Immobilization of biomolecules on natural clay minerals for medical applications

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ABSTRACT

Biomolecules are a group of organic entities that are important in many areas of research on nanomaterials and for biomedical and pharmaceutical applications. Advanced systems have been developed to attempt to protect the activity of biomolecules from rapid degradation and instability. Among these techniques, the incorporation or immobilization of biomolecules has become popular in the development of biocomposites. As such, clay minerals appear to be promising materials; combining a nanometer-scale size with their adsorptive capacity, lack of toxicity, and biocompatibility would result in enhanced biomaterial properties. This mini-review discusses the recent advances concerning biological molecules immobilized on clay minerals and their biomedical applications as biosensors, in regenerative medicine, and even as controlled delivery systems.

1. Introduction

Biomolecules are a group of organic entities of biological origin, such as polysaccharides, lipids, vitamins, enzymes, amino acids, peptides, proteins, and nucleic acids. A variety of biomolecules have been proposed with properties derived from the functions of those molecules. However, systems containing well-preserved catalytic activity and enhanced properties. Systems containing biomolecules have a wide variety of applications in clinical or industrial use; thus, inorganic solids and their assemblies play an important role as immobilizing matrices.

Clay minerals are solids of the phyllosilicate family with the potential for biomolecule immobilization, resulting from their specific physicochemical characteristics, such as high surface reactivity. In addition, these materials exhibit antimicrobial properties with good biocompatibility. The advantages of these materials include their abundance, low cost, and potential as regional products.

The interaction between nanostructures and organic compounds has been studied in different areas of research, such as engineered nanomaterials for biomedical and pharmaceutical applications. The proposed applications for nanocomposites include the use of biomaterials as scaffolds, drug carriers for delivery systems, patches for wound healing, and as modifiers of biological substrates in electronic or implantable devices.

The present review focuses on studies related to different types of biological molecules immobilized on natural clay minerals published in the last ten years. We review the main experimental research in the biomedical application of clay nanocomposites, including their use as biosensors and controlled delivery systems and in regenerative medicine.

2. Clay minerals – major characteristics

Alumino-silicates, such as montmorillonite, kaolinite, illite, sepiolite, and palygorskite (or attapulgite) belong to two types of abundant inorganic solids in nature. There are certain differences between layered and fibrous clay minerals, i.e., expanding and non-expanding types. As an example of layered clay, montmorillonite shows expansibility, 1-nanodimensional particle, high charge density and cation exchange capacity, low-density silanol groups at the edges, and particles in layered stacks. By contrast, fibrous clays, such as sepiolite and palygorskite, exhibit a non-swelling process, 2-nanodimensional particles, low charge density and cation exchange capacity, high-density silanol groups (Si=OH) at the broad external surface area, and particles in bundles.

Both classes are micro- and nano-sized, and present strong adsorption strength and ion exchange abilities, and a high internal surface area. The layers or sheets are constituted by basic arrangements of clay mineral tetrahedral silicates and octahedral hydroxide sheets, giving rise to various classes of clay minerals of type 2:1 or 1:1. The permanent net negative charge of the layers or sheets, resulting from the substitution of Al3+ by Fe3+ or Mg2+, the presence of hydroxyls at the limits, and compensatory cationic ions located in interlayer/sheets spaces are responsible for cation exchange abilities. Broken edges of clay show pH-dependence, staying positive at low pH and negative at high pH, originating from the surface reactivity of the clay mineral. Thus, biomolecules, either negatively or positively charged, can be immobilized on the surface, edges, or interlayer/microchannels of clay particles. Adsorption of organic molecules on clay minerals reported in the literature includes hydrophobic interactions, hydrogen bonding, protonation, ligand exchange, cation exchange, cation bridging, and water bridging.

Natural clay minerals are used for medical purposes and are used in the purification of natural clay minerals, which are used for medical applications, they remain an attractive choice.

3. Diversity of biomolecules associated with clay minerals

Many biological agents incorporated to clay minerals can be released in organic systems for a range of biomedical applications. The diversity of biomolecules used to form new materials in association with natural clay minerals, as well as the forms of incorporation and the state of the molecules, are summarized in table 1.

As seen in table 1, clay minerals can adsorb various biomolecules, including proteins, nucleic acids, and carbohydrates. The majority of the reports on the use of biomolecules refer to polymer and enzyme immobilization. In the field of release systems, the number of reports on the use of clay minerals has increased in the last four years. Controlled drug delivery systems allow temporal and/or spatial control of release rates, thus, allowing acceleration, delay, or prolongation of release, as well as site-specific targeting.

Among different types of clay minerals, montmorillonite has been studied more frequently in biological applications, possibly because of its high ion exchange capacity and because it is widely distributed in nature. Chen and coworkers reported that effective intercalation of proteins within the galleries of montmorillonites can be achieved via space enlargement and exchange processes, while retaining the native conformation of the guest proteins and the multi-layered structure of the biocarbon host plates. Despite this, according to Ruiz-Hitzky and coworkers, in certain cases, fibrous clays are more interesting than layered clays and can display higher enrichment of the mechanical properties of biomaterials.

Furthermore, biomacromolecules can be processed as films or as porous cellular materials, using solvent casting and freeze-drying processes. The following sections discuss the biomedical applications of clay minerals.
Table 1 - Diversity of immobilized biomolecules on natural clay minerals reported in the literature in the last ten years.

<table>
<thead>
<tr>
<th>Biomolecule</th>
<th>Clay/clay mineral</th>
<th>Form of Incorporation</th>
<th>Condition of the molecule in the clay</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrageenan</td>
<td></td>
<td>Suspension in solution</td>
<td>Intercalated</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electropinning from mixing in solution</td>
<td>Intercalated by ion exchange</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixing in solution</td>
<td>Intercalation with a planar conformation</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dispersion in acidic aqueous solution</td>
<td>Intercalated by ion exchange</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>montmorillonite</td>
<td>Electropinning for mixing in solution</td>
<td>Intercalated by ion exchange</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dispersion in aqueous solution</td>
<td>Intercalated complexes</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adsorption in phosphate-buffered saline (PBS) solution</td>
<td>Intercalated with diffusion of vitamin B12 to the interlayer spaces</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution mixing process</td>
<td>Intercalation</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension in solution containing the lipid to form microparticles</td>
<td>Not determined; however, clay exfoliation was proposed to form the microparticles, as observed by scanning electron microscopy (SEM).</td>
<td>25</td>
</tr>
<tr>
<td>Pectin/chitosan</td>
<td></td>
<td>Solubilization of chitosan, followed by addition of the clay under ultrasound, and formation of the hydrogel with the addition of pectin under vigorous shaking</td>
<td>Amorphous phases were identified.</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clay was dispersed in water and stirred with CMS, glycerol, and citric acid. The mixture was poured into a polytetrafluoroethylene (PTFE) mold to form a film</td>
<td>Intercalated</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension in solution</td>
<td>Intercalated</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension in solution</td>
<td>Intercalated</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension in seawater</td>
<td>Adsorption with a smaller expansion of the layer</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adsorption in double-deionized water followed by precipitation in a microcentrifuge</td>
<td>Intercalated</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melt extruded</td>
<td>Dispersed in polymer</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adsorption on buffer solution</td>
<td>Not indicated in the text</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clay films were prepared by dropping a known volume of clay colloids – soaked in methyl viologen, or by dropping of Hb clay aqueous mixture onto the electrode</td>
<td>Not indicated in the text</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1 - Diversity of immobilized biomolecules on natural clay minerals reported in the literature in the last ten years (cont.)

<table>
<thead>
<tr>
<th>Biomolecule</th>
<th>Clay/clay mineral</th>
<th>Form of Incorporation</th>
<th>Condition of the molecule in the clay</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Hemoglobin (Hb) or meth-
yl viologen |                   | Clay films were prepared by dropping a known volume of clay colloids – soaked in methyl viologen, or by dropping of Hb clay aqueous mixture onto the electrode | Not indicated in the text | 34   |
| L-DOPA (precursor of dopamine) | saponite | Adsorption in aqueous solution at pH 7.5 | Intercalated – theoretical and experimental study | 35   |
|                      |                   | Films were prepared from the solidification of the chitosan and saponite dispersion in the presence of glycerol | Coplanar alignment of saponite nanolaminites with two monolayers of chitosan macromolecules in the glass | 36   |
|                      |                   | Suspension in seawater                 | Adsorption with a smaller expansion of the layer | 30   |
|                      |                   | Suspension in seawater                 | Intercalated                           | 37   |
|                      |                   | Clay was modified with oil, followed by modification with epoxy resin, and cured | Intercalated | 38   |
|                      |                   | Suspension in seawater                 | Intercalated                           | 37   |
|                      |                   | Hydrogel was prepared with dispersion of gellan gum, followed by clay addition under sonication | Not indicated in the text | 39   |
|                      |                   | Polymers were dissolved and added to a dispersion of clay, and then mixed using a processor | Strong interactions were indicated by the considerable perturbation of the stretching vibration band of –OH in the silanized groups | 43   |
|                      |                   | Clay was dissolved in acidic acetate, clay was dispersed in water, and the solutions were mixed to form a film | The materials interact on the surface of the clay without penetration inside the tunnels | 44   |
|                      |                   | Dispersion of clay in the solution containing the polymer | Not indicated in the text | 15   |
|                      |                   | Polymer and clay were solubilized and suspended in water separately, and mixtures were degassed by ultracentrifugation and then added onto plates to form a film | The SEM images showed a good dispersion of clay in the films | 45   |
|                      |                   | Polymer and clay were solubilized and suspended in water separately, and mixtures were degassed by ultracentrifugation and then added onto plates to form a film | Polyammonylamin | 46   |
|                      |                   | Adsorption on buffer solution          | Not indicated in the text              | 33   |
|                      |                   | Clay films were prepared by dropping a known volume of clay colloids – soaked in methyl viologen, or by dropping of Hb clay aqueous mixture onto the electrode | Not indicated in the text | 34   |
**Table 1** - Diversity of immobilized biomolecules on natural clay minerals reported in the literature in the last ten years (cont.)

<table>
<thead>
<tr>
<th>Polymer (co-glycolic acid) - PLGA</th>
<th>Poly(lactic-co-glycolic acid) - PLGA</th>
<th>Poly(lactic-co-glycolic acid) - PLGA</th>
<th>Poly(lactic-co-glycolic acid) - PLGA</th>
<th>Poly(lactic-co-glycolic acid) - PLGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(lactic-co-glycolic acid) - PLGA was dissolved in a mixed solvent of tetrahydrofuran - dimethylformamide, clay was added to form a homogeneous solution for electropinning</td>
<td>Not indicated in the text</td>
<td>Not indicated in the text</td>
<td>Not indicated in the text</td>
<td>Not indicated in the text</td>
</tr>
</tbody>
</table>

**Table 2** - Biosensors based on clay modifier electrodes and immobilized biomolecules.

<table>
<thead>
<tr>
<th>Biomolecules</th>
<th>Clay modifiers</th>
<th>Electrode</th>
<th>Biosensor</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyranose oxidase</td>
<td>montmorillonite/polyglycolide (PGA)</td>
<td>glassy carbon</td>
<td>glucose</td>
<td>60</td>
</tr>
<tr>
<td>Catechol oxidase</td>
<td>montmorillonite/polyglycolide (PGA)</td>
<td>glassy carbon</td>
<td>glucose</td>
<td>60</td>
</tr>
<tr>
<td>Enzymes</td>
<td>halloysite</td>
<td>glassy carbon</td>
<td>cancer cells</td>
<td>62</td>
</tr>
<tr>
<td>Horseradish peroxidase</td>
<td>sepiolite/carbon nanotubes (CNT)/PVA</td>
<td>-</td>
<td>peroxidase</td>
<td>63</td>
</tr>
<tr>
<td>Glucose oxidase</td>
<td>montmorillonite/ Glys. Lys. Gli</td>
<td>glassy carbon</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Bovine serum albumin (BSA), glutaraldehyde (GA) and pyranose oxidase</td>
<td>montmorillonite/ calcires-NH2</td>
<td>glassy carbon</td>
<td>-</td>
<td>65</td>
</tr>
<tr>
<td>Laccase</td>
<td>montmorillonite/ histidine</td>
<td>glassy carbon</td>
<td>phenol</td>
<td>66</td>
</tr>
<tr>
<td>Glucose oxidase</td>
<td>polyglycolic-poly(o-phenylenediamine)-glutaraldehyde</td>
<td>-</td>
<td>glucose</td>
<td>67</td>
</tr>
<tr>
<td>Horseradish peroxidase</td>
<td>polyglycolic-poly(o-phenylenediamine)-glutaraldehyde</td>
<td>-</td>
<td>hydrogen peroxide</td>
<td>68</td>
</tr>
<tr>
<td>Lactobacillus bulgaricus, Strep. coccus thermosphilus</td>
<td>polyglycolic-poly(o-phenylenediamine)-glutaraldehyde</td>
<td>oxygen</td>
<td>lactate</td>
<td>69</td>
</tr>
<tr>
<td>Horseradish peroxidase</td>
<td>polyglycolic-poly(o-phenylenediamine)-glutaraldehyde</td>
<td>glassy carbon</td>
<td>hydrogen peroxide</td>
<td>70</td>
</tr>
<tr>
<td>Tyrosinase</td>
<td>polyglycolic-poly(o-phenylenediamine)-glutaraldehyde</td>
<td>glassy carbon</td>
<td>phenol</td>
<td>71</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>nonronite, montmorillonite and saponite</td>
<td>-</td>
<td>hydrogen peroxide</td>
<td>33</td>
</tr>
<tr>
<td>Glucose oxidase</td>
<td>polyglycolic-poly(o-phenylenediamine)-glutaraldehyde</td>
<td>glassy carbon</td>
<td>glucose (blood and urine samples)</td>
<td>72</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>polyglycolic-poly(o-phenylenediamine)-glutaraldehyde</td>
<td>glassy carbon</td>
<td>hydrogen peroxide</td>
<td>73</td>
</tr>
<tr>
<td>Cytochrome c</td>
<td>polyglycolic-poly(o-phenylenediamine)-glutaraldehyde</td>
<td>glassy carbon</td>
<td>hydrogen peroxide</td>
<td>74</td>
</tr>
</tbody>
</table>

*The term “bentonite” refers to a mixture of minerals from the smectites group with a predominance of montmorillonite clay mineral; however, we prefer to use the term as reported in the articles cited in the table.*

### 4. Applications of biomolecules immobilized on clay minerals

#### 4.1. Biosensors

Biosensors are chemical sensors in which the recognition system uses a biological mechanism to measure the interaction between the analyte and the sensor device, transforming quantitative or qualitative information into a measurable electrical signal.

Clay minerals have been used as supports or modifiers of substrates in the field of electronic devices for electroanalytical purposes. These inorganic solids have received increasing attention since they were first used in these systems by Ghosh and Bard in 1983, who reported the first electrode modified with a clay film. Following the use of natural zeolite on modified carbon paste electrodes for analytical purposes, the clay mineral sepiolite has also been applied for the same purpose.

Some studies have described the use of clays as electrode modifiers or as clay-containing matrices. However, only a few have studied the biomedical applications of clay biosensors or the diversity of biomolecules associated with clay minerals. These materials can be used in electroanalysis because of their electrocatalytic properties and capacity to immobilize biocatalytic enzymes to improve the sensitivity and/or selectivity of the detection process. Biomolecules immobilized on clay minerals supports to develop biosensors that have been reported in literature are summarized in table 2.

Nanostructured materials can be formed by the intercalation of organic molecules, such as antibodies, peptides, proteins, genes, bacteria, cells, polymers, or enzymes within the interlayer, edges, or surface space of the clay minerals. Notably, reports show that enzymes are the most frequently immobilized entities on clay matrices, including their use as amperometric biosensors, because of the sensitivity and specificity of their chemical reactions in these systems. For example, enzymatic biosensors for the detection of catechol, glucose, hydrogen peroxide, and phenol have been developed.

Immobilization should ensure that the biological activity of the immobilized biomolecule is maintained and its stability is preserved or enhanced while providing accessibility to the analytes. In this regard, clay minerals have proved to be suitable materials. Palygorskite represents an excellent inorganic material for the development of biosensors because of its electrocatalytic activity, which may be attributed to its high adsorption capability and the presence of OH groups on its surface. These features allow electron transfer between the electrode and the detected analytes. Furthermore, its large surface area, high biocompatibility, and stability make it a promising material for enzyme immobilization.

Recently, halloysite nanotubes have been developed by evaporative assembly. They are promising natural materials because of their rough surfaces, which provide higher cell capture efficiency compared with blank capillary glass surfaces. Their tubular structure makes them suitable candidates for biomolecule capture and development of enzymatic biosensors. The challenges regarding the development of biosensors based on nanocomposites include the ability of detecting lower concentrations of the analyte of interest, often at the trace level, to ensure the selectivity, sensitivity, and reproducibility of the system.

#### 4.2. Regenerative medicine

Different strategies are required to develop a biomaterial, such as a suitable scaffold, which satisfies the requirements of cells in a three-dimensional support system or as a delivery vehicle incorporating bioactive compounds. Hydrogels, containing including natural polymers, such as chitosan, gelatin, starch, and recently gelan gum, act as integrated networks of scaffolds because of the structural similarity of these components and have the potential to regulate cellular responses. However, their use has some limitations, such as relatively poor mechanical properties, high water sensitivity, or limited ability to support cell adhesion. These difficulties can be overcome by modification of their structure or the incorporation of bioactive molecules, such as proteins, peptides, or clay minerals.

Polymer-clay mineral nanocomposites can contribute to this field because of their high porosity and compressive strength, which remains an ongoing challenge in scaffold design, particularly in bone repair. Another challenge is retaining the growth factors in the matrix in the gel network. In this regard, clay concentrations under 5% (w/w) have shown improvements in the modulus and strength of 3-D materials.
application as drug or biomolecule delivery systems, which rely on their properties of bioadhesion, biodegradability, and cell uptake. These features contribute to maintaining a constant dosage of the bioactive substance within the therapeutic dosage throughout the treatment course.

An experimental study reported the use of montmorillonite/lipid microparticles (75% w/w) under simulated intestinal conditions suggested their development as oral bioadhesive and that encapsulation optimized lipase efficiency as a smart delivery system for lipophilic biomolecules.

In recent studies, a sustained release system based on clay and montmorillonite prepared by ion exchange, differentiation of cells, without changing the uniform morphology and hemocompatibility of the scaffolds.

Another study by Mohd and coworkers, described the use of sodium montmorillonite (Na-MMT) modified with trimethyl ammonium bromide (CTAB-MMT) incorporated into a gellan gum (GG) hydrogel to improve its thermal stability. Cell studies showed that the Na-MMT composite was non-cytotoxic to skin fibroblast cells (CRL2522). In contrast, hydrogels with CTAB-MMT caused death and growth depletion of cells after 72 h.

Another advantage of fibrous clays compared with layered silicates is their very high density of silanol groups, which facilitate in their application to Van der Waals forces at the polymer-silicate interface.

The incorporation of palygorskite nanorods into poly (lactic-co-glycolic acid) matrices contributed to the osteogenic differentiation of cells, without changing the uniform morphology and hemocompatibility of the scaffolds.

Another study by He and coworkers, showed the use of nanopolyglutamate-enhanced virus vector cell productivity, without inducing cytotoxicity. This result suggested a useful strategy to reduce the cost of producing mammalian cell cultures for large-scale tissue engineering.

According to Birowo and coworkers, classical research has focused on bone regeneration; however, recent advances have also enabled the use of clay minerals at the soft tissue sites in the body. For these purposes, greater control of the physico-chemical properties of the biomaterials and their interactions at the body sites need to be evaluated. Future studies might focus on electro-spinning techniques or deposition in layers to develop new nanocomposite materials.

5. Toxicity of clay minerals

Till date, studies elucidating the toxicological effects of clays at physiological concentrations are not conclusive. Importantly, the oral administration of MMT in rats at high doses (1000 mg/kg) did not lead to accumulation in any organ, and cell viability and proliferation remained close to 100% for any concentration of MMT tested in ovine Hamster cells. However, low concentrations of MMT (5 mg/mL) in human intestinal cells led to an acute inflammation, inhibiting cell proliferation after 24 h of incubation, and the same effect was observed in the HepG2 hepatic cell line.

According to Mousa and coworkers, this behavior is closely related to the flocculation of the clay, as well as the high concentration of salts in the culture medium, which contributed to the formation of agglomerates that accumulated around the cells, leading to cellular damage. Ruiz-Hitzky blockage, change, and alteration of cellular metabolism. Thus, it appears that the inhibition of cell proliferation is an indirect effect of clay aggregation rather than a cytotoxic effect of clay itself. This aggregation depends on the surface charge, ion exchange capacity, and the size and morphology of the particles. The authors concluded that the in vitro and in vivo cytotoxicity studies available clearly showed the biocompatibility of the nanomaterials with which they remained stable, i.e., without precipitation. According to the literature, these clay materials are inert. However, there is a lack of information concerning their biodistribution and clearance, and if this depends on whether the clays are solely surgically implanted or administered parenterally. The literature review on the toxicological effects of clays and clay minerals by Maisanaba and coworkers provided conflicting information, wherein in vitro assays generally suggest that clays are cytotoxic, whereas in vivo experiments in rodents showed no systemic toxicity. However, several authors concluded that toxicity should be assessed on a case-by-case basis, because it depends on the modifiers used, experimental methodology to assess cytotoxicity, concentration range, purity of the sample, type of deposit used, and its geological formation conditions and time of exposition.

6. Conclusions

Clay minerals have technological advantages in medical sciences provided by their structural, morphological, and textural characteristics. Clay minerals also have several advantages in biosensor applications, controlled release systems, and tissue engineering, especially their biocompatibility and biodegradability. Notably, possible adverse effects of clay minerals on human health remain unclear and could be related to the presence of impurities in the sample, exposure time, or limitations of the experimental biological studies. Such inorganic nanoparticles, either lamellar or fibrous, are expected to be used in association with a wide variety of biomolecules in biotechnological applications. Recent research reinforces the promising potential of clay minerals in the development of biomaterials.

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