

## Review

## Kaolinite in pharmaceutics and biomedicine



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## ARTICLE INFO

## Keywords:

Kaolinite

Excipient

Active pharmaceutical ingredient

Drug carrier

Cosmetic

Pelotherapy

New health care uses

## ABSTRACT

Kaolinite  $\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4$  is an abundant and inexpensive geomaterial regarded as one of the most common clay minerals in the earth's crust and the most widespread phase among the other kaolin polymorphs (halloysite, dickite and nacrite). Structurally, it is a hydrous aluminum phyllosilicate member belonging to the dioctahedral 1:1 kaolin mineral group. The particle size of the pseudohexagonal kaolinite platelets is normally  $< 2 \mu\text{m}$  (if compared to a human red blood cell of a typical diameter  $6.2\text{--}8.2 \mu\text{m}$  or to a virus particle of about  $50 \text{ nm}$  diameter). The kaolinite platelets, either stacked together with a common booklet-like shape in a highly ordered structure (well crystallized) or disordered structure (poorly crystallized), consist of layers considered as a strong dipole of hydrophobic siloxane surface dominated by negative charges, and the other hydrophilic aluminol surface carries positive charges.

Kaolinite has been used in many pharmaceutical applications as excipient or active ingredient, because it exhibits excellent physical, chemical and surface physicochemical properties. In addition to their classical pharmaceutical uses, kaolinite and its derivatives have been recently considered as a promising material in many biomedical innovation areas such as drug, protein and gene delivery based on the high interaction capacities with organic and biochemical molecules, bioadhesion and cellular uptake.

Pharmaceutical kaolin grades are considerably demanded for usage as excipient in formulations of solid and semi-solid dosage forms. The most important functionalities of kaolin used as excipient are reported as diluent, binder, disintegrant, pelletizing and granulating, amorphizing, particle film coating, emulsifying and suspending agent. Because of its uninjured bioactivity, kaolinite has been also used as active agent for treatment of some common diseases. It can be topically administered as hemostatic agent, dermatological protector, anti-inflammatory agent and in pelotherapy, or orally as gastrointestinal protector, and antibacterial, antiviral, detoxification or antidiarrheal agent.

With these premises, the future of kaolinite in health-care uses is strongly interesting, especially in the development of pharmaceutical and cosmetic industries. In biomedical investigations, it can be considered as a promising natural geomaterial for designing new derivatives that can contribute in the trials of discovering new therapeutic systems and treatment pathways of global challenge diseases such as cancer, viruses, antibiotic resistant bacteria, alzheimer, chronic skeletal muscular and geriatric diseases.

## 1. Introduction

Kaolinite has been used in medicine for centuries. In fact, their healing utilities (and those of other clay minerals, and thus the name of “healing clays”) have been discovered and preserved on papyrus, clay tablets and manuscripts since the antique civilizations (Egyptians, Assyrians, Babylonians, Indians, Chinese), Greeks, Romans, and medieval Arab Muslims till the recent times (Duffin et al., 2013). The

medicinal use of kaolinite, and other clays, became rooted in post-medieval western literatures, especially after appearance of the more empirical approach to pharmacology, the establishment of pharmacopoeias, the developments of mineralogy, chemistry and pharmaceutical technology, advancements in instrumental techniques and enhancement of the therapeutic reputation of minerals by research scholars. In the recent decades, attentions have been paid to use kaolin minerals, with specific requisites, for solid and semisolid pharmaceutical

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preparations used as topical and oral administrations as well as cosmetic formulations. The applications depend on the physical, chemical, mechanical, and rheological properties of kaolin minerals, that act as active component or as excipient by controlling the efficiency of the dosage forms, and/or improving the drug bioavailability (Heinz, 2012; Carretero et al., 2013; Zhu and Njuguna, 2014; Ghadiri et al., 2015; Khurana et al., 2015; Kim et al., 2016; Yuan et al., 2016; Rautureau et al., 2017; Williams, 2017).

## 2. Some generalities about kaolin minerals

The term “kaolin” is the name of a clay mineral group, but it is also used to describe argillaceous rocks very rich in kaolinite or halloysite (> 75%), considered as raw material of greatest industrial importance.

Kaolinite is one of the most common clay minerals in the earth's crust; it is more abundant than the fibrous attapulgite and sepiolite, but follows illite and montmorillonite in their geological relative distribution. It is hydrous aluminum phyllosilicate member belonging to the dioctahedral 1:1 kaolin mineral group. Indeed, kaolinite is the most widespread phase amongst the other kaolin polymorphs, namely halloysite, dickite and nacrite (Weaver and Pollard, 1973). This predominance is due to differences on the original prevailed processes involved: kaolinite is usually formed as a secondary mineral through several sedimentary depositional processes, whereas halloysite is frequently formed as *in situ* alteration products of aluminous felsic igneous and metamorphic rocks, by hydrothermal or weathering processes giving rise to residual (saponite) deposits; dickite and nacrite are normally restrained to primary hydrothermal deposits. Potassium feldspars and muscovite are the most common primary minerals of all kaolin polymorphs, which are transformed into kaolinite by leaching out potassium and silica during weathering or hydrothermal alteration processes.

Frequently, low quantities of silt to clay sized particles of other minerals are associated with secondary kaolinite, particularly quartz, illite and anatase, but also smectite, hematite, goethite, pyrite and marcasite, while in primary kaolin deposits significant amounts of quartz, feldspars, muscovite, tourmaline, zircon, rutile and pseudorutile are common (Pruett, 1993; Hurst and Pickering, 1997).

The theoretical structural formula of kaolin minerals is  $\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4$ , that means 46.54%  $\text{SiO}_2$ , 39.50%  $\text{Al}_2\text{O}_3$  and 13.96% loss on ignition as structurally bonded hydroxyls. Raw kaolin, however, shows some contents of other elements, due to the presence of the cited associated mineral impurities. Essentially,  $\text{SiO}_2$  is increased with quartz content,  $\text{K}_2\text{O}$  and  $\text{SiO}_2$  is increased proportional to mica content,  $\text{MgO}$ ,  $\text{CaO}$  and  $\text{SiO}_2$  are typically raised according with the smectite content,  $\text{TiO}_2$  is normally identical with anatase, rutile or pseudorutile contents,  $\text{Na}_2\text{O}$  and/or  $\text{K}_2\text{O}$  are related to feldspars contents, and  $\text{Fe}_2\text{O}_3$  content is mainly considered to iron oxo-hydroxides minerals and rarely to iron-substituted kaolinite (Kogel et al., 2006; Bleam, 2017). Occasionally, noticeable contents of  $\text{CaO}$  and/or  $\text{MgO}$  are owed to carbonate minerals (calcite, dolomite), and significant  $\text{Cl}^-$  with or  $\text{SO}_3^{2-}$  to halite or gypsum, respectively (Schroeder et al., 2004; Kogel et al., 2006; Wilson, 2013). Trace amounts of Cr, Zr and Nb in raw kaolin deposit are mainly due to substitution for Ti in anatase. In relation to color, the whiteness of kaolinite is normally directly correlated with Fe and Ti minerals (Awad et al., 2017).

Kaolinite normally appears as stacked pseudo-hexagonal platelets, < 2  $\mu\text{m}$  in size, with a common booklet-like shape (Fig. 1). Each platelet is considered as an arrangement of several layers, each of which consists of two basal (001) planes: the tetrahedral silica sheet, with O atoms bonded to Si atoms, and called the “siloxane surface”, and the octahedral alumina sheet, with OH groups bonded to Al, called the “aluminol surface”. Both sheets share the apical O atoms (Fig. 2). Each kaolinite layer is considered as a strong dipole, where the siloxane surface is hydrophobic and dominated by negative charges, while the aluminol surface exhibit positive charges and is hydrophilic. Thus, the

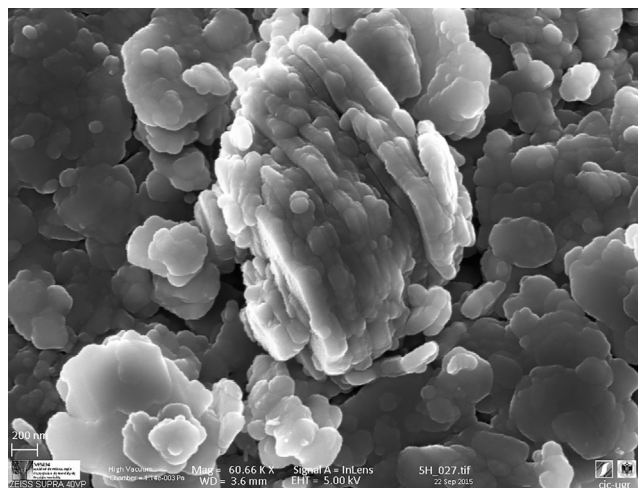


Fig. 1. Scanning electron microscopy (SEM) image of kaolinite particles showing aggregates of booklet-like stacked platelets.

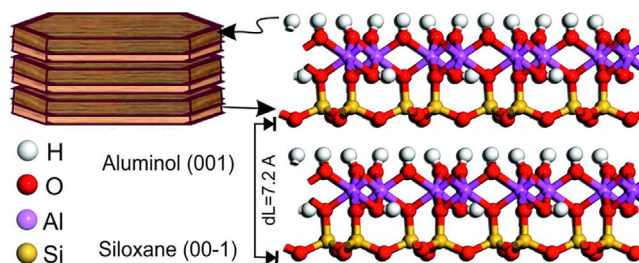


Fig. 2. Molecular simulation model of kaolinite structure (1 × 2 × 2 unit cells) showing siloxane and aluminol surfaces.

individual layers of kaolinite are strongly bonded by hydrogen and dipolar interactions.

The edges of these layers contain O atoms and OH groups. In an acidic medium (pH < 3.6), the hydroxyls take up a proton from the solution to form protonated OH groups, or release a proton to the solution to form  $\text{O}^-$  at pH > 3.6. Therefore, there are two types of charges on the kaolinite surfaces: the permanent negative charge on the tetrahedral face and the variable pH-dependent charge, either positive or negative, caused by the protonation or deprotonation of hydroxyls on the amphoteric sites, at the edges and the octahedral faces (Murray and Keller, 1993; Conley 1996; Galagay, 2006; Tombácz and Szekeres, 2006; Murray, 2007; Hu and Yang, 2013).

The platelets of the dickite and nacrite exhibit a rather similar planar pseudo-hexagonal morphology, but halloysite particles appear as spheres or tubes of typically 0.5–10  $\mu\text{m}$  in length and 30 nm in diameter. The structural differences among these polymorphs resulted from the distribution of vacant sites in the octahedral sheet, the stacking interlayer expansion and the hydroxyl group orientations. Notably, the larger  $\text{Fe}^{+3}$  substituted  $\text{Al}^{+3}$ , and interlayer water molecules are accommodated within the halloysite structure (Joussein et al., 2005; Kogure et al., 2005; Brigatti et al., 2006; Detellier and Schoonheydt, 2014).

Kaolinite crystallinity, as a measure of stacking order or disorder in kaolinite platelets, is generally expressed by the Hinckley Index (HI, Hinckley, 1963) into poorly ordered or poorly crystallized kaolinite (HI < 0.6) and well ordered or well crystallized kaolinite (HI > 0.7, Kogel et al., 2006). Other indices have been proposed (Aparicio and Galán, 1999; Chmielová and Weiss, 2002). Besides the particle size and surface area, most of the physicochemical, mechanical and rheological properties of kaolinite depend on its crystallinity. In fact, well crystallized kaolinite is typically soft with coarse particle size (< 70 wt % < 2  $\mu\text{m}$ ), whereas poorly crystallized kaolin is typically hard with

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