NANOMEDICINE AND NANOTECHNOLOGY JOURNAL Open Access

SCIENTIFIC LITERATURE

REVIEW ARTICLE

Chitosan-Clays Based Nanocomposites: Promising Materials for Drug Delivery Applications

Onnainty R* **and Granero G**

Department of Pharmaceutical Sciences, National University of Cordoba, Argentina

ARTICLE INFO

Article history:
Received: 12October 2017
Accepted: 17November 2017
Published: 23 November 2017

Keywords:
Bionanocomposites;
Drug delivery systems;
Chitosan;
Montmorillonite

Citation this article: Onnainty R, Granero G.Chitosan-Clays Based Nanocomposites: Promising Materials for Drug Delivery Applications.NanomedNanotechnol J. 2017; 1(1):114.

Correspondence:
Dr.Onnainty R,
Faculty of Chemical Sciences,
National University of Cordoba,
X5000HUA, Argentina,
Tel: 54-351-5353865;
Email: glagra@fcq.un.edu.ar

ABSTRACT

There is an increasing interest of using materials called "bionanocomposites" composed of natural biopolymers and mineral clays as promising systems in bionanotechnology. Chitosan (CS) and mineral clays are renewable friendly compounds owing their properties of biocompatibility, biodegradability and low toxicity. These advantageous properties, among others, make the CS-based bionanocomposites in extremely interesting materials for a variety of applications, including drug delivery, medical and pharmaceutics aims. This chapter provides an overview of the most important processing strategies and characterization methods, as well as aspect related to their mucoadhesive, biopharmaceutics and drug release behaviors as requirements like nanocarriers for controlled and targeted drug delivery systems.

Introduction

In the last decade, nanocomposites based on clay minerals and biopolymers for pharmaceutical applications have attracted a great attention [1]. Complex materials constituted by two or more solid phases are often called composites. Most of these materials are commonly constituted by a polymer and an inorganic solid. Nanocomposites are a new class of composites, for which at least one of the dimension of the dispersed particles, is in the nanometer range.

These hybrid materials can, in fact, combine the properties of both inorganic and organic components, such as swelling, water uptake, mechanical properties, thermal behavior, rheology and bioadhesion [2]. Nanocomposites can be constituted by numerous biopolymers (polylactic acid (PLA), polycaprolactone (PCL)) proteins and polysaccharides, like as chitosan (CS), alginate (ALG) and starch, among others) combined with clay minerals such as microfibrous clays (silicates, sepiolite and palygorskite) forming materials with superior properties to those from their individual components. Natural polymer begins to partially replace to synthetic polymers in nanocomposites preparations, mainly in food package and biomedics applications. New nanocomposites are more respectful with environment and recyclable, so they are called green nanocomposites or bionanocomposites. It is especially relevant, the case where the inorganic substrate is also organic, like silicates, including clay family [3].

Nanocomposites obtained by the combination of clay minerals and biopolymers for pharmaceutical applications have attracted a great interest [4], where applications includes, antibacterial coatings for medical instruments and wound dressings, the use of nanoencapsulation technology for improved drug delivery as well as exploiting the optical properties of nanomaterials for enhanced medical imaging [5].

1. Inorganic compound: montmorillonite

The physical and chemical properties of a particular clay mineral are dependent on its structure and composition. These properties of the main industrial clays, i.e., kaolins (1:1 phyllosilicates), smectites (2:1 phyllosilicates) and sepiolite (2:1 inverted ribbons), are very different, even though each of these materials is composed of octahedral and tetrahedral sheets as their basic building blocks. However, the arrangement and composition of these octahedral and tetrahedral sheets, account for the most of the differences in their physical and chemical properties [6]. As previously indicated, a layer is the elementary building block of clay minerals and it consists of sheets of SiO4 4 – tetrahedral and Al3+ or Mg2+octahedral (Figure 1).

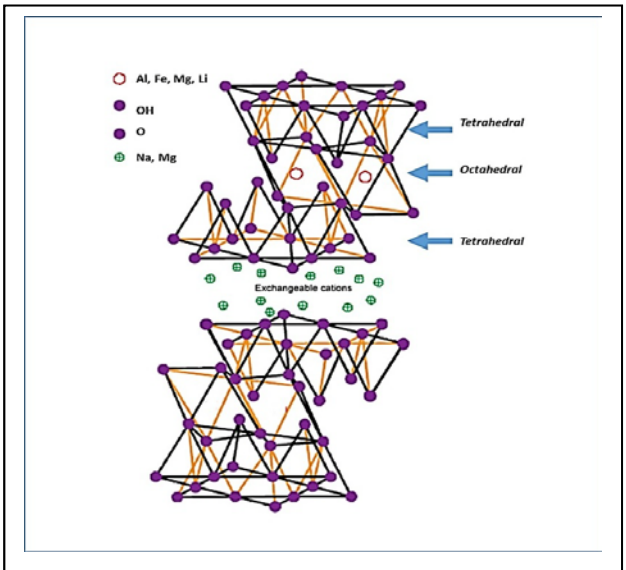

Figure 1: Schematic illustration of the montmorillonite (MMT) structure.

The smectites are within the group of 2:1 clay minerals, consisting of an Al3+, Mg2+ or Fe2+/3+ octahedral sheet, sandwiched between two Si tetrahedral sheets. Because an isomorphs substitution occurs in the octahedral or tetrahedral sheets, layers have a negative charge, which is compensated by exchangeable cations located in the interlayer space. Instead, 1:1 clay minerals consist of layers of Si tetrahedral sheet and Al octahedral sheet (kaolin group) or Mg octahedral sheet (serpentin group). As these materials do not present an isomorphic substitution, their layers are not charged, feature that sets them apart from 2:1 layers clay minerals [7].

The most frequently used solidsto form bionanocomposites are laminar clays as smectites type, like as montmorillonite, hectorite, bentonite and their derivatives with alkylammonium; other solid used are lamellar double hydroxides (HDLs) [8–11]. Zirconium-phosphate (α-ZrP) [12,13] or lamellar perovskites [14].

Montmorillonite (MMT) is a member of the smectite´s minerals group, which is characterized by having a layered structure and a great capacity of adsorption of polymer molecules due to its unique crystal structure. MMT is a phyllosilicate clay, consisting of a multilayered structure of Si/Al oxide arranged in multilayer stacks, characterized by a sandwich structure, comprising two tetrahedron sheets with an edge-bridged octahedral sheet (general structure 2:1 type). MMT possesses a net negative charge due to isomorphs ionic substitutions in its layered structure. This charge is compensated by interlayer cations (mainly Na+ and Mg2+), which can be exchanged by a variety of organic molecules [1]. Silicate minerals are characterized by a layered structure and exhibit properties such as good water absorption, swelling, adsorb and cation exchange abilities that are considered beneficial from the viewpoint of synthesis of pharmaceutical products, as both inactive and active substances [15].

MMT and other mineral clays such as bentonite, combine with polymeric substances, provide materials that have become key resources in the pharmaceutical and biomedical industries as a result of their improved properties and great flexibility [16].

In this regard, these materials may adopt three different clay dispositions according to how they interact with polymersas following (Figure 2):

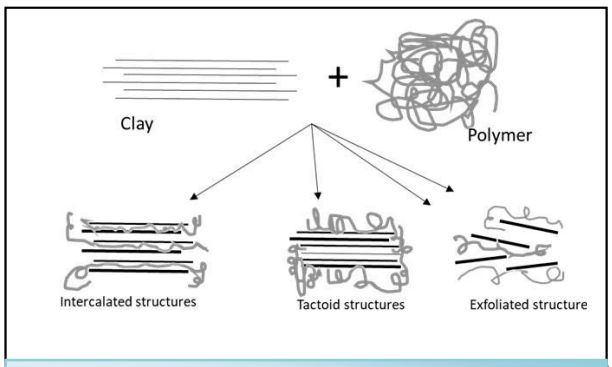

Figure 2: Schematic representation of different clay conformations in the nanocomposite structure.

(1) Tactoidstructures remain in a polymer when the interlayer space of the clay gallery does not expand, usually due to its poor affinity with the polymer. No true nanocomposites are formed with this way.

(2) Intercalated structures are obtained at moderate expansion of the clay interlayer. In this case, interlayer spaces expand slightly as polymer chains penetrate the basal spacing of the clay, but the shape of the layered stack remains. This is the result of moderate affinity between polymer and clay.

(3) Exfoliated structures, clay clusters lose their layered identity and are well separated into single sheets within the continuous polymer phase. This is due to a high affinity between polymer and clay [6].

2. Organic compound: chitosan (CS)

The most of the reported studies on bionanocomposites are related to materials as PLA, PCL, proteins and polysaccharides which incorporating layered silicates of the smectite group. Particularly, the polysaccharides show different charges in their structure: chitosan derived from chitin is provided with positively charged amino groups; alginate extracted from sea algae, is negatively charged bearing carboxylate groups in its structure; and starch obtained from maize, does not have ionic sites in the polymer backbone (neutral charge) [17].

Chitosan (CS), a polysaccharide composed mainly of β-(1,4)-linked 2-deoxy-2-amino-D-glucopyranose units, is the deacetylated product of chitin, poly(N-acetyl-D-glucopyranose) (Figure 3). Next to cellulose, is the second most plentiful natural biopolymer [18]. It is natural amino polysaccharide with a structure with multidimensional properties, highly sophisticated functions and wide-ranging applications in biomedical and other industrial areas. CS is considered to be a material of great futuristic potential due to its great possibilities of structural modifications to impart desired properties and functions, research and development work on CS have reached a status of intense activities in many parts of the world. The positive attributes of excellent biocompatibility and admirable biodegradability with ecological safety and low toxicity with versatile biological activities and low immunogenicity, have provided large opportunities for further development [19]. Also, this polymer has extremely high affinity for many classes of clays [20].

In addition to the important characteristics mentioned, CS has mucoadhesive properties, whereby it is used in pharmaceutical applications to improve the drug retention time in the mucosa membranes of the body, increasing in this way, the bioavailability of compounds [21].

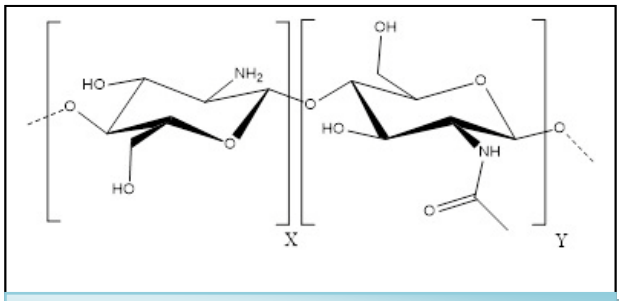

Figure 3: Schematic representation of the structure of chitosan

On the other hand, polymers are usually filled with mineral particles to enhance their stiffness, toughness and other mechanical properties or to simply reduce cost. As the particle size decreases from micro- to nanoscale, the properties of polymer composites also improve significantly. Among all the potential nanocomposites, the composites with clay minerals have attracted much attention because of their availability [22].

Strategies of bionanocomposites synthesis

The polymers in the MMT dispersions interact with the clay particles, according to their ionic or non-ionic

character. The ionic polymers induce electrostatic interactions, but the non-ionic polymers are adsorbed on the surface of clay minerals by the steric interactions. The polymer concentration, as well as its molecular weight and the polymer´s hydrolyzing groups, with the size and shape of the clay particle, its surface charge and the clay concentration in suspension, the pH, and the temperature may all affect the clay/polymer interactions [2].

Several strategies have been developed to synthetize nanocomposites and according to their preparation method,nanocomposites can be divided in five families, as proposed by Kormarneni´s classification:

(I) Nanocomposites prepared by the low temperature sol-gel method;

(II) Nanocomposites obtained by the polymer intercalation in the mineral layers;

(III) Nanocomposites obtained by the polymer entrapment in the solid, resulted in a tridimensional structure like zeolites;

(IV) Electroceramics, derived from ferroelectric materials, dielectrics and superconductors and;

(V) The structural ceramic nanocomposites, prepared by the traditional preparation methods at high temperatures [23].

Herein, it is compiled the four principal methods for producing polymer–layered silicate nanocomposites: intercalation of polymer or pre-polymer from solution; in situ intercalative polymerization; melt intercalation and template synthesis [7,24].

1. Intercalation of polymer or pre-polymer from solution

Here, the layered silicate is exfoliated into single layers using a solvent in which the polymer (or pre-polymer in case of insoluble polymers, such as polyimide) is soluble. It is well known that such layered silicates, owing to weak forces that stack the layers together can be easily dispersed in an adequate solvent. After the organo-clay has swollen in the solvent, the polymer is added to the solution, intercalating between the clay layers. The final step of the process consists of removing the solvent, either by vaporization, usually under vacuum, or by precipitation. Upon solvent removal the sheets reassemble and sandwiching the polymer to form a nanocomposite structure.

The same process is also following to obtained nanocomposites through the emulsion polymerization method, where the layered silicate is dispersed in the aqueous phase. The major advantage of this method is that intercalated nanocomposites can be synthesized with little polar or non-polar polymers. However, the solvent approach is difficult to apply in industry owing to problems associated with the use of large quantities of solvents.

2. In situ intercalative polymerization

In this technique, the layered silicate is swollen within the liquid polymer monomer (or a monomer solution), therefore the polymer is formed and intercalated between sheets of the clay mineral. The polymerization process can be initiated by heat or radiation, by the diffusion of a suitable initiator or by an organic initiator or catalyst fixed through cationic exchange inside the interlayer before the swelling step by the monomer.

3. Melt intercalation

The layered silicate is mixed with the polymer matrix in the molten state. Under these conditions and if the layer surfaces are sufficiently compatible with the chosen polymer, the polymer can crawl into the interlayer space and form either an intercalated or an exfoliated nanocomposite. In this technique, no solvent is required.

4. Template synthesis

This technique, where the silicates are formed in situ in an aqueous solution containing the polymer and the silicate building blocks has been widely used for the synthesis of double-layer hydroxide-based nanocomposites but it is far less developed for obtaining layered silicates. In this technique, based on self-assembly forces, the polymer aids the nucleation and growth of the inorganic host crystals and gets trapped within the layers as it grows.

Of these methods, the most used technique to obtain nanocomposites based in organic and inorganic compounds are the sol-gel and the polymer intercalation in layer solid. In the latter case, the polymer intercalation occurs due to interactions as electrostatics,

hydrogen bound, ion-dipole coordination, etc. between both components [3].

Nanocomposites for drug delivery applications

For therapeutic purposes, a drug must reach specific targeted sites of the organism and maintaining adequate concentration levels in them for longer period of times, in order not to reach the toxic and sub-therapeutic concentrations of the drug.

For the desired effects to be exerted, drug delivery systems are designed to maintain drug levels within a therapeutic window (high enough to be effective but not so high as to be toxic) over extended periods. To achieve this goal, biopolymer/layered silicate material composites as controlled drug delivery vehicles and biomedical engineering have been attracting much attention owing to their unique structure and functional properties.

Specifically, biopolymer-clay composites have a great potential to develop critical formulations for biomedical applications, tissue engineering and controlled drug delivery matrixes. The nanohybrid materials are derived from organic and inorganic solids interacting at nanoscale level. These organic-inorganic hybrids show extraordinary and versatile properties, as they could be formed from a large variety of biopolymers and various nanoscale particles such as layered silicates. Hybrid particles whereby polymer is hosted within a porous carrier matrix can be specifically tailored to modulate the drug release kinetics.

Layered silicate materials, have been used for preparing for this class of composites. Within this group of clay minerals, MMT is an ideal material for the formulation of drug delivery vehicle because it exhibits good adsorption and adhesive abilities, swelling capacity, cation exchange capacity, and drug-carrying potential. Also, MMT is a FDA approved biocompatible clay mineral and it is extensively used as an inert excipient in pharmaceutical products. Nevertheless, the release of drugs from MMT has been tested to be initially very fast, owing to the weak interaction between the drug and the MMT particles [25,26].

Natural polysaccharides are widely being studied for drug delivery and tissue engineering applications. Within this group, it is found CS, which is characterized by to be biocompatible, biodegradable, non-toxic, and a mucoadhesive polymer. However, its limited solubility in water and other organic solvents, in addition to its poor colloidal stability, limits its full exploitation in drug delivery systems. Also, due to its poor mechanical strength and high swelling ratio, CS may lead to burst release of the drug by breaking down the 3D network of the polymer [27].

To overcome these individual limitations, mineral-organic interactions can be used to sustain the release of active ingredients to improve their therapeutic utility, which may provide drug delivery systems with improved properties [28].

Methods to determinate the in vitro drug release from bionancocomposites

1. Dialysis bag technique: Dialysis is a simple process in which small solutes diffuse from a high concentration solution to a low concentration solution across a semipermeable membrane until equilibrium is reached. Since the porous membrane selectively allows smaller solutes to pass while retaining larger species, dialysis can effectively be applied in in vitro drug release studies (Figure4).

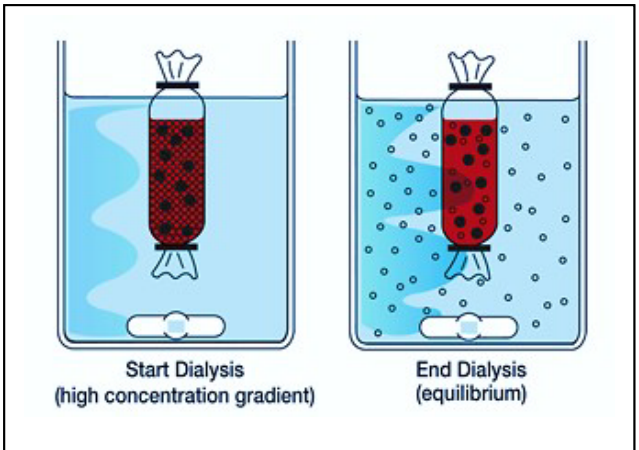

Figure 4: Schematic representation of the Dialysis method.

In these experiments, the nanocomposite system is dispersed in PBS buffer solutions and then sealed in a dialysis bag which is submerged in an appropriated solution. At selected time intervals, appropriate aliquots

from the outside the dialysis bag are removed for drug analysis and replaced with the same volume of the media solution, which is preheated to the corresponding temperature (generally 37 °C) in order to keep the volume of the system identical.

6.1.1. Franz-diffusion cell: In vitro drug release studies of nanocomposites particles could be performed in a Franz-Diffusion cell containing PBS and using a dialysis membrane with a Molecular Weight Cutoff (MWCO) of 10kDa [29]. The membrane is placed over the mouth of the cell, to which the nanocomposite particles is loaded. A magnetic peddle is placed in the cell and maintained at 100 rpm in a magnetic stirrer for uniform mixing. At appropriate intervals, adequate aliquots are removed using a syringe, from the receiver compartment of the Franz-Diffusion cell and replaced with the same volume of fresh phosphate buffer (Figure 5).

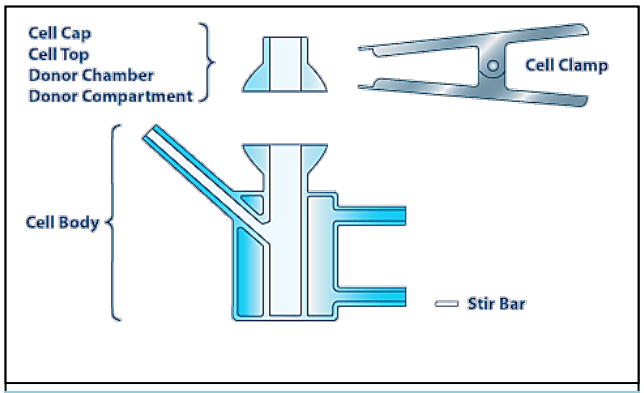

Figure 5: Schematic illustration of the Frank Diffusion Cell.

2. Mechanisms of controlling drug release from nanocomposite systems

2.1. Burst release effect: In controlled-release nanocomposite systems sometimes when the drug delivery system first becomes in contact with the release medium, a rapid and short release of the drug is observed, followed by a stable "plateau" profile. The former is usually referred to as the initial "burst release" (Figure 6).

Although, under certain circumstances, an initial sharp release of the therapeutic could be desirable, it is often unpredictable with uncontrollable duration and dose. However, for the most part, avoiding the burst release effect is desirable to minimize any initial toxicity associated with a high dose.

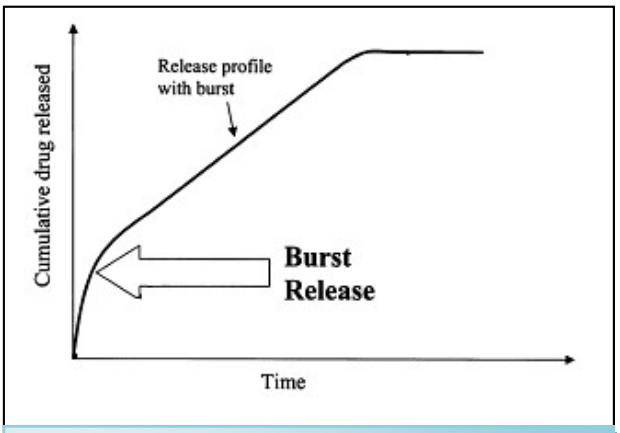

Figure 6: Schematic illustration of a drug release profile from a bionanocomposite system showing an initial short drug release followed by a stable "plateau" stage.

The rapid initial release in nanocomposite systems is thought to occur mainly by the dissolution and diffusion of the drug entrapped close to or at the surface of the formulation. The second and slower release phase may involve the diffusion of the drug entrapped within the inner part of the polymer matrix by means of water channels of the network of the pores. An initial burst effect is observed especially when the drug solubility is high, and when the drug loading dose in the polymeric matrix is large.

2.2. Mechanisms of release of the drug incorporated deeply into the polymer/clay mineral composite system:

Nanocomposites obtained to be used as drug delivery systems are intended to control the drug concentrations on the target site with the aim of maintaining the constant level of the drug over an extended period of time.

In order to understand the release kinetics of the drug from polymer/mineral clay systems, the release data of the drug are fitted to kinetics models including zero-order, first-order, Higuchi, Korsmeyer and Hixson-Crowell equations, among the most frequently used. Also, the Korsmeyer-Peppas model, which is often used to describe the drug release behavior from polymeric systems, may be applied to allow the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix [30].

Particularly, the Korsmeyer-Peppas model is based on the Fick's Law. This model is used to describe the release

of solutes when the prevailing release mechanism is the drug diffusion (Fickian transport), and also in the Case II transport (non-Fickian) controlled by the relaxation of polymer chains.

When the release of the drug from the nanocomposite system can be well modeled by an exponential equation of the type of Korsmeyer-Peppas ($M_t/M_\infty = K.t^n$), the values of n and K may be estimated. According to this model, the value of n identifies the release mechanism of the drug. Values of n between 0.5 and 1.0 indicate anomalous transport kinetics, a value of n approximately of 0.5 indicates a pure diffusion controlled mechanism (Fickian diffusion) and finally, smaller n values than 0.5 may be due to the partially drug diffusion through the swollen matrix and water filled pores in the formulations [31].

The addition of a mineral clay into the polymer matrix could retard the drug release and the matrix erosion because the clay could interact with amino groups of CS, leading to the reduction of CS swelling and to a decrease of the matrix erosion.

The extent of biopolymer´s swelling has been proposed as the dominant mechanism for the drug release in this class of systems. Also, the clay sheets of layered silicate clays such as MMT can create a tortuous path that retards the diffusion of drug molecules through the clay-polymer nanocomposites [32]. By applying a Kormeyer-Peppas model, Onnainty et al,. 2016 obtained n values < 0.5 from the release data of chlorhexidine (CLX) loaded into CS and MMT nanocomposites. Here, the controlled release mechanism of CLX from the carriers was attributed to the diffusion of the drug through the swollen matrix with water filled pores.

On the other hand, the drug release mechanism from polymer-mineral clay systems may be not solely controlled via diffusion and swelling processes, but also by matrix erosion. Mijowska et al., 2015 found that the release kinetics of methotrexate (MTX) is well-defined by Higuchi and Korsmeyer-Peppas models, which suggests parallel processes of diffusion through water-filled mesopores and degradation of the mSiO2 matrix (erosion), so called anomalous diffusion as drug release mechanisms. By fitting the first 60% of the drug release data of the MTX from mesoporous silica nanoflakes to the Korsmeyer-Peppas model, they obtained n values of 0.592 (37 °C) and 0.773 (42 °C), corresponding to so called anomalous diffusion (non-Fickian), and thus MTX release from the mSiO2 nanoparticles was controlled by more than one process.

Determination of in vitro mucoadhesion of the nanocomposites

Mucoadhesive formulations are developed for buccal, nasal, ocular, vaginal, pulmonary and oral applications. Bioadhesion or mucoadhesion is described as the binding ability of a substance, such as natural or modified natural hydrophilic polymers, to biological tissues.

The mucosal surfaces of the body are covered with a layer of mucus gel, which is comprised of water and mucin. Mucus consists mainly of water, inorganic salts, cahrbohydrates, lipids and glycoproteins. Mucus glycoproteins, which are also called mucins, consist of a protein core with branched oligosaccharide chains attached over 63 % of its length. Mucins are also responsible for the gel-like properties of the mucus [35].

Mucus is an entangled fiber matrix with many weak non-covalent interactions such as hydrogen bonding and electrostatic interactions. Mucins form a fully hydrated viscoelastic gel layer. Almost all mucins are negatively charged due to the presence of anionic sialic, sulfate and carboxyl functional groups [36]. Thus, mucins are a negatively charged hydrogel with the matrix tangled in a randomly woven polyionic network.

Humans secrete liters of mucus each day to protect mucosal surfaces, including those of the airways, gastrointestinal tract, female reproductive tract, respiratory tract and surface of the eye. Therefore, bioadhesive materials are promising substances for designing site-specific drug delivery systems to the mucosal surfaces of the body.

One approach to increase the mucoadhesion properties of drug delivery systems involves the use of polymer materials with mucoadhesive properties such as chitosan (CS). Positively charged CS can adhere to negatively charged sialic and sulfonic acids in the mucus layer via electrostatic interactions, but also CS possesses

mucoadhesive properties due to the presence of many amino groups in the polymer chains that form hydrogen bonds with mucins in the mucus [37]. This CS´s last property is associated with optimal mucoadhesion characteristics of the polymer, since it has been demonstrated that polymers with low swelling degrees show a higher mucoadhesion characteristics, which could be attributed to the dehydration of the mucus gel to form adhesive joints at low hydration. Thus, as the swelling degree of the polymer is reduced, the mucoadhesion increased [39]. It has been reported that the incorporation of montmorillonite (MMT) into the hydrogel matrix of starch-graft-poly (methacrylic acid) can significantly enhance the mucoadhesion properties of the hydrogel [40].

One of the methods employed to determinate mucoadhesion is by Scanning Electron Microscopy (SEM), were a 0.1 mg/ml mucin solution is brought into contact with the formulation in PBS buffer pH 7.4. After a suitable equilibration time, a drop of the resulting mucin gel dries by vacuum and then it is sputtered with gold before obtaining the SEM images. Herein, the in vitro mucoadhesion is indicated by the changes observed in the SEM image of mucinfibers after incubation with the formulation to be studied. Onnainty et al. 2016 showed by using this technique the mucoadhesive properties of the chlorhexidine (CLX) loaded intothe CS/MMT nanocomposite. They observed that the SEM image of the pig gastric mucin (PGM) without contact with the formulation, whichis hydrated, displays an elastic dominant gel structure, and looks as a swollen network due to mucinfibers are expanded and occupy the entire volume of the mucin gel layer (Figure 7a). However, the SEM image of PGM with added the CLX/CS: Na+MMTnanocomposite exhibits a noticeable change in the mucin network (Figure 7b).

Potential applications of nanocomposite as bioadhesive-drug delivery systems

The new hybrid materials based on the combination of a natural polymer, such as CS, with a clay mineral, like MMT, are interesting strategies in the field of the controlled delivery of therapeutics due to the characteristics of these materials, since they not only allow the release of drug molecules at the correct target place, but also they could decrease the toxicity of many therapeutics due to they are able to release theencapsulated or entrapped therapeutics slowly in a localized and controlled and in a sustained manner.

These hybrid systems could also enable routes of drug administration with limited systemic absorption and enhance the drug bioavailability by localizing the drug delivery system to mucosal surfaces.

For example, the administration of drugs into the oral cavity presents many limitations such as the significant loss of drug due to the uncontrolled swallowing and salivary flow. Therefore, a delivery system intended for the oral administration of a therapeutic agent for the local treatment of the oral cavity should maintain therapeutic levels of the drug over an extended period of time [41]. To meet these requirements, the formulation should adhere to the oral mucosa and stay in the place for an extended period of time to allow the treatment be effective.

In this context, Onnainty et al. 2016 proposed a CLX nanocomposite system combining CS and MMT for the controlled oral mucosal delivery of this drug. Chlorhexidine is considered the gold standard antiseptic that is active against Gram-positive and Gram-negative bacteria, molds, yeasts and viruses [42]. CLX hybrid nanosystems exhibited good mucoadhesive properties and they were able to release the drug in a sustained way, without a burst effect being observed.

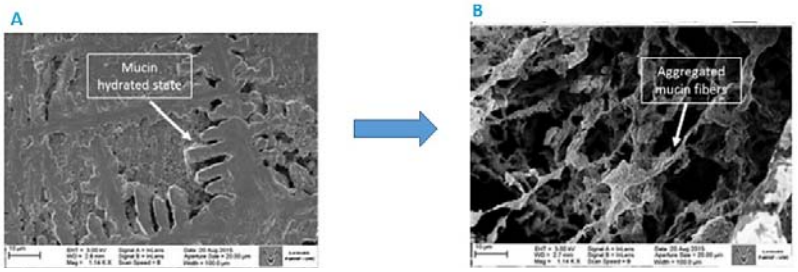

Figure 7: SEM images of, A: hydrated Pig Stomach Mucin (PSM) and B: PSM incubated with the CLX/CS: Na+MMTnanocomposite formulation.

Mucoadhesive controlled drug delivery systems have the following advantages in comparison to conventional formulations:

1) The ability to adhere to specific sites of the body, such as the oral, nasal, buccal, respiratory, vaginal cavities, to improve drug bioavailability.

2) The formation of an optimum contact with mucosa of the body, increasing drug absorption.

3) They are able to prolong the residence time of the dosage form in the place of absorption and therefore,to decrease the need for multiple dosing and increasing the drug absorption.

A sustained drug delivery to the mucosal surfaces of the body has also the potential for improving the treatment and prevention of many diseases, including sexually transmitted infections, inflammatory bowel disease, lung inflammation, and degenerative eye conditions, among others.

To mention an example, within the chemotherapeutic drugs used for the treatment of different types of cancer, such as the colorectal cancer, among others, one available option is 5-fluorouracil (5-FU). However, this drug presents many limitations such as short biological half-life, incomplete oral absorption, toxic side effects on bone marrow and gastrointestinal tract (TGI) and non-selective action against healthy cells [43]. To overcome all these constraints, [44] it was proposed to obtain 5-FU nanocomposite systems combining Na+montmorillonite (Na+MMT) and CS. The 5-FU hybrid systems obtained allowed maintaining the plasma drug concentrations within the drug therapeutic window when these systems were administered in rats orally. Moreover, the maximum drug plasma concentration (C max) achieved by the pristine drug after a single oral dose administration was much higher than the highest tolerance level of the drug concentration in the plasma, which could be associated with serious side effects. Also, it was found that the 5-FU nanocomposites improved the residence time of the drug in the plasma in comparison with the pristine 5-FU, which may reduce the drug toxicity. Also, the drug was release in a controlled way from clay and clay/polymer nanocomposites and efficiently distributed to various tissues of the rat, showing a marked reduction of the drug hepatotoxicity.

Joshi et al. 2012 proposed a controlled delivery system of quinine (QUI), an antiprotozoal agent, loaded in CS/MMT nanocomposite systems for the colon specific drug delivery [45]. These QUI nanocomposite systems were placed into gelatin capsules coated with Eudragit® L 100 to prevent the drug release in the gastric environment after the oral administration of the QUI formulation. It was found that the release rate of QUI could be controlled by varying the proportion of CS in these systems.

Otherwise, the nanocomposite vehicles based on CS and MMT also demonstrated utility to improve the intestinal permeability of drugs, such as, for example, the broad-spectrum antimicrobial agent oxytetracycline (OXT). Salcedo et al., 2014 found that the OXT loaded nanocomposite system, although in a first stage slightly decrease the drug permeability, subsequently the drug permeation was kept linear during in vitro permeability tests across Caco-2 cell monolayers, unlike what happens with the drug alone, where the drug permeability was almost constant [46]. These behaviors were attributed to the limited permeability of OXT across the intestinal epithelium due to this drug is subject to P-glycoprotein (P-gp) efflux, while the nanocomposite could elude the P-gp efflux, which may increase the drug permeability.

Conclusion

In conclusion, the hybrid materials especially that combining chitosan and a layered mineral clay like montmorillonite are promising materials candidates as drug delivery systems of a wide variety of therapeutic agents.

References

1. Aguzzi C, Cerezo P, Viseras C, Caramella C. (2007). Use of clays as drug delivery systems: Possibilities and limitations. Appl Clay Sci. 36: 22–36.

2. Günister E, Pestreli D, Ünlü CH, Atici O, Güngör N. (2007). Synthesis and characterization of chitosan-MMT biocomposite systems. CarbohydrPolym. 67: 358–365.

3. Darder M, Ruiz-hitzky E. (2007). InvestigaciónQuímica Bio-nanocomposites : nuevosmaterialesecológicos ,biocompatibles y funcionales. 103: 21–29.

4. Viseras C, Cerezo P, Sanchez R, Salcedo I, Aguzzi C. (2010). Current challenges in clay minerals for drug delivery. Appl Clay Sci. 48: 291–295.

5. Besinis A, De Peralta T, Tredwin CJ, Handy RD. (2015). Review of nanomaterials in dentistry: Interactions with the oral microenvironment, clinical applications, hazards, and benefits. ACS Nano. 9: 2255–2289.

6. Maisanaba S, Pichardo S, Puerto M, Gutiérrez-Praena D, Cameán AM, et al. (2015). Toxicological evaluation of clay minerals and derived nanocomposites: A review. Environ Res.138: 233–254.

7. Alexandre M, Dubois P. (2000). Polymer-layered silicate nanocomposites: Preparation, properties and uses of a new class of materials. Mater SciEng R Reports. 28: 1–63.

8. Parello ML, Rojas R, Giacomelli CE. (2010). Dissolution kinetics and mechanism of Mg-Al layered double hydroxides: A simple approach to describe drug release in acid media. J Colloid Interface Sci. 351: 134–139.

9. San Román MS, Holgado MJ, Salinas B, Rives V. (2012). Characterisation of Diclofenac, Ketoprofen or Chloramphenicol Succinate encapsulated in layered double hydroxides with the hydrotalcite-type structure. Appl Clay Sci. 55: 158–163.

10. Fernandes FM, Baradari H, Sanchez C. (2014). Integrative strategies to hybrid lamellar compounds: An integration challenge. Appl Clay Sci. 100: 2–21.

11. Amaro LP, Cicogna F, Passaglia E, Morici E, Oberhauser W, et al. (2016). Thermo-oxidative stabilization of poly(lactic acid) with antioxidant intercalated layered double hydroxides. PolymDegrad Stab. 133: 92–100.

12. Bhowmick A, Jana P, Pramanik N, Mitra T, Banerjee SL, et al. (2016). Multifunctional zirconium oxide doped chitosan based hybrid nanocomposites as bone tissue engineering materials. CarbohydrPolym. 151: 879–888.

13. Bhowmick A, Pramanik N, Jana P, Mitra T, Gnanamani A, et al. (2017). Development of bone-like zirconium oxide nanoceramic modified chitosan based porous nanocomposites for biomedical application. Int J BiolMacromol. 95: 348–356.

14. Liu P, Zhu L, Guo J, Wang A, Zhao Y, et al. (2014). Palygorskite/polystyrene nanocomposites via facile in-situ bulk polymerization: Gelation and thermal properties. Appl Clay Sci. 100: 95–101.

15. Yuan Q, Shah J, Hein S, Misra RDK. (2010). Controlled and extended drug release behavior of chitosan-based nanoparticle carrier. ActaBiomater. 6: 1140–1148.

16. Xie DF, Martino VP, Sangwan P, Way C, Cash GA, et al. (2013). Elaboration and properties of plasticised chitosan-based exfoliated nano-biocomposites. Polym (United Kingdom). 54: 3654–3662.

17. Alcântara ACS, Darder M, Aranda P, Ruiz-Hitzky E. (2014). Polysaccharide-fibrous clay bionanocomposites. Appl Clay Sci. 96: 2–8.

18. Wang SF, Shen L, Tong YJ, Chen L, Phang IY, et al. (2005). Biopolymer chitosan/montmorillonitenanocomposites: Preparation and characterization. PolymDegrad Stab. 90: 123–131.

19. Pillai CKS, Paul W, Sharma CP. (2009). Chitin and chitosan polymers: Chemistry, solubility and fiber formation. ProgPolym Sci. 34: 641–678.

20. Monvisade P, Siriphannon P. (2009). Chitosan intercalated montmorillonite: Preparation, characterization and cationic dye adsorption. Appl Clay Sci. 42: 427–431.

21. Ayensu I, Mitchell JC, Boateng JS. (2012). In vitro characterisation of chitosan based xerogels for potential buccal delivery of proteins. CarbohydrPolym. 89: 935–941.

22. Hsu SH, Wang MC, Lin JJ. (2012). Biocompatibility and antimicrobial evaluation of montmorillonite/chitosan nanocomposites. Appl Clay Sci. 56: 53–62.

23. Komarneni S. (1992). Feature article. Nanocomposites. J Mater Chem. 2: 1219–1230.

24. Pavlidou S, Papaspyrides CD. (2008) A review on polymer-layered silicate nanocomposites. ProgPolym Sci. 33: 1119–1198.

25. Kevadiya BD, Joshi GV, Patel H, Ingole PG, Mody HM, et al. (2010). Montmorillonite-alginate nanocomposites as a drug delivery system: intercalation and in vitro release of vitamin B1 and vitamin B6. J Biomater Appl. 25: 161–177.

26. Kevadiya BD, Joshi GV, Bajaj HC. (2010). Layered bionanocomposites as carrier for procainamide. Int J Pharm. 388: 280–286.

27. Dinu MV, Cocarta AI, Dragan ES. (2016). Synthesis, characterization and drug release properties of 3D chitosan/clinoptilolitebiocompositecryogels. CarbohydrPolym. 153: 203–211.

28. Kevadiya BD, Rajkumar S, Bajaj HC. (2015). Application and evaluation of layered silicate–chitosan composites for site specific delivery of diclofenac. Biocybern Biomed Eng. 35: 120–127.

29. Subramanian SB, Francis AP, Devasena T. (2014). Chitosan–starch nanocomposite particles as a drug carrier for the delivery of bis-desmethoxycurcumin analog. CarbohydrPolym. 114: 170–178.

30. Dash S, Murthy PN, Nath L. Chowdhury P. (2010). Kinetic modeling on drug release from controlled drug delivery systems (review). Acta Pol Phamaceutica - Drug Res. 67: 217–223.

31. Jose S, Fangueiro JF, Smitha J, Cinu T, Chacko J, et al. (2013). Predictive modeling of insulin release profile from cross-linked chitosan microspheres. Eur J Med Chem. 60: 249–253.

32. Ambrogi V, Pietrella D, Nocchetti M, Casagrande S, Moretti V, et al. (2016). Montmorillonite–chitosan–chlorhexidine composite films with antibiofilm activity and improved cytotoxicity for wound dressing. J Colloid Interface Sci. 491: 265-272.

33. Onnainty R, Onida B, Páez P, Longhi M, Barresi A, et al. (2016). Targeted chitosan-based bionanocomposites for controlled oral mucosal delivery of chlorhexidine. Int J Pharm. 509: 408–418.

34. Mijowska E, Cendrowski K, Barylak M, Konicki W. (2015). Sandwich-like mesoporous silica flakes for anticancer drug transport-Synthesis, characterization and kinetics release study. Colloids Surfaces B Biointerfaces. 136: 119–125.

35. Depan D, Kumar AP, Singh RP, Han YS, Lee SH, et al. (2014). *In vitro* biocompatibility and mucoadhesion of montmorillonite chitosan nanocomposite: A new drug delivery. CarbohydrPolym. 6: 196–205.

36. Ashton L, Pudney PDA, Blanch EW, Yakubov GE. (2013). Understanding glycoprotein behaviours using Raman and Raman optical activity spectroscopies: Characterising the entanglement induced conformational changes in oligosaccharide chains of mucin. Adv Colloid Interface Sci. 199–200: 66–77.

37. Bravo-Osuna I, Vauthier C, Farabollini A, Palmieri GF, Ponchel G. (2007). Mucoadhesion mechanism of chitosan and thiolated chitosan-poly (isobutyl cyanoacrylate) core-shell nanoparticles. Biomaterials. 28: 2233–2243.

38. Liu KH, Liu TY, Chen SY, Liu DM. (2007). Effect of clay content on electrostimulus deformation and volume recovery behavior of a clay-chitosan hybrid composite. ActaBiomater. 3: 919–926.

39. Mortazavi ASSJD. (1994). An in-vitro method for assessing the duration of mucoadhesion. J Control Release. 31: 207–212.

40. Guler MA, Gok MK, FigenAyselKanturk, Ozgumus S. (2015). Swelling, mechanical and mucoadhesion properties of Mt/starch-g-PMAA nanocomposite hydrogels. Appl Clay Sci. 112–113: 44–52.

41. Aduba DC, Hammer J, Yuan Q, Andrew Y, eudall W, et al. (2013). Semi-interpenetrating network (sIPN) gelatin nanofiber scaffolds for oral mucosal drug delivery. ActaBiomater. 9: 6576–6584.

42. Kolahi J, Soolari A. (2006). Rinsing with chlorhexidinegluconate solution after brushing and flossing teeth: a systematic review of effectiveness. Quintessence Int. 37: 605–612.

43. Li S, Wang A, Jiang W, Guan Z. (2008). Pharmacokinetic characteristics and anticancer effects of 5-fluorouracil loaded nanoparticles. BMC Cancer. 8: 103.

44. Kevadiya BD, Patel T, Jhala DD, Thumbar RP, Brahmbhatt H, et al. (2012). Layered inorganic

nanocomposites: A promising carrier for 5-fluorouracil (5-FU). Eur J Pharm Biopharm. 81: 91–101.

45. Joshi GV, Kevadiya BD, Mody HM, Bajaj HC. (2012). Confinement and controlled release of quinine on chitosan-montmorillonitebionanocomposites. J PolymSci Part A Polym Chem. 50: 423–430.

46. Salcedo I, Sandri G, Aguzzi C, Bonferoni C, Cerezo P, et al. (2014). Intestinal permeability of oxytetracycline from chitosan-montmorillonitenanocomposites. Colloids Surfaces B Biointerfaces [Internet]. 117: 441–448.