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Review Article

Interaction of biologically relevant ions and organic molecules with titanium oxide (rutile) surfaces: A review on molecular dynamics studies

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ABSTRACT

The surface of a biomaterial can play a major role in its biological fate since the surface is the primary pathway for its interaction with the body. As the natural response of the body to a foreign material is to encapsulate it with a fibrous material, the interactions between the body and the biomaterial are mediated by this fibrous layer. Initial interactions occur between the biomaterial surface, water, ionic species and organic molecules, which then mediate further interactions with body tissues. Surface engineering can influence these interactions and hence, improve the biocompatibility of the biomaterial. Therefore, both experimental and computational studies have been interested in phenomena happening at the solid-solution interface as their mechanisms and driving forces can point to new directions for biomaterial design and evaluation. In this review, we summarize the computational work on the interaction of titanium oxide surfaces (mainly rutile) with solvated ions and organic molecules by means of molecular dynamics, with a certain relevance to bioactivity testing protocols. The primary goal of this review is to present the current state of the art and draw attention to points where further investigations are required.

Contents

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1. Introduction

Titanium alloys are nowadays extensively used for biomedical applications since they have proven to be biocompatible (the ability to exist in contact with human body tissue without causing an unacceptable degree of harm to the body [1]) for many biomedical applications (*e.g.*, artificial bones, joints and dental implants [2]). It is argued that they owe their biocompatibility for such applications to the oxide layer that forms when the metal is in contact with either oxygen or water [2]. The oxide layer on Ti implants that interacts with the surrounding environment is a mixture of amorphous and crystalline forms of titanium oxide (hereafter, titanium oxide will refer to both crystalline and amorphous states) [3]. The three major crystalline polymorphs of titanium dioxide are rutile, anatase and brookite, rutile being the most abundant naturally occurring phase at ambient pressure, while anatase is stable in nanomaterials [2,4–8]. At high temperatures, anatase and brookite can irreversibly transform to rutile [9,10]. Chemical treatments are often used to render inert surfaces bioactive. For example, Kokubo *et al.* showed that a sodium titanate hydrogel layer forms on a titanium metal surface after its immersion in sodium hydroxide [11]. Heat treatment of this sodium titanate hydrogel layer-covered titanium showed that it transforms into an amorphous sodium titanate at 400–500 °C and crystalline sodium titanate and rutile at temperatures above 700 °C [12]. These chemically modified surfaces show an excellent biocompatibility for specific applications and are under clinical trials for artificial hip joints and spinal fusion devices [13]. This highlights the importance of rutile, which is the titanium oxide phase studied in most publications on this topic.

The biocompatibility of an implant with a given surface preparation can most reliably be evaluated by *in vivo* testing where the assessment is done with the implant inserted in a living body. However, for economic as well as ethical reasons it is desirable to perform reliable *in vitro* tests, in which samples are tested in laboratories and outside any living bodies. In the latter case, researchers try to achieve experimental conditions close to those found *in vivo*. While in some cases *in vitro* results agree with *in vivo* results, other studies have shown that there are unidentified factors during *in vitro* tests that cause discrepancies between the results obtained by these two methodologies [14,15]. In a recent study, eight different European universities carried out *in vivo* and *in vitro* studies on 93 different biomaterials, showing a weak correlation between *in vivo* and *in vitro* results [16].

One of the sources of this discrepancy is the solution used for *in vitro* testing [17,18]. Depending on the purpose of the study, different aqueous *in vitro* solutions have been proposed, Simulated Body Fluid solutions (SBFs) being a popular category [19,20]. The ionic concentrations in different SBFs (Table 1) are very close to those in blood plasma. The variations say between the Kokubo and Bohner solutions have a minor effect on supersaturation [18] and it is the possible specific adsorption of ions onto different surfaces that should be of importance in the hydroxyapatite formation on implants. There are certainly differences between blood plasma and SBF solutions; for example, the buffer used to maintain the solution pH near the 7.4 found in human blood. The use of a carbonate buffer (*i.e.*, a P_{CO_2} of 5%) instead of an organic molecule such as Tris should render the *in vitro* test more representative. This can change the amount of carbonate or bicarbonate species in solution [18], which may lead to modifications in the inorganic species adsorbed on implant surfaces. This, in turn, may influence the nucleation and growth of calcium phosphates on implant surfaces *in vitro*. Also, one of the most commonly used SBF solutions, proposed by Kokubo *et al.* and used in the ISO standard [21], lacks the proteins present in the blood plasma [17,22]. In the human body proteins adsorb onto an implant surface in a variety of orientations and configurations shortly after implantation. Further interactions between the cells and the implant surface will occur through this organic layer [2,23,24]. Since cells recognize only a few specific proteins in well-defined orientations and configurations, the composition and structure of the adsorbed organic layer will influence the biocompatibility of the biomaterial [25–28]. Therefore, the absence of proteins during *in vitro* testing could be another reason for the discrepancies found between *in vivo* and *in vitro* testing.

Understanding protein adsorption on biomaterial surfaces is therefore of great importance since, alongside water-surface interactions, it can significantly affect the performance of a biomaterial [19,24,30]. With this knowledge, it would be possible to design implants with surfaces that trigger or boost biocompatibility and bioactivity when in contact with blood-plasma proteins [14,25],

Table 1
Ionic concentration [mM] of the human blood plasma and some Simulated Body Fluid solutions (SBFs) [18,21,22,29].

	Human blood plasma	ISO 23317 (pH 7.4)	Kokubo *et al.*	Bohner *et al.*
Na^+	142.00	142.00	142.00	142.00
K^+	5.00	5.00	5.00	–
Mg^{2+}	1.50	1.50	1.50	–
Ca^{2+}	2.50	2.50	2.50	2.31
Cl^-	103.00	147.80	148.80	109.90
HCO_3^-	27.00	4.20	4.20	34.88
HPO_4^{2-}	1.00	1.00	1.00	1.39
SO_4^{2-}	0.50	0.50	0.50	–