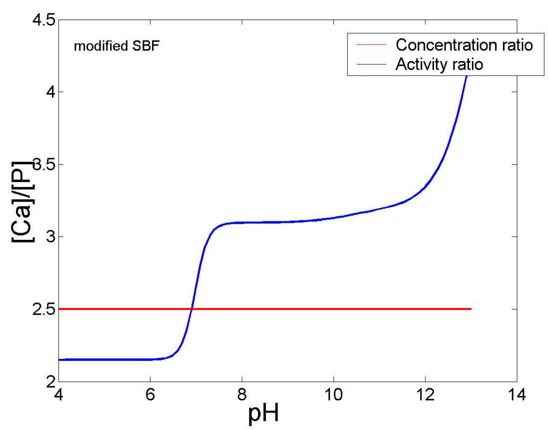

Figure 7 – Ratio of total Ca/P for modified SBF.

4. Conclusion

In this work was studied the homogenous precipitation of calcium phosphate with biomedical interest at 25 ^{o}C. Two solutions were considered in this paper: a standardized SBF and a modified one that has only the ions necessary to allow the precipitation. The thermodynamics approach takes into account the non-ideality of these solutions that were modeled by Debye-Hückel activity coefficient. Besides, the Gibbs free energy change for the precipitation reaction of three phosphates was calculated in pH range from 4 to 13. The brushite energy change is positive; consequently its precipitation is impossible (as also observed by Lu et al., 2005). The other two, HA and OCP, have negative values and they are able to precipitated. The supersaturation index of standard and modified solutions of HA and OCP are bigger than one and for OCP reaches a maximum near pH 7. Moreover, for the modified solution both the Gibbs free energy changes as well as supersaturation are more favorable than that of standard SBF, probably due to less electric charge interactions of electrolytes.

5. Acknowledgements

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6. References

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