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Pharmaceutical Studies on Egyptian Kaolins for Healthcare Uses

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INDEX

RESUMEN

El presente estudio tiene como objetivo evaluar, por primera vez, la potencialidad de los depósitos de caolín egipcio de Abu Zenimacon una reserva estimada de 120 millones de toneladas, para su empleo en ámbito farmacéutico. El distrito del caolín estudiado cubre aproximadamente 333 Km^2 de tierras cultivadas y accesibles que se encuentra en la parte oeste de la península central del Sinaí, entre la longitud 33˚ 14 00″ y 33˚ 24 00″ E y la latitud 28˚ 52 00″ y 29˚ 10 00″ N. Los objetivos del estudio se centran en conocer las características de calidad farmacéutica, que incluyen parámetros mineralógicos y tecnológicos destinados a establecer la identidad, pureza y riqueza de las muestras de caolines y sus posibilidades de empleo farmacéutico y aplicaciones biomédicas.

Sesenta y cinco muestras representativas de las siguientes localizaciones: tres secciones compuestas expuestas en WadiKhaboba (12 muestras, codificadas por K, espesor total 20 m, a 29˚ 05 01″ N y 33˚ 14 46″ E), GabalHazbar (5 muestras, codificadas por H; 12 m ; a 29˚ 04 45″ N y 33˚ 22 05″ E) y Wadi Abu Natash (12 muestras, codificadas por N; 19 m; 28˚ 56 45″ N y 33˚ 19 24″ E) en lugares que pertenecen a sedimentos carboníferos; además de otras tres secciones relacionadas con los sedimentos cretáceos que afloraron en Gabal El Dehessa (10 muestras, codificadas por D, 14 m, a 28˚ 55 55″ N y 33˚ 17 59″ E), GabalFarsh El Ghozlan (13 muestras, codificadas por F; 21 m; a 28˚ 55 40″ N y 33˚ 18 10″ E) y WadiBudra (13 muestras, codificadas por B; 20 m; a 28˚ 55 06″ N y 33 ˚ 19 16″ E).

Paralelamente al trabajo de recogida de muestras se llevó a cabo una profunda revisión bibliográfica del empleo farmacéutico de la caolinita, para comprender sus funciones, especificaciones, límites, criterios de uso y parámetros de control. Los resultados y conclusiones

de estos estudios previos se consideran información y orientación importantes para las posibilidades de explotación, así como también revelan nuevas hipótesis y tendencias para las funcionalidades de los grados variados de caolín.

Los estudios preformulativos se llevaron a cabo estableciendo la identidad de las muestras mediante análisis mineralógicos (XRD) y químicos (XRF) para determinar los óxidos principales, oligoelementos y para calcular el contenido mineral de caolín y las impurezas asociadas, además del caolinita, grados de desorden de orden estructural y tamaño de cristal.

La caracterización farmacéuticase completó con estudios de colorimetría mediante espectrofotómetro para medir los parámetros cromáticos y de blancura del laboratorio CIE, propiedades reológicas y tixotropía de las suspensiones acuosas de las muestras, geometría de partículas y distribución de tamaños y parámetros de clasificación mediante granulometría láser y micromorfología de partículas (SEM).

Otros estudios específicos se realizaron a las muestras de mayor pureza: análisis químico complementario para determinar micromposicionesel ICP para cuantificar la presencia de metales pesados. Asimismo, se determinó la cinética de enfriamiento de suspensiones de arcillas en agua, en vistas a su empleo en termoterapia.

Los resultados demostraron que la mitad de las muestras estudiadas contenían valores superiores al 75% m/m de caolinita, siendo superior al 90% m/m en 1 de cada cinco. Las muestras de alta pureza cumplen con los requisitos de empleo como excipientes farmacéuticos Las muestras de menor pureza podrían tener utilidad, una vez tratadas. El presente sirve de orientación, con un valor económico añadido para la explotación y comercialización de los recursos de caolín egipcio, sirviendo además para futuras investigaciones de desarrollo

decaolinita para aplicaciones en salud. El estudio confirmó, además, la idoneidad de algunos de los caolines egipcios en peloterapia.

ABSTRACT

The present study aims to evaluate, by the first time, the potentiality of the Egyptian Abu Zenima kaolin deposits of the estimated reserve 120 million tons, for healthcare uses. The studied kaolin district covers about 333 Km^2 of cultivated and accessible land that lies at west central Sinai Peninsula, between longitude 33° 14′ 00″ and 33° 24′ 00″ E and latitude 28° 52′ 00″ and 29° 10′ 00″ N. The objectives of the study are also to conclude the pharmaceutical quality characteristics that considered as mineralogical and technological parameters used for controlling the kaolins purity upgrading with limiting the applicability of exploiting their low grade zones, and criteria of developments for functionality in pharmaceutical and biomedical applications.

Sixty-five representative samples were collected carefully to avoid any contaminations and properly as proportional with both of layers thicknesses and their lateral extents within the outcropped sections of the studied kaolin deposits. Three composite sections exposed at Wadi Khaboba (12 samples, coded by K; total thickness 20 m; at 29° 05′ 01″ N and 33° 14′ 46″ E), Gabal Hazbar (5 samples; coded by H;12 m; at 29° 04′ 45″ N and 33° 22′ 05″ E) and Wadi Abu Natash (12samples; coded by N;19 m;28° 56′ 45″ N and 33° 19′ 24″ E) sites which belong to the Carboniferous sediments; besides other three sections related to the Cretaceous sediments that outcropped at Gabal El Dehessa(10 samples, coded by D, 14 m, at 28° 55′ 55″ N and 33° 17′ 59″ E), Gabal Farsh El Ghozlan (13 samples, coded by F;21 m; at 28° 55′ 40″ N and 33° 18′ 10″ E)and Wadi Budra (13 samples, coded by B;20 m; at 28° 55′ 06″ N and 33° 19′ 16″ E) localities.

Firstly, all the pharmaceutical and therapeutical uses of kaolinite, that have been studied so far and reported through this recent decade, were critically reviewed and analyzed in order to understand their roles, specifications, limits, criteria, activities and controlling parameters

required for these applications. The results and conclusions of these previous studies are considered as important information and guidance for the possibilities of exploitations as well as revealing new hypotheses and trends for functionalities of the variant kaolin grades. For kaolin pre-formulation assessment, the studied samples were prepared and characterized generally by means of mineralogical(XRD) and chemical (XRF) analyses for determining the bulk major oxides, trace elements and for calculating the kaolin mineral and associated impurities contents, besides the kaolinite structural order-disorder degrees and crystallite size. In additions, the performed pharmaceutical technological characterizations and pharmacopoeial specifications include: the colorimetry by spectrophotometer for measuring the CIE-lab chromatic and whiteness parameters, rheological properties and thixotropy, particle geometry and size distribution and grading parameters by laser granulometry and particle micromorphology by scanning electron microscopy (SEM); other specific studies were performed to the highest grade samples include: complementary chemical analysis by the TEM for determining kaolinite micrompositions and by the ICP for assaying the toxic heavy metals, as well as pharmacopoeial tests. On the other hand, thermal properties of 50% kaolin aqueous suspensions were characterized by means of cooling kinetics using differential scanning calorimetry (DSC).

The results proved that 50% of the total raw samples of the economic Egyptian Abu Zenima kaolin deposits contain > 75%, and 20% of the samples showed > 90% of kaolinite. The high grade samples are suitable for pharmaceutical industries. The lower grades have specific functionalities and they also can be easily upgraded and improved to reach the pharmaceutical grade. The present study summarized all the possible uses and recent applications of kaolins that have been known so far, and hence this is considered as important orientation regarded to an added economic value for exploitation and marketing of the Egyptian kaolin resources as well as

an academic vale for the future developmental researches on kaolinite for healthcare applications. Moreover, the present study also confirmed the suitability of the Egyptian kaolins in pelotherapy and tested new technological parameters for developing this application from pharmaceutical point of view, as one of the major medicinal branches of applied clays in the physical therapy.

1. INTRODUCTION

1. INTRODUCTION

Kaolinite is a planar hydrous aluminum phyllosilicate belonging to the dioctahedral 1:1 kaolin group (Guggenheim et al., 2006) with an ideal structural formula of $Al_2Si_2O_5$ $(OH)_4$. Indeed, it is the most widespread phase amongst the other 1:1 dioctahedral phyllosilicates (halloysite, dickite and nacrite). The term “kaolin” is the name of a clay mineral group, but it is also used to describe argillaceous rocks enriched in kaolinite and/or halloysite (> 75%) and it is considered as abundant and inexpensive geomaterial of greatest industrial importance.

Kaolinite normally appears as stacked pseudohexagonal platelets forming a common booklet-like shape. Each platelet is considered as an arrangement of several layers, each of these 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. 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 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 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.

The particle size of the kaolinite platelets is normally < 2 μm (for comparison, a human red blood cell has a typical diameter of around 6.2–8.2 μm). The kaolinite platelets exist either stacked together with a common booklet-like shape in a highly ordered structure (well crystallized) or aggregated in a disordered structure (poorly crystallized). Hence, kaolinite "crystallinity", as a measure of the diversity of defect structures in kaolinite samples, is usually expressed by the Hinckley Index (HI) into poorly ordered or poorly crystallized kaolinite (HI< 0.6) and well ordered or well crystallized kaolinite (HI> 0.7) (Hinckley, 1963; Kogel et al, 2006), although this index is not a quantitative measure of "crystallinity" (Guggenheim et al, 2002) Other indices have been proposed to determine the kaolinite crystallinity by other approaches (Plançon et al., 1988; Plançon and Zacharie, 1990; Galán et al., 1994; Aparicio and Galán, 1999; Chmielová and Weiss, 2002; Aparicio et al., 2006). In fact, the well crystallized kaolinite is typically soft (Kogel et al, 2006) with coarse particle size, while the poorly crystallized kaolin is typically hard with finer size. The hard kaolin exhibits particles of lower crystallite size values (i.e., maximum coherent domain thickness of the platy phyllosilicate layer stacking) and more resistant against the mechanical strains than the soft kaolin (Murray and Keller, 1993). In addition, most of the physicochemical, mechanical and rheological properties of kaolinite are controlled by its "crystallinity".

Substantially, the chemical composition and purity, particle size, morphology and crystallinity of clay minerals are generally sensitive to the environmental changes and geologic settings. Hence, mineralogical and chemical characteristics of kaolin deposits are mainly influenced by provenance, climate, erosion, weathering, transport, orogenic evolution and diagenesis, which have strong effects on their physical

properties such as mechanical hardness (i.e., compactness), plasticity, rheology, color, opacity and whiteness; and also on the physicochemical properties, including the sorption and cationic exchange capacities. Consequently, they are considered as important controlling factors that affect the quality and hence the economic values and uses of kaolin deposits.

Kaolin minerals exhibit physical, chemical, and physicochemical characteristics which make them very useful in many different applications. Because of its resistance to heat and chemicals (fusion point at 1785 °C) and electrical non-conductivity, kaolin is a fundamental raw material during the manufacturing of original porous non-glazed ceramic products (like bricks, potteries, water-filter candles, or automotives catalytic converter) and non-porous strong glazed ceramic products (like white wares, white tiles, electrically insulated porcelain, refractories and the translucent bone china, for instance, Ciullo, 1996; Murray, 1999 and 2007; Kogel et al, 2006; Chatterjee, 2009).

Moreover, the whiteness, brightness, high reflectivity, chemical inertness over relatively wide range of the pH (4-9), relatively high specific gravity, softness, hydrophilicity and high readily dispersion in water, ability to produce slurries with low viscosity and high solid content, fine particle size, high chemical purity and low shrinkage are important for the utilization of kaolin in many industrial applications, like textile filler to improve weight and strength to the body of cloth, both filler and surface coating material in paper industry and rubber manufacturing as reinforcing and stiffening material, imparting strength, electrical resistance, gloss and low water absorption in plastic industry, suspending agent and white pigment in both water and oil paints, essential chemical component in white cement manufacturing, carrier and distributing agent of insecticides and pesticides, fertilizers, food additives, suspending

agent in printing inks, pencil leads, desiccants, synthesis of ultramarine (i.e., Prussian blue powder used in painting, bluing correction of yellowish spots in washing white cloths, in makeup as mascaras or eye shadows, printing of paper calico, etc), synthesizing of zeolite, catalyst in petroleum refining and some organic polymerization, dehydration, hydrolysis and isomerization processes, dehydrating agent in manufacture of soap and detergents, filler in the fiber glass manufacturing, as adhesive and sealants, production of white concrete, etc. (Chatterjee, 2009).

Clay minerals, under specific requisites, are used in solid and semisolid pharmaceutical preparations for topical and oral administration, as well as cosmetic formulations. These health-care applications of clays depend on their physical, chemical, surface physiochemical, mechanical, and rheological properties that make them useful as active ingredient or as adjuvant components by controlling the efficiency and consistency in the dosage formulations and/or improving the drug bioavailability.

Kaolin exhibit a rather simple structure, high plasticity, alkaline pH, suitable rheological, thixotropic and colloidal properties, high influence on the viscosity of organic polymer dispersions, as well as suitable specific surface area, surface charge, sorption capacity and desirable particle morphology and particle size distribution, that functionalize them as pharmaceutical drug and cosmetic excipients (e.g., diluent and binder, disintegrant, pelletizing, granulating, emulsifying, amorphizing, particle film coating, suspending and carrier-releaser agents) in many orally or topically administered solid and semisolid dosage forms such as powders, pellets, granules, tablets, capsules, pastes, poultices, ointments, creams, lotions and suspensions (Nesbitt, 1994; Zoglio et al., 1996; Chow and Leung, 1996; Kristensen et al., 2002; Niazi, 2004a&b; Nokhodchi, 2005; Mallick et al., 2007; Viseras et al., 2007; Dogan et al., 2012; Jämstorp et al.,

2012; Goyanes et al., 2013; Onyishi et al., 2013; Duarte-Silva et al., 2014; Kpogbemabou et al., 2014; Tan et al., 2014; Tawfeek et al., 2014; Hu et al., 2015; Ndlovu et al., 2015; Yu and Bi, 2015).

Because of their uninjured bioactivity and therapeutic effects, kaolin minerals may also be used as active ingredients. They are formulated in health-care topical products as hemostatic agent, dermatological protector, anti-inflammatory agent and in pelotherapy, or oral products as gastrointestinal protector, antimicrobial, detoxification or antidiarrheal agent. In addition, kaolin and their modified 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 (Aguzzi et al., 2007; Lee et al., 2007; Guerrero, 2010; Viseras et al., 2010; Hoang-Minh et al., 2010 & 2011; Rebelo et al, 2011; Shi et al., 2011; Qadir and Hafeez, 2012; Vergaro et al., 2012; Dlova et al., 2013; Etich et al., 2014; Garg et al., 2014; Pura et al., 2014; Marcotegui et al., 2015; Pasbakhsh and Churchman, 2015; Silva et al., 2015). Moreover, recent trials have been attempted to develop new kaolin-based drugs for inhibiting antibiotic-resistant bacteria as well as hepatitis C antiviral and anticancer activities (Otto and Haydel, 2013; Ali et at, 2014; Misyak et al., 2016; Williams, 2017).

Foremost, the evaluation, the appropriate upgrading method and the possible functionalities of kaolin deposits in health-care uses are determined on the basis of their chemical purities and/or the quantities of associated minerals. In secondary kaolin deposits, quartz, illite and anatase are the main accessory phases, with lesser amounts of smectite, hematite, goethite, pyrite and marcasite, while in primary kaolins significant

amounts of quartz, feldspars, muscovite, tourmaline, zircon, rutile and pseudorutile are common.

In order to ensure the suitability of kaolin grades for pharmaceutical uses, they must comply requisites specified on European, British, United States and Japanese pharmacopoeias regarding their mineralogy, color, organic impurities, adsorption power, swelling power, substances soluble in mineral acids, loss on ignition, chemical composition (particularly chlorides, sulphates, iron, calcium and heavy metals) and microbial contamination (United States Pharmacopeia 32; British Pharmacopeia BP 2009 & 2012 in Volume I and II; European Pharmacopeia PhEur 6.3 in monograph 0503; PhEur 7.0 in Volume 2).

In addition, handbooks of pharmaceutical excipients cite other technical properties that kaolins must have, including particle size distribution expressed as mean size, dynamic viscosity, whiteness, acidity or alkalinity, refractive index, equilibrium moisture content and specific gravity (Rowe et al., 2009 and 2012).

The quality of industrial kaolinite is influenced, among other factors, by the quantities of mineral impurities such as quartz, anatase, rutile, mica, feldspar, calcite, dolomite, magnetite, hematite, illite, smectite or pyrite. The economic value of kaolinite is highly regarded as the purity increases, because this minimizes the processing cost. Pharmaceutical grade kaolin is mined, powdered and freed of coarse gritty particles of quartz or heavy mineral impurities (e.g., anatase, ilmenite, rutile, magnetite, etc.) either by elutriation or by screening with other applied new processing methods (Conley, 1996; Bu et al., 2017). Impurities such as ferric oxide, calcium carbonate, and magnesium carbonate, that usually accompany kaolinite, are removed easily with an

electrophoresis and by treatment with hydrochloric acid and/or sulfuric acids (Segura et al., 2012; Chouafa et al., 2015).

With the exception of Antarctica, noticeable kaolinite occurrences are recorded in all continents. However, significant deposits of economic interests are relatively few. The most remarkable kaolinite mining districts worldwide are allocated in the United States (the upper coastal plain areas of Georgia and South Carolina), Uzbekistan, Brazil (eastern Amazon region), the United Kingdom (Cornwall–Devon), Germany (Bavaria and Saxony), Czech Republic, Republic of Korea, Ukraine and Bulgaria, as well as other minor kaolinite occurrences at different localities in the rest of the European, American and Asian's countries. In Africa, the most prominent kaolinite occurrences are mainly distributed in Egypt, Nigeria, South Africa, Eritrea and Uganda. On the other hand, the only major worldwide commercial halloysite deposits occurred in the North Island of New Zealand and the Dragon halloysite mine in the Tintic district of Utah (USA), while lesser quantities are found in Morocco, Japan, Korea and Czech Republic; pure dickite is mined in Russia (Kogel et al, 2002; Wilson, 2004; Kogel et al, 2006; Murray, 2007; Kennedy, 2009; Ekosse, 2010).

Egypt has numerous and big sedimentary kaolin deposits, ranging in age from Carboniferous to Neogene. The most important deposits are located at Abu Zenima and El Tih plateau (West-Central Sinai), Abu El Darag area (approximately 85 Kms south of Suez city), Wadi Qiseib area (about 90 Kms south of Suez city), Wadi Abu Sanduk area (94 Kms south of Suez city), Wadi Abu Had area (at 80 Kms west of Ras Gharib city), Wadi Abu Sobeira area (15 Kms north east of Aswan city), and Wadi Kalabsha area (105 Kms southwest of Aswan city) (Abdel Shafy, 1967; Soliman et al., 1969; Amer et al., 1971; Abd El-Razik, 1972; Qusa, 1986; Hegab et al., 1992; Abdel Razek,

1994; Boulis and Attia, 1994; Rashed and Amer, 1994; Kamel et al., 1997).The reserves are estimated to be around 120 million tons in west central Sinai deposits, about 17 million tons in the Wadi Kalabsha area, and 5 million tons in the Wadi Abu Sobeira area. The exploited Egyptian kaolins are mainly used in ceramics, refractories, white ware, heavy-clay products, Portland cement, paints and paper on the basis of the great demand and importance of such industries in Egypt. According to the global statistical Mundi Index (2007), Egypt is the first kaolin producer in Africa and the Middle East, with the rank 19th worldwide. The total production of Egyptian kaolins in the last decade is about 3,702,000 metric tons, with an average of 375,000 metric tons per year, representing 1% of the worldwide production (Ekosse, 2010; Taib, 2012, 2015; Virta, 2015).

However, these Egyptian kaolin deposits have never been submitted to special characterizations to evaluate their suitability for pharmaceuticals, cosmetics and other health-care applications. Even if the output value of kaolinite in pharmaceutical industries is greater, because the price of pharmaceutical grade quality may be up to ten times that of the same grade dedicated to the above mentioned uses. Consequently, the kaolin raw materials have to completely comply with stringent and precise chemical, physical, toxicological and microbiological specifications regulated by the Pharmacopoeias.

A few mineralogical and geochemical studies have been done so far on the west-central Sinai kaolin deposits. In relation to the source rocks and depositional environment, the influence of the compositional and isotopic changes of kaolin samples from west-central Sinai on their provenance, paleoclimatic conditions and post-depositional alterations has been investigated (Boulis and Attia, 1994; Kamel et al.,

1994; Baioumy et al., 2012; Baioumy, 2013; Baioumy, 2014a&b). In regard to kaolin quality, physiochemical properties and industrial applications, some studies characterized the suitability and the depositional controlling factors of the west-central Sinai kaolins for uses in paper, paint pigments, ceramics and fire clay bricks industries (Hegab et al., 1992; Abdel Razek, 1994; Rashed and Amer, 1994; Nour and Awad, 2008; Gaber and Hassanien, 2011; Masoud et al., 2013). On the other hand, zeolite has been synthesized from Abu Zenima kaolin by some studies, and their efficiency in treatment of highly Fe-Mn polluted groundwater has been investigated (Farrag et al., 2017).

2. OBJECTIVES

2. OBJETIVES and WORK PROGRAM

This study aims to evaluate by first time the suitability and potentialities of the Egyptian Abu Zenima (Sinai Peninsula) kaolins to be used in pharmaceutical and cosmetic industries and other health-care applications.

The main objectives of this study are focusing on:

(1) Intensive reviewing of all the pharmaceutical and biomedicinal applications of kaolinite.

(2) Carrying out integrated mineralogical, geochemical and technological characterizations on the collected kaolin samples for evaluating their qualities and to specify their pharmacopeial and pharmaceutical pre-formulation characteristics for potential uses and applications.

(3) Technological evaluation and investigating a new submitted hypothesis related to functionality in pelotherapeutic applications.

The present study also provides developmental recommendations as well as some new ideas and further research points important for the future post-doctoral studies on the Egyptian economic kaolin deposits.

To achieve these objectives, the work program of the Thesis was divided in the following tasks, corresponding to papers discussed latter in this memory:

Chapter 3. Comprehensive revision of the previous studies on kaolinite and related materials as pharmaceutical ingredients.

Awad, M.E., López-Galindo, A., Setti, M., El-Rahmany, M.M., Viseras, C. (2017). Kaolinite in pharmaceutics and biomedicine. Int. J. Pharm., 533(1), 34-48.

Chapter 4. Fully characterization of kaolin samples, including identity, purity and richness, as well as technical specifications.

Awad, M.E., López-Galindo, A., El-Rahmany, M.M., El-Desoky, H.M., Viseras, C. (2017). Characterization of Egyptian kaolins for health-care uses.App. Clay Sci. 135, 176-189.

Chapter 5. Specific evaluation of selected kaolin samples to be used in thermal peloids.

Awad, M.E., López-Galindo, A., Sánchez-Espejo, R., El-Rahmany, M.M., Viseras, C. (2017). Thermal properties of some Egyptian kaolin pastes for pelotherapeutic applications: Influence of particle geometry on thermal dosage release. App. Clay Sci. In press.

3. KAOLINITE IN PHARMACEUTICS AND BIOMEDICINE

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Review

Kaolinite in pharmaceutics and biomedicine

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ABSTRACT

Kaolinite $Al_2Si_2O_5(OH)_4$ 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 μm (if compared to a human red blood cell of a typical diameter 6.2–8.2 μm or to a virus particle of about 50 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 biomedicinal 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 skeletomuscular 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 (saprolite) 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 $Al_2Si_2O_5(OH)_4$, that means 46.54% SiO_2, 39.50% Al_2O_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, SiO_2 is increased with quartz content, K_2O and SiO_2 is increased proportional to mica content, MgO, CaO and SiO_2 are typically raised according with the smectite content, TiO_2 is normally identical with anatase, rutile or pseudorutile contents, Na_2O and/or K_2O are related to feldspars contents, and Fe_2O_3 content is mainly considered to iron oxi-hydroxides minerals and rarely to iron-substituted kaolinite (Kogel et al., 2006; Bleam, 2017). Occasionally, noticeable contents of CaO and/or MgO are owed to carbonate minerals (calcite, dolomite), and significant Cl^- with or SO_3^{--} 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 pseudohexagonal platelets, < 2 μm 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

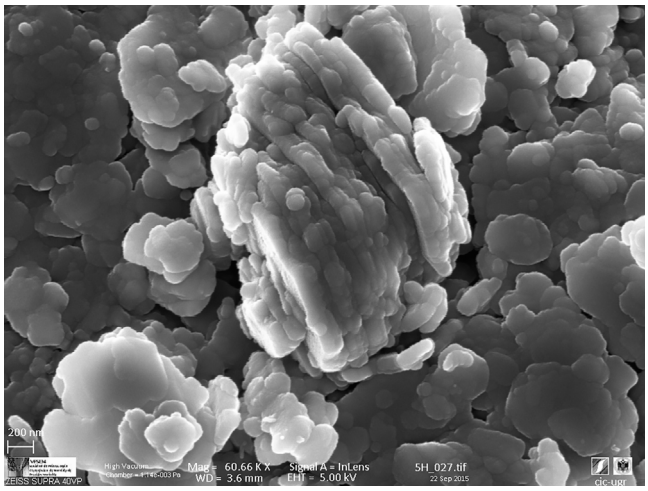

Fig. 1. Scanning electron microscopy (SEM) image of kaolinite particles showing aggregates of booklet-like stacked platelets.

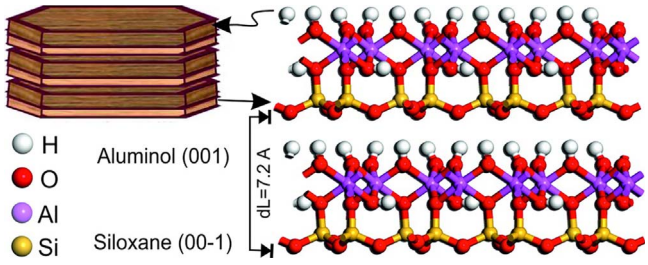

Fig. 2. Molecular simulation model of kaolinite structure (1 × 2 × 2 unit cells) showing siloxane and aluminol surfaces.

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 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; Lagaly, 2006; Tombácz and Szekeres, 2006; Murray, 2007; Hu and Yang, 2013).

The platelets of the dickite and nacrite exhibit a rather similar planar pseudohexagonal morphology, but halloysite particles appear as spheres or tubes of typically 0.5–10 μm 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 Fe^{+3} substituted 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 μm), whereas poorly crystallized kaolin is typically hard with

fine particle size (> 80 wt% < 2 μm) (Kogel et al., 2006).

Because of the limited substitutions in the kaolinite structure, kaolinite under normal conditions exhibits very low cation exchange capacity (1–5 meq/100 g). The low sorption capacity of kaolinite is attributed to its low specific surface area (around 8–15 m^2/g) and surface charge of the particle, as compared with other clay minerals. Other technical characteristics of kaolinite and halloysite are: the water of plasticity is 8.9-56.03% by weight, green strength is 0.34–3.2 kg/cm^2 and linear drying shrinkage is 3–10% (for kaolinite) and 33–50% by weight, > 5 kg/cm^2 and 5–15% (for halloysite) (Murray, 2007).

With the exception of Antarctica, noticeable kaolinite occurrences are recorded in all continents. However, significant deposits of economic interest are relatively few. The most remarkable kaolinite mining districts worldwide are allocated in the United States (the upper coastal plain areas of Georgia and South Carolina), Uzbekistan, Brazil (eastern Amazon region), the United Kingdom (Cornwall–Devon), Germany (Bavaria and Saxony), Czech Republic, Republic of Korea, Ukraine and Bulgaria, as well as other minor kaolinite occurrences at different localities in the rest of the European, American and Asian's countries. In Africa, the most prominent kaolinite occurrences are mainly distributed in Egypt, Nigeria, South Africa, Eritrea and Uganda. On the other hand, the only major worldwide commercial halloysite deposits occurred in the North Island of New Zealand and the Dragon halloysite mine in the Tintic district of Utah, USA, and lesser quantities in Morocco, Japan, Korea and Czech Republic; pure dickite is mined in Russia (Kogel et al., 2002, 2006; Wilson, 2004; Murray, 2007; Kennedy, 2009; Ekosse, 2010; Awad et al., 2017).

3. Industrial usage of kaolin minerals

Kaolin minerals exhibit physical, chemical, and physicochemical characteristics which make them very useful in many different applications. Because of its resistance to heat and chemicals (melting point at 1785 °C) and electrical non-conductivity, kaolinite is a fundamental raw material during the manufacturing of original porous non-glazed ceramic products (like bricks, potteries, water-filter candles, or automotives catalytic converter) and non-porous strong glazed ceramic products (like white wares, white tiles, electrically insulated porcelain, refractories and the translucent bone china, for instance) (Ciullo, 1996; Murray, 2007; Chatterjee, 2009). Moreover, its whiteness, brightness, high reflectivity, chemical inertness over relatively wide range of the pH 4–9, relatively high specific gravity, softness, hydrophobicity and high readily dispersion in water, kaolinite produces slurries with low viscosity and high solid content, fine particle size, high chemical purity and low shrinkage. These are important technical properties for the utilization of kaolinite in a varied field of industrial applications, like textile filler to improve weight and strength to the body of cloth, both filler and surface coating material in paper industry and rubber manufacturing as reinforcing and stiffening material, imparting strength, electrical resistance, gloss and low water absorption in plastic industry, suspending agent and white pigment in both water and oil paints, essential chemical component in white cement manufacturing, carrier and distributing agent of insecticides and pesticides, fertilizers, food additives, suspending agent in printing inks, pencil leads, desiccants, synthesis of ultramarine (i.e., Prussian blue powder used in painting, bluing correction of yellowish spots in washing white cloths, in makeup as mascaras or eye shadows, printing of paper calico, etc.), manufacturing of synthetic zeolite as a source of alumina and silica, catalyst in petroleum refining and some organic polymerization, dehydration, hydrolysis and isomerization processes, dehydrating agent in manufacture of soap and detergents, filler in the fiber glass manufacturing, as adhesive and sealants, production of white concrete, etc (Ciullo, 1996; Murray, 1999, 2007; Kogel et al., 2006; Chatterjee, 2009).

4. Requisites of pharmacopoeias and in handbooks of pharmaceutical excipients for the use of kaolin minerals

According to the United States Pharmacopeia 32, British Pharmacopeia BP 2009 & 2012 (Volume I and II) and European Pharmacopeia PhEur 6.3 (monograph 0503) & 7.0 Volume 2, kaolin is described as a native hydrated aluminum silicate, powdered and freed from gritty particles by elutriation. The British Pharmacopeia divided the pharmaceutical grades into light, light natural and heavy kaolins. They considered that light kaolin contains a suitable dispersing agent, while light kaolin (natural) contains no dispersing agent. Heavy kaolin is considered by BP and PhEur 7.0 Volume 2, as a purified, natural hydrated aluminum silicate of variable composition.

In order to ensure the suitability of kaolin minerals as pharmaceutical grade products, they must comply some requisites specified on the main pharmacopoeias (European, British, United States and Japanese) regarding their mineralogy, color, organic impurities, adsorption power, swelling power, substances soluble in mineral acids, loss on ignition, chemical composition (particularly chlorides, sulphates, iron, calcium and heavy metals) and microbial contamination. Handbooks of pharmaceutical excipients (Rowe et al., 2006, 2009, 2012) cites other technical properties that kaolins must have, including particle size distribution expressed as mean size, dynamic viscosity, whiteness, acidity or alkalinity, refractive index, equilibrium moisture content and specific gravity.

4.1. Toxicity

Many reported cases in WHO (2000, document 24) indicated that patients who had been occupationally (e.g., mining and refining workers) exposed to high doses of quartz dust (inhalation, spontaneous ingestion or epidemiological contact) are infected by abnormal autoimmunity disorders and cancer. This is because the high surface reactivity of the quartz nanoparticles are capable to alter the blood biochemical and histochemical systems as well as penetrate cells and interact with DNA causing malignant tumors. Such dangerous diseases are represented by acute and chronic silicosis and lung cancer, autoimmune diseases (including: scleroderma, systematic lupus erythematosus, rheumatoid arthritis, autoimmune haemolytic anaemia, and dermatomyositis or dermatopolymyositis) as well as chronic renal disease, ataxic sensory neuropathy, chronic thyroiditis, hyperthyroidism, monoclonal gammopathy and polyarteritis nodosa.

On the other hand, elemental impurities control is important role of the overall control strategy for a drug product to be assured that these do not exceed the Permitted Daily Exposure (the maximum acceptable intake of elemental impurity in pharmaceutical products per day), and they should be reflected in the risk assessment of any medicinal product including these materials in their composition (ICH-Q3D, 2014). Elements have been classified for impurity control according to their probable sources, abundances, occurrences and degree of toxicity effects. In particular, As, Cd, Hg and Pb are considered as the class 1 elements, and require evaluation during the risk assessment as they are commonly present in drug products due to their high natural abundance in the environment. They typically come from commonly used materials (*e.g.*, mined excipients). Nevertheless, the normatives for kaolins to be used as excipient only include Pb limit for topical (< 50 ppm) or oral use (< 25 ppm) (EP 8.0, 2014). Class 2A (Co, Ni and V; high probability of occurrence) and 2 B (Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl; reduced probability of occurrence) elements also requires control. Elements belonging to Class 3 (Ba, Cr, Cu, Li, Mo, Sb, and Sn) show low oral toxicities and only require consideration in the risk assessment for inhalation and parenteral routes.

4.2. Kaolin upgrading

The kaolin upgrading is costly and technically controlled by the

mineral composition (kaolinite or halloysite richness and types and amounts of the clay and non-clay phases). Thus, the selection of the beneficiation process must be directly related to the physical and chemical differences existing among the detected mineral species, i.e. particle size, specific gravity and/or magnetic susceptibility (Kogel et al., 2006).

Normally, kaolin processing is better performed in the wet state, where the raw kaolin is highly pulverized to meet the size necessary for the pharmaceutical grade particle kaolin. Kaolin slurry is prepared by mechanical blunging of 35–70% kaolin-water suspension for particles disaggregation with chemical dispersant (e.g. sodium hexametaphosphate, sodium silicate, tetrasodium polyphosphate and sodium polyacrylate, 0.75%) depending on the dry kaolin, added to keep the particles flocculated and preventing their agglomeration, due to the increase of the negative charge on mineral surfaces, and hence, increasing the particles repulsion. The pH is adjusted to the range 6.5 to 7.0 using 0.25% sodium carbonate to induce a negative charge on both edges and faces of kaolinite particles (Conley, 1996). The slurry is then subjected to desanding and degritting processes to remove by screening the sand grains present usually in the primary kaolin, and the gritty particles of mineral impurities (> 44 μm) that are common in sedimentary kaolins, particularly, quartz, mica, feldspars and titaniferous oxide minerals (e.g., anatase, brookite, rutile, ilmenite, goethite, hematite and magnetite). Besides, the coarser silt-sized kaolinite particles must be re-pulverized and recovered.

5. Use of kaolinite as pharmaceutical excipient

Excipients, either natural (i.e., vegetal, animal and mineral sources) or synthetic, are inert additive ingredients used as indispensable adjuvants in pharmaceutical industry. The inertness of excipients is strictly required to avoid its own side pharmacological activity. Depending on excipient suitability to the standard desired criteria and attributes, these are chosen to facilitate processes of drug formulation design, improve appearance, keep stability and consistency of final dosage forms, and improve bioavailability and control release of active components in drug administration and delivery.

Performance of excipient is affected by impurities, which can have impact over the adequate functions and behaviors (Haywood and Glass, 2012; Fox, 2014; Ravi et al., 2015; Narang and Boddu, 2015). Similar to human healthcare uses, excipients are also involved during the manufacturing of veterinary medicinal products as well as compounding and dispensing of agrochemicals (Connick et al., 1993; Gan et al., 1994; Moore and Caudwell, 1997; Knowles, 1998; Greene and Pohanish, 2005; Alavo et al., 2010).

Pharmaceutical kaolin grades are considerably demanded for usage as excipient in formulations of solid and semi-solid dosage forms, including tablets, capsules, pellets, granules, powders, pastes, poultices, ointments, creams, lotions and suspensions. At critical requisites of chemical purity and acceptance limits of physical and chemical criteria, various kaolin concentrations are prescribed by many drug formularies to perform certain roles in pharmaceutical manufacturing processes.

The most important functionalities of kaolin used as excipient (Table 1) are reported as diluent, binder, disintegrant, pelletizing and granulating, amorphizing, particle film coating, emulsifying and suspending agents (Alexander et al., 1989; pez-Galindo and Viseras, 2004,b; Niazi, 2004a,b; Viseras et al., 2007; Rowe et al., 2009; Dogan et al., 2012).

5.1. As diluent

The choice of a proper diluent depends basically on the hydrophobicity and bioavailability of the active component. Water-soluble diluents are recommended in case of formulations with low-water soluble active drugs, and vice versa, in order to avoid bioavailability troubles.

The most important physical tests and parameters recommended to qualify kaolin grades as diluents in solid dosage forms include bulk and tapped density of powder, powder fineness, moisture or loss on drying, hardness, friability, disintegration time, dissolution or drug release profile (Mathur et al., 2015; SahabUddin et al., 2015).

Additionally, kaolin, as used in tablet formulations, is a compactable and non-hygroscopic substance. It exhibits low moisture (< 1%) content that can be considered as advantage where the high moisture affects: 1) the compressibility degree during the preparation; 2) the physical stability of the solid dosage forms; 3) the chemical stability of the active ingredients in the final product. By its hand, compressibility has a direct effect on the physicochemical parameters that arise from kaolin pore fluids. These parameters gradually decrease with increasing overburden stress, until become ineffective completely under 300 KPa (Scott et al., 1963; Lachman, 1965; Chen et al., 2000; Gerhardt, 2009; Shalini, 2012).

The formulated kaolin grade should be compatible with both, the active components and other involved excipients. Highly adsorbent excipients are not acceptable at critical limits for the formulation of tablets or capsules with active drugs that must be consumed clinically in small doses (e.g., the cardiac glycosides, alkaloids, and the synthetic estrogens), because the active ingredient could be adsorbed in high amounts, and it becomes not entirely bioavailable after administration (King and Schwartz, 1985; Niazi, 2004a; Shalini, 2012).

Many pharmaceutical studies have been attempted to determine kaolin behaviors, as diluent or other excipient roles, to adsorb and release active drug molecules. Kaolin-drug interactions could occurred either, as reducing dissolution of active drug molecules that could be affected by strong adsorption on kaolin surfaces in the same dosage form, or diminishing drug availability when multi-dosages are administrated concomitantly and one of them is formulated with kaolin. In case of low drug doses, diluents are added, by 90% or more, into ingredients of tablets or capsules to bulk up the volume, facilitate compression and/or adequate the weight and size of the solid dosage forms. For instance, both light and heavy kaolin grades (E559) are used in two traditional herbal slimming tablet products (Slimwell® and Quantrim®, traditional herbal registration THR 15670/0020), heavy grade is used in Mecysteine Hydrochloride 100 mg gastro-resistant tablets (PL 14894/0297), and as adjuvant in the formulation of both Riclasip® and Co-amoxiclav DST Grünenthal® (PL: 21727/0018-23) granules for oral suspension (NICE, 2017).

Numerous unique and relevant studies stated that ingested kaolin reduced the bioavailability of some antibiotics such as lincomycin, clindamycin, tetracycline and ciprofloxacin (McCall et al., 1967; Gouda, 1976; Albert et al., 1978b; Tuncel and Bergisadi, 1992). *In-vivo* pharmacokinetic study by Khalil et al. (1984) reported that light kaolin ingested 2 h before some antibiotics reduces the bioavailability of ampicillin from 76.3 to 51.2%, and amoxycillin from 80.6 to 63.6%. *In-vivo* study by Gouda (1993) concluded that bioavailability of tetracycline co-administrated with Kaopectate® (kaolin-pectin suspension) is reduced by 50%, while it decreased by 20% with the same dosages consumed 2 h before or after kaopectate administrations. Aleanizy et al. (2015) studied the interaction between kaolin and metronidazole (antibiotic and antiprotozoal drug) and concluded that the Langmuir adsorption isotherm of this drug at different pH onto kaolin is pH-dependant and controlled by the clay concentrations. Moreover, the concomitant administration of kaolin-metronidazole tablets (Riazole®) affects the release and diffusion of metronidazole.

On the other hand, kaolinite can also interacts with other drug types, including digoxin (treatment of heart diseases), pseudoephedrine (nasal/sinus decongestant, stimulant, or wakefulness-promoting agent), oral hypoglycemic agents (treatment of diabetes mellitus), diphenoxylate (antidiarrheal drug), mepyramine maleate (antihistamine and anticholinergic agent), flurazepam (treatment of insomnia), quinine (prevent and treatment of malaria), acebutolol (treatment of hypertension and arrhythmias), allopurinol and probenecid (treat

Table 1
Kaolin functionalities as pharmaceutical excipient.

Excipient functionality	Kaolin grades/composites	Commercial/Experimental dosage forms	References
Diluent	Light and heavy kaolin	Herbal slimming tablet: products (Slimwell® and Quantrim®).	NICE (2017).
	Heavy kaolin	Gastro-resistant tablets: Mecysteine Hydrochloride® 100 mg. Granules for oral suspension: Riclasip® and Co-amoxiclav DST Grünenthal®.	
		Riboflavin (vitamin B2) hard gelatin capsules.	Stewart et al. (1979) and Khalil et al. (1987).
		Pyridoxine hydrochloride (vitamin B6) kaolin capsules.	Onyishi et al. (2013).
		Thiamine (vitamin B1) and ascorbic acid (vitamin C) tablets and capsules.	Wai et al. (1962).
Binder	kaolin/Eudragit® E30D mixture	Tablets and capsules.	Ghebre-Sellassie et al. (1986) and Nesbitt (1994).
Disintegrant	Heavy kaolin	Tablets and pellets.	Ward and Trachtenberg (1962); Safiulin et al. (1963) and Kristensen et al. (2002).
	Chitosan/kaolin	Microcrystalline cellulose and hydrochlorothiazide (HCT) pellets.	Goyanes et al. (2013).
Pelletizing agent	Heavy kaolin	Pellets (5% sodium lauryl sulphate) of size range (850–1180 μm).	Law and Deasy (1997).
		Pellets (25% kaolin and 5% crospovidone).	Kristensen et al. (2002).
		Pellets (kaolin with microcrystalline cellulose and lactose).	Goyanes et al. (2013).
		Pellets (45% kaolin, 5% aerosil® 200, 39.5% lactose, 2.5% liquid paraffin and 8% hydroxypropylmethylcellulose phthalate).	Deasy and Gouldson (1996).
Granulating agent	Heavy kaolin	Granules: (10% sodium chloride).	Travers (1975).
	Light kaolin	Granules: (20% calcium chloride, with polyethylene glycol and polyvinyl alcohol).	Chow and Leung (1996).
Amorphizing agent	Light kaolin	kaolin-ibuprofen solid dosage forms.	Mallick et al. (2007).
Film-coating additive	Kollicoat IR® system and Kaolin-Eudragit® E30D dispersion.	- Hypericon® and Metformin® tablets. - Pseudoephedrine hydrochloride, theophilline and diphenhydramine hydrochloride pellets. - Dyphylline® coated tablets.	Ghebre-Sellassie et al. (1987) and Zoglio et al. (1996).
Wetting and emulsifying agent	Light kaolin	Sulphur ointment.	Niazi (2004b)
		Oil-in-water Pickering emulsions.	Kpogbemabou et al. (2014).
		Non-aqueous oil-in-oil emulsions.	Tawfeek et al. (2014).
Suspending and anticaking agent	Heavy kaolin	Toxiban®, Kaolin-Pectin®, Kapect®, Kaolin and Morphine mixture BP® suspensions.	Drugs.com (2017)
Drug carrier	Heavy and light kaolin	Kaolin powder (high and low kaolinite crystallinity) loaded by sodium amylobarbitone.	Delgado et al. (1994).
	Light kaolin	Porous kaolin-based pellets loaded by Diltiazem HCl.	Byrne and Deasy (2005).
	Metakaolin	Pellets loaded by highly potent opioids.	Jämstorp et al. (2012).
	Methoxy-modified kaolinite.	The derivative powder loaded by anticancer 5-fluorouracil drug and herbicide amitrole.	Tan et al. (2014, 2015).
	kaolin and metakaolin	Powder loaded by α-lactalbumin, bovine serum albumin and β-lactoglobulin proten.	Duarte-Silva et al. (2014).

hyperuricemia and gout), hyoscine N- butyl bromide (crampy abdominal pain, renal colic, and bladder spasms) and cimetidine (treatment of heartburn and peptic ulcers; McGehee et al., 1968; Lucarotti et al., 1972; Brown and Juhl, 1976; Albert et al., 1978a; Alestig et al., 1979; Ganjian et al., 1980; Said and Al-Shora, 1980; Thoma and Lieb, 1983; Naggar, 1985; El Gamal et al., 1986; Ozdemir et al., 1986; Al Gohary et al., 1988; Nada et al., 1989). Experimental *in-vitro* gross adsorption chromatographic studies by Bonner and Flores (1973) confirmed that there is no asymmetric adsorption of D,L-phenylalanine enantiomers (used as analgesic and antidepressant drug) by kaolin, and found that 31.4% and 6.5% of D,L-phenylalanine are adsorbed by slurry of colloidal kaolin in aqueous solutions at pH 2 and pH 6, respectively. McElnay et al. (1980) studied the *in-vitro* effect of kaolin on phenytoin (used as an anti-seizure drug) absorption by segments of rat's intestine, and concluded that kaolin light decreases the availability of phenytoin, reducing the absorption by 60.2% because gastric coating by kaolin probably acts as a physical barrier to this absorption. Another *in-vitro* study conducted by Naggar et al. (1986) showed that kaolin exhibits a high adsorption capacity (97%) to promethazine-HCl (sedative and antiallergic drug) dissolved from tablets in both, HCI and pure water medium. McElnay et al. (1986) demonstrated that kaolin interacts with chloroquine (used to prevent and treatment of malaria) leading to significant decrease of its bioavailability at pH value 8.5. Moustafa et al. (1986, 1987a, 1987b) and Al-Shora et al. (1988) studied *in-vitro* and *in-vivo* interactions of propranolol (used to treat high blood pressure and to prevent migraine headache), quinidine sulphate (cardiac antiarrhythmic agent), antipsychotic phenothiazines (including trifluperazine, fluphenazine, perphenazine and thioridazine), guanethidine and hydralazine (used as antihypertensive drugs) as well as procainamide and verapamil (antiarrhythmic drugs) with antidiarrheal Kaopectate® drug. They found that the ingested drug doses were adsorbed significantly by kaopectate suspension and mostly follow the Langmuir isotherm. Hence, the bioavailability extents, but not the rates, of these drugs were reduced in cases of concomitant administrations with kaolin. *In vitro* and *in vivo* studies by Al Gohary (1997) demonstrated that adsorption of mebeverine hydrochloride (musculotropic antispasmodic drug) onto kaolin light in aqueous suspensions at pH 1.8 or 7.5, with added various electrolytes, follows a double-layered adsorption pattern in accordance with Langmuir isotherm, being the adsorption process affected by the pH, electrolyte concentration and valency. The presence of different kaolin concentrations in a dissolution medium of duspatalin (mebeverine-HCl), tablets or capsules, adversely affected the release rate of the drug. Hu et al. (2015) showed a strong physical exothermic adsorption between kaolinite surface and atenolol (β-blocker drug) that was reduced by increasing the ionic strength of the drug solution. They suggested that the linkage of NH, −O-, and benzene ring are the main chelating ligands that responsible for this interaction. Yu and Bi, (2015) studied the sorption of naproxen (acidic anti-inflammatory drug) onto kaolinite surface in the water-soil environment. They attributed this strong adsorption to the interaction between the diaromatic ring of the drug and the siloxane surface of kaolinite.

On the contrary, some studies stated that kaolin has no significant drug-interaction effects. The study carried out by Gouda (1976) show

that ampicillin absorption is not significantly affected by kaolin in the antidiarrheal kaolin-pectin mixture as concurrent administration. Similarly, warfarin (anticoagulant drug) absorption is not affected by kaolin with the same antidiarrheal drug, according to Albert et al. (1978b). The *in-vitro* and *in-vivo* studies conducted by Stewart et al. (1979) and Khalil et al. (1987) illustrated that the low-dose of the slightly water soluble riboflavin (vitamin B2) cationic drug is more relatively released, under various physiochemical conditions, from hard gelatin capsules formulated with kaolin as diluent when compared to other commonly used diluents. Moreover, different kaolin grades and concentrations, as well as variations in pH-values and electrolytes in the dissolution media, show significant differences in the drug adsorption and release extent. *In-vitro* studies (Khalil et al., 1984) confirmed that the presence of kaolin in the dissolution testing medium of ampicillin and amoxycillin capsules, at pH 2.0 and 6.5, did not significantly change their levels in the solutions. Onyishi et al. (2013) demonstrated that capsules formulated with kaolin as diluent afford successful sustained release of the water-soluble pyridoxine hydrochloride (vitamin B6).

It is found that high moisture contents (> 1%) lead to catalyze and accelerate the degradation of vitamin drugs. In addition, kaolin exhibits low equilibrium moisture content conversely to organic sugar, polymers and crystalline hydrate excipients. Hence, thiamine (vitamin B1) and ascorbic acid (vitamin C) tablets and capsules formulated by kaolin, as diluent, exhibit higher stability (Wai et al., 1962; Nokhodchi, 2005).

In overall, kaolinite may be considered as a suitable inexpensive excipient with particular attention to the interaction with active pharmaceutical ingredients. Interaction of kaolinite with drugs may be useful in the design of modified drug delivery systems (Viseras et al., 2010).

5.2. As binder

Binders are substantial components added during the blending process in order to cohere all ingredients and maintain the integrity of the final dosage form. The binder solutions should meet the requirements (i.e., acceptable friability and desired mechanical strength, as well as the hydrophobic or hydrophilic characteristics of the drug powder blend) needed for granulation, tableting or encapsulation processes.

Ghebre-Sellassie et al. (1986) and Nesbitt (1994) mentioned that, in accordance with friability as a measure of binder acceptability and using a 8% w/w binder solution, kaolin/Eudragit® E30D mixture is one of the best binders (after gelatin, sodium carboxymethylcellulose and hydroxypropyl cellulose) for tableting or encapsulation (Eudragit is an acrylic resin which is based on poly(ethylacrylat-methylmethacrylate) esters). This polymer is hydrophilic and neutral in character, and hence is not sensitive to differences in pH. Moreover, kaolin additive exists as discrete water-insoluble and hydrophilic particles within the polymeric matrix providing homogenous aqueous polymeric dispersion. Therefore, this binder solution exhibits suitable permeability amenable to blend all hydrophilic drugs and the limited water soluble drugs, irrespective of their physicochemical properties, as well as the mixture provides adequate sustained drug release. In addition to its role as binder, the mixture can be applied also in film coatings depending on the kaolin concentration (Aection 5.7).

Thus, kaolinite particles as a hydrophilic, fluid-permeable and water-insoluble substance are suitable, as homogeneous dispersed matrix in the binder solution, for cohering ingredients during the blending process in solid dosage forms.

5.3. As disintegrant

Disintegrants are additive components used to facilitate fragmentation or breaking up of solid dosage forms rapidly into smaller friable particulates and readily dissolution of the active ingredients for absorption, once these contacted with fluids in the gastrointestinal tract after administration. The best choice of disintegrant substances is mainly based on poor solubility, good hydration capacity, poor gel formation capacity, good molding and flow properties as well as non-tendency to form complexes with the drugs. Promotion of tablet disintegration by kaolin deals with kaolinite inter-particles repulsive forces resulting from the permanent negative surface charges of moistened kaolinite particle (Mohanachandran et al., 2011; Gopinath et al., 2012).

Kaolin as a porous, non-swelling, moldable, water absorbent and insoluble material has been customized as disintegrant agent in solid dosage formulations. Ward and Trachtenberg (1962) recommended that a 20% mixture made up of kaolin, sodium lauryl sulphate and purified cellulose, added to starch as disintegrant, is suitable for maintaining stability of tablets stocked for long times under different storage conditions, especially with tablets containing highly soluble drugs, and Safiulin et al. (1963) stated that the kaolin utilized as disintegrant is even better than starch. Kristensen et al. (2002) studied the quality and efficiency of disintegrating pellets formulated with kaolin heavy, and compared them to others formulated with bentonite. They confirmed that kaolin provides complete and fast disintegration to the pellet, while bentonite formulated pellet is erodible but not disintegratable. Goyanes et al. (2013) evaluated a coprecipitate of chitosan/kaolin as disintegrant in formulation of microcrystalline cellulose and hydrochlorothiazide (HCT) pellets. They demonstrated that these pellets led to complete and rapid disintegration in the dissolution medium, and do not significantly affect the dissolution of HTC, but increased the drug dissolution rate.

In summary, kaolinite as a porous and highly friable material with low swelling by hydration, can be considered as a good disintegrant in solid dosage forms. The porosity aids in water penetration by capillary forces leading to break-down of the larger particles into smaller fragments. In addition, the hydrated surfaces of kaolinite particle as dominated by permanent negative charges are responsible for increasing the disintegration due to electrostatic repulsion.

5.4. As pelletizing agent

Pelletization is a systematic formulation process aims to agglomerate the powdered ingredients, either by layering or extrusion-spheronization compaction methods, into free-flowing, spherical or semi-spherical solid units (pellets) with homogeneous size. Pellets are intended mostly for oral administration.

The primary mechanism of the layering pelletization process is nucleation (i.e., particles are dragged together to form three phase air-water-liquid nuclei that are attached by liquid bridges), followed by coalescence (i.e., as the surfaces of the well-formed nuclei are slightly moistened, large-sized particles are formed by random collision of nuclei) and finalized by layering (i.e., a slow cumulative addition of fine fragments over the already formed particles). By its hand, the extrusion-spheronization compaction process initiated by dry mixing of the active ingredients with the excipients, wetting the mass, extrusion of the wetted mass, feeding the extrudates into spheronizer to produce spherical pellets, drying the pellets in a dryer and, finally, screening the product to obtain the desired size distribution.

Pellets have to meet some quality requirements regarding their spherical shape and smooth surface, which are considered for adjusting a uniform weight of capsules and tablets, besides the film coating as well, and the quantity of the active ingredient should be at the maximum permitted level to aid on maintaining pellet size.

Micropellets (< 500 μm in size) can be applied as oral dry suspension like sachets; pellets having sizes in the range 800–1000 μm may be compressed to tablets that can be disintegrated in the stomach into free multiparticulate units (i.e., each single sub-unit acts as an individual modified release entity); and pellets up to 2 mm can be conventionally dosed and filled into capsules (Manivannan et al., 2010; Srivastava and

Mishra, 2010).

Kaolin can be utilized as pelletizing agent, in both aqueous and non-aqueous medium, for improving the pellet yield with desired size and sphericity besides providing the acceptable dissolution rate. Law and Deasy (1997) examined the effects of kaolin heavy as pelletizing agent, and compared the results with other silicates, including bentonite, talc, Veegum® (magnesium aluminum silicate) and Bentone® (organically modified hectorite), and concluded that the formulations containing kaolin produces the highest and narrowest yield pellets range (49–84%) of the desirable size range (850–1180 μm) and high pellet tapped density (0.9 g/ml), as well as the most spherical and smooth pellets can be obtained with adding 5% of sodium lauryl sulphate.

Kristensen et al. (2002) confirmed that a mixture of 25% w/w kaolin and 5% w/w crospovidone (polyvinylpolypyrrolidone) with lactose is considered as better pelletizing agent than the addition of kaolin alone for enhancing the sphericity and roundness of pellet agglomerate. *In-vitro* experiments (Goyanes et al., 2013) show that kaolin containing pellets exhibit faster drug dissolution rate (complete riboflavin released after 8 min) than pellets formulated with a dry mix of microcrystalline cellulose with lactose (only 40% of the drug released after 2 h). Similarly, addition of kaolin provides adequate size, roundness, mechanical strength and good flow properties to the microcrystalline cellulose-based pellets elaborated by aqueous extrusion–-spheronization.

By non-aqueous spheronization, some coprecipitates containing 50% kaolin heavy with 39.5% lactose, 2.5% liquid paraffin and 8% hydroxypropylmethylcellulose phthalate (HP-55) can be formulated (Deasy and Gouldson, 1996). This high kaolin content provides an average pellet yield of 88.6% in the desirable sizes range (850–1180 μm) and improved sphericity (aspect ratio AR 35.2%). The pellet morphology appears mainly as smooth cylinders with rounded ends. Moreover, the highest improvement in sphericity (AR 81.2%) occurred by adding 5% aerosil® 200 (hydrophilic fumed silica) with 45% kaolin.

Briefly, kaolinite proved to be a good pelletizing agent in solid formulations. Because, it frequently yields pellets of pharmaceutically desirable characteristic ranges of size, roundness, sphericity, mechanical strength and dissolution rate.

5.5. As granulating agent

Granules are coarser agglomerates (up to 4 mm in size) than pellets, formed by a size enlargement of fine powders through a granulation process. The process could be considered as a material preparation step for tableting or preparing granules to be administrated directly by the patient.

Granulation, either by wet or dry processes, is conducted to improve flowing, density, appearance and uniform contents, to reduce dust generation as well as to facilitate compressibility of granules. The wet granulation process is the most widely method used in production of granules, and can be done by fluid bed, extrusion-spheronization, spray drying or other advanced granulation techniques. It started by wetting, nucleation, coalescence and, finally, by breakage and attrition. Hence, the granules should be meet more special quality requirements, including granule size, uniformity and crushing strength. On the other hand, dry granulation process can be conducted mainly by roller compaction or slugging (Agrawal and Naveen 2011; Shanmugam, 2015).

The experimental study achieved by Travers (1975) confirmed that, from a mixture of heavy kaolin and sodium chloride (10% w/w), granules with sufficient cohesion, strength, suitable uniformity and average sizes larger than 3 mm, can be produced in a wet granulation process. Chow and Leung (1996) studied the mechanism and characteristics of wet spherical agglomeration for light kaolin formulated with calcium chloride (20% w/v) as bridging solvent, cyclohexane as external phase, polyethylene glycol (PEG) and polyvinyl alcohol (PVA) as binders. The agglomerations attain hard spherical granules of narrow size range and smooth surfaces; kaolin agglomerated with PVA was much larger in size and yield (52% yield with an average diameter around 6.5 mm, binding strength of 83%) than that with PEG (14% yield with an average size around 3.4 mm, binding strength of 100%).

Thus, kaolinite can be used as a good granulating agent in pharmaceutical solid formulations. By mixing kaolinite with chemical additives in certain proportions, it can be agglomerated perfectly to yield granules of desirable size and morphology.

5.6. As amorphizing agent

Amorphization is a pharmaceutical process used to convert the solid form of the water-insoluble, or the poorly water-soluble, active ingredients from the crystalline state into an amorphous phase in order to increase their solubility, dissolution rate and bioavailability. Normally, from a thermodynamic point of view, the amorphous state of poorly water-soluble drugs is more unstable and dissolves more quickly than its crystalline form. Consequently, an amorphizing agent is necessary to help this process and to stabilize amorphous drug in the solid dosage form. The most used technologies are named solvent method, hot-melt and milling process (Mallick et al., 2007; Panchagnula and Bhardwaj, 2008; Jójárt-Laczkovich and Szabó-Révész, 2010; Qi et al., 2014).

Mallick et al. (2007) found that the light kaolin behaves as a good co-milling amorphizing agent for transforming ibuprofen (a non-steroidal anti-inflammatory drug) from its acid crystalline form to salt amorphous phase using a milling process. Amorphization is significantly increased as the drug/kaolin ratios decreased. Moreover, the kaolin-ibuprofen solid dosage form was found to be stable during storage. *In-vitro* dissolution studies of the ibuprofen released from the kaolin co-milled powder demonstrated that the drug/kaolin 1:2 ratio provides the highest release, followed by the ratios of 1:1, 2:1, 1:0.1, 1:0 (ibuprofen milled without kaolin).

In overall, kaolinite particles exhibit good surface catalytic capacity to transform the water-insoluble crystalline active ingredients into soluble amorphous state mainly by the milling process, and hence to increase the drug bioavailability.

5.7. As film-coating additive

Insoluble excipients have been added to the polymeric film coating formulations in order to improve the aesthetic appearance (*i.e.*, color, taste and odor) of solid dosage forms, enhance the chemical stability of the active drugs in storage conditions, and to modify drug (sustained or delayed) release profile. These are mainly controlled by concentration, particle size, morphology and surface chemistry of the insoluble excipient (Felton and McGinity, 2002; Felton and Porter, 2013).

Kaolin has been used to reduce tackiness of polymeric film coating formulations. For instance, it has been formulated into the film coating of Hypericon® (THR: 18397/0006) tablets and also incorporated into formulation of the Kollicoat IR® system that used as instant-release film coating of Metformin® tablets. The effect of the additive kaolin on the release of pseudoephedrine hydrochloride, theophilline and diphenhydramine hydrochloride pellets that coated with Eudragit® E30D dispersion has been studied by Ghebre-Sellassie et al. (1987), which showed that the rate of drug release decreased with the ratio of resin to kaolin 3:1 in the coating formulation. A comparative sustained release of dyphylline coated tablets studied by Zoglio et al. (1996) indicated that the controlled-release of the drug from a triple-pressed coated tablet follows a quadratic function in case of kaolin incorporation into the outer compressed shell.

After all, the kaolinite particles dispersed as a reinforced matrix with polymers in the film coating formulations, provide chemical stability of the loaded active ingredients as well as modify their rates of release.

5.8. As wetting and emulsifying agent

Insoluble solid additives are used as wetting and emulsifying agents in health care semisolid formulations including lotions, creams, ointments and pastes. Hydrophobic drugs are usually immiscible with water and, hence, these are incorporated with an adequate amphiphilic wetting agent (*i.e.* possessing dual hydrophilic and lipophilic properties). In this way, the surface tension of the hydrophobic phase is minimized, the miscibility is increased and a final homogenous dispersion is produced.

Emulsion formulations require the addition of emulsifying agents, not only to perform but also to stabilize the miscibility of oil and water phases either as oil-in-water or water-in-oil emulsions without phase separation. Emulsification mechanisms imply either by reduction of interfacial tension between two immiscible phases or repulsive forces that maintain both phases suspended in the dispersion medium. Emulsification also depends on the three-phase (oil-water-solid) contact angle (Viseras et al., 2007; Ueda et al., 2009; Premjeet et al., 2012; Bora et al., 2014).

Kaolin can be used in ointment to facilitate sulfur dispersion in the oil phase before emulsification with the aqueous phase (Niazi, 2004b). Kpogbemabou et al. (2014) studied the ability of kaolin to stabilize oil-in-water Pickering emulsions, where dodecane ($C_{12}H_{26}$) is the oil phase used in the formulation. They showed that kaolin (15% wt) added to the aqueous phase (at pH = 7.2) promoted the long-term stability of the emulsion without any additive surfactant or surface treatment. Tawfeek et al. (2014) investigated the effect of kaolinite on the stabilization of non-aqueous oil-in-oil emulsions. They found that kaolinite admixed with paraffin oil/formamide gave no stable emulsion systems at all concentrations, while addition of the nonionic surfactant Noigen RN10 (polyoxyethylene alkylphenyl ether) enhanced the emulsion stability. This surfactant enhances the wettability of kaolinite particles, hence the stability of these emulsions increased.

Thus, in topical semisolid formulations, kaolinite surfaces can be activated to act as amphiphillic agent for enhancing and stabilizing water-miscibility of hydrophobic drugs in order to be in a dispersed homogeneous phase.

5.9. As suspending and anticaking agent

Coarse suspensions are a class of dispersion systems which have a disperse phase with particle sizes larger than 1 μm, while colloidal sols exhibit particle diameters less than 1 μm. Suspending and anticaking agents are additives used to stabilize the deflocculating state of suspended particles to be redispersed easily when shaking the medicine container gently before use. Also, they maintain the homogeneity of the system and prevent the caking of solid content at the bottom of the container. Suspension stability is due to the effect of the electrostatic potential energy of repulsions arising among the charged particles (zeta potential) of the excipient. For an adequate performance, suspending agents should exhibit yield stress (*i.e.*, a critical value of the shear stress below which a viscoplastic material behaves like a solid, while above this value it flows) and high viscosity at low shear rates, withstand diverse temperatures, steady throughout long-term storage, afford significant concentrations of electrolytes, and also should act consistently over a wide pH range (Viseras et al., 2007; Kulshreshtha et al., 2010).

Kaolins are frequently used as suspending and anticaking agents in pharmaceutical formulations of many oral and topical coarse suspension dosage forms. For instance, kaolin is used in the formulation of Toxiban® (List No. 1151-0410) suspension and Kaolin-Pectin® (NDC:58005-501-50) suspension (oral suspensions for veterinary use), Kapect® suspension, Kaolin and Morphine mixture BP® (PL: 12965/0021) oral suspension.

Kaolin suspensions are mainly characterized by non-Newtonian pseudoplastic (shear thinning) flow behavior with a Bingham yield stress, where the viscosity decreased with the increase of the shear rate. Changes in the rheological characteristics and stability of kaolin aqueous suspensions are due to differences in particle surface charges (zeta potential), that are affected by variations in the kaolinite crystallinity, electrolyte concentrations and pH values. Generally, yield stresses and settling rate of kaolin suspension decrease with the increase of pH and zeta potential (Vie et al., 2007; Teh et al., 2009; Gupta et al., 2011). Aqueous suspensions formulated with low crystallinity kaolinite exhibit higher yield stresses and viscosities than those formulated with high crystallinity kaolinite (Ndlovu et al., 2015).

The dominant negative charges on the kaolinite hydrated surfaces lead to create permanent electrostatic repulsions among particles. Hence, the particles tend to be stabilized in a deflocculation state and giving rise to a viscose suspension form. Thus, kaolinite is used frequently as a suspending and anticaking agent in pharmaceutical formulations.

5.10. As drug carrier

Several clay-based systems have been developed as carrier of antibiotics, anticancer, vitamins, peptides, nucleotides, anticardiovascular, antidiabetic, antifibrinolytic, antihypertensive, antimycotic, anticoagulant, osteoporosis, antioxidant and anti-inflammatory drugs. These systems include natural clay minerals (*e.g.* kaolinite, halloysite, montmorillonite and palygorskite), synthetic clays (*e.g.* layered double hydroxides LDHs), clay-polymers or polysaccharides composites, clay-polymer composite hydrogels and films as well as clay-polymer nanocomposites (Bonina et al., 2007; Choy et al., 2007; Viseras et al., 2010; Rodrigues et al., 2013; Yu et al., 2013).

The reported interactions of several active drugs co-administrated with clays formulated as antacid and antidiarrheal products have paid attentions of pharmaceutical technologists to develop modified drug release systems as an alternative strategy to the conventional immediate release dosage forms. The main target of modified drug delivery systems is to maintain the plasmatic drug level between both, the minimum effective and the toxic concentrations, just to avoid therapeutic deficiencies and/or minimizing undesirable side effects. Mechanisms of the drug loading capacity and release are mainly based on the drug physicochemical and biopharmaceutical characteristics.

Delgado et al. (1994) investigated the effect of kaolinite crystallinity on the release of sodium amylobarbitone. They concluded that the release of the drug increases with kaolin crystallinity. Porous kaolin-based pellets prepared by cryptopelletization (*i.e.* freezing droplets of aqueous suspensions containing kaolin, sodium silicate solution and sodium lauryl sulphate, Byrne and Deasy, 2005) were loaded with Diltiazem HCl, and the system gave good sustained drug release which depends on the porous microstructure of the pellets.

Jämstorp et al. (2012) prepared pellets with methacrylic acid–ethyl acrylate, polyethylene-glycol (PEG), alginate and metakaolin to improve the release characteristics of Zolpidem©. Drug release experiments showed that the geopolymer/polymer composites exhibit good release under gastric (pH 1) and intestinal (pH 6.8) conditions and they were considered as promising oral dosage forms for sustained release of highly potent opioids.

Methoxy-modified kaolinite was prepared for testing the loading capacities of the anticancer 5-fluorouracil drug as well as the herbicide amitrole (Tan et al., 2014, 2015). The results demonstrated that this modified kaolinite product is a promising drug and agrochemical carrier, because of its high affinity to retain drug molecules both in the interlayer space and the external surface of the clay mineral.

Duarte-Silva et al. (2014) studied the adsorption capacity of three whey proteins (α-lactalbumin, bovine serum albumin and β-lactoglobulin) on kaolinite and metakaolin at pH 5. They found that kaolinite acts as a strong adsorbent for the α-lactalbumin and bovine serum albumin, and exhibits a very high affinity for β-lactoglobulin. Metakaolinite shows a good retention capacity for α-lactalbumin and β-lactoglobulin, but does not retain significant amounts of the bovine serum

Table 2
Therapeutical uses of kaolin as pharmaceutical active ingredients.

Therapeutical uses	Commercial products/derivatives	References
Hemostatic wound dressing	QuikClot Combat Gauze™(QCG), QuikClot Combat GauzeXL (QCX), QuikClot Combat Gauze TraumaPad (QCTP) and QuikClot® Interventional™(QCI).	Chávez-Delgado et al. (2014); Pourshahrestani et al. (2016). Z-Medica (2017).
Dermatological protector	Barrier creams (e.g., Kerodex 51®, Kerodex 71®, REINOL Aquagard®, REINOL Drygard® and DP1®).	Schliemann et al. (2013); Sadhra et al. (2014).
	Sunscreen creams.	Hoang-Minh et al. (2010, 2011) ; Dlova et al. (2013); Etich et al. (2014).
	Dusting powders.	Qadir and Hafeez (2012); Garg et al. (2014).
	Facial masks: (OFFECTS®, AIN'T misbehavin®, CALMA®). Cream: (ZO® cream). Lotion: (LACTO® Calamine lotion).	ZO® Skin Health (2017). Lacto® Calamine (2016). DERMAdoctor (2017).
Anti-inflammatory and topical analgesic	Cataplasms (e.g., Caloplast®, One Minute® and KL® kaolin B.P).	Intekom (2017). Drugs.com (2017).
Gastrointestinal protector and antidiarrheal	ASDA® upset stomach tablets, Entrocalm®; Morphine Mixture B.P.; Kaopectate® and Kaomix® suspensions; kaolin Antacil®; relief® and Treda® tablets.	Drugs.com (2017). NDrugd.com (2017).
Antibacterial	Kaolinite modified with cetyltrimethylammonium bromide and copper.	Malek et al. (2013).
	TiO_2/kaolinite and ZnO/kaolinite nanocomposites.	Dědková et al. (2014,2015.
	Fe-porphyrins/kaolinite hybrid materials.	Carvalho et al. (2014).
	Kaolinite modified with cetylpyridinium bromide.	Malek and Ramli (2015).
	Chlorhexidine loaded silver-kaolinite.	Jou and Malek (2016).
	Kaolinite loaded by chlorhexidine dihydrochloride.	Holešová et al. (2016).
Antiviral	Viruses/Kaolinite surface interactions.	Chrysikopoulos and Syngouna (2012); Bellou et al. (2015); Syngouna and Chrysikopoulos (2015); Silva et al. (2015).
	Kaolinite derivatives against hepatitis C virus.	Ali et al. (2014).
Detoxificant and antitumor	Detoxificant: ToxiBan®	Drugs.com (2017).
	Antitumor activity of kaolinite.	Misyak et al. (2016).
Pelotherapy	Medicinal peloids (Pastes or poultices).	Veniale et al. (2004); Tateo et al. (2010); Gomes (2013).

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albumin.

Therefore, kaolinite and its modified derivatives can be used as drug and protein carrier, based on the interaction between the clay surfaces and the organic molecules.

6. Use as active pharmaceutical ingredient

Kaolinite has been employed as a drug in traditional healings for thousands of years and, due to its uninjured bioactivity, the use as active agent for treatment of some common diseases is still under study. 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 (Table 2).

6.1. As hemostatic wound dressing agent

Wounds caused by accidents, military or surgical operations (e.g., abrasions, gunshot, incisions, amputation, etc) are vascular damages and skin breakdown, which facilitates toxicity and microbial invasion, may produce uncontrolled massive bleeding causing hemorrhagic shock which could lead to death (Hermans, 2010).

Coagulation mechanism occurs in three main successive hemostasis phases: initiation (thrombin formation), amplification (platelet aggregation and activation), and propagation (fibrin formation and stabilization of the platelet clot). The activity of physical hemostatic agents (*i.e.* minerals and biopolymers-based products) usually occurs in the amplification and propagation phases of hemostasis, by creating a physical mesh which facilitate platelet aggregation and coagulation (Glick et al., 2013).

Because it helps on accelerating clot formation within wounds, kaolinite is considered as a potent activator of substantial clotting pathway (Smith et al., 2013). The blood-clotting potential is directly influenced by the negatively charged surface of kaolinite at the pH of blood and human plasma. Hence, once the kaolin contacts the blood, it instantly begins the clotting process by transforming and enhancing the blood coagulation factor XII to its active form which activates the factor XI (plasma thromboplastin antecedent) and pre-kallikrien, which are directly responsible for bleeding prevention and wound dressing (Glick et al., 2013). Therefore, kaolin has been applied as topical hemostatic agent (procoagulant supplements) in the common wound dressing commercial products (Chávez-Delgado et al., 2014; Pourshahrestani et al., 2016). QuikClot Combat Gauze™(QCG), QuikClot Combat GauzeXL (QCX), QuikClot Combat Gauze TraumaPad (QCTP) and QuikClot® Interventional™ (Z-Medica, 2017).

6.2. As dermatological protector

The skin is the largest organ of the body. Because it acts as a fence (stratum corneum) between the internal members and the external surroundings, it is frequently exposed to harmful exterior impacts (sun and radiations, allergenic materials, dryness or excessive moisture, chemical caustics and toxins, microbial and parasitic infections, insect bites, etc.). It is also sensitive to symptoms of internal diseases by suffering rashes, exudations, pigmentations, boils, ulcers, chafing, fissuring, itching and tumors. The common superficial infections, syndromes and diseases of skin include dermatitis (eczema), acne, seborrhea, erythema, maceration, abscess, xerosis, ichthyosis, psoriasis, pityriasis rosea, tinea, candidal intertrigo, miliaria, impetigo and skin cancer (Hall, 2000; Krieg et al., 2010; Chong, 2013).

Minerals useful in skin care must be non-cytotoxic, non-reactive to cellular components, non-allergenic and non-penetrative into the internal tissues in order to avoid any secondary effects (Viseras et al., 2007). Kaolin, talc and montmorillonite are the common suitable clay minerals used as active ingredients in preparations for skin protection and treatment products, such as barrier, healing and sunscreen creams, dusting powders, ointments, poultices, masks and lotions (Carretero et al., 2006; Carretero and Pozo, 2010). Kaolin is one of the most important skin protectants, identified by the US food and drug administration, formulated into barrier creams (e.g., Kerodex 51®, Kerodex 71®, REINOL Aquagard®, REINOL Drygard® and DP1®) used to prevent and treat mild irritant and allergic contact dermatitis originated at home and workplace with daily-used agents such as weak solvents, detergents or even water by forming a thin impervious film (De Fine Olivarius et al., 1996; Schluter-Wigger and Elsner, 1996; Zhai et al., 1999; Diepgen et al., 2003; Yokota and Maibach, 2006; Zhai and Maibach,

2007; Schliemann et al., 2013; Sadhra et al., 2014).

Kaolinite has been also topically used as active sunscreen agent to attenuate the effects of solar ultraviolet radiations (UV-B and UV-A, spectral wavelength range 290–320 nm and 320–400 nm, respectively) that are responsible for skin damage and cancer. In general, the UV filtration mechanism of sunscreen products depends on the ability of the microfine particles to absorb, reflect and scatter efficiently the incident UV rays. The UV blocking capacity is mainly affected by the particle size of the active ingredients. Although rutile (TiO_2) and zincite (ZnO) are common constituents in sunscreen formulation, both metallic oxide nanoparticles penetrate into the skin in very low amounts, and may induce free radical formation by photocatalytic activity (photomutagenicity) on particle surfaces surrounded by water, which may cause damage of skin cells (More, 2007; Manaia et al., 2013). Kaolin formulated sunscreen creams are safer and exhibit high UV-protection capacity (60–80% of the incident UV-B and UV-A rays), particularly with kaolinite having high Fe_2O_3 contents (Hoang-Minh et al., 2010, 2011; Dlova et al., 2013; Etich et al., 2014).

On the other hand, the use of dusting powders for adsorption of excess moisture from the skin has a special interest to dermatologists. Kaolinite powder is one of the common recognized classes used for this target. It can adhere easily to skin forming a thin film which enable to absorb oils, lipids, surplus moisture and exudations from the skin surface to maintain and keep dryness conditions suitable for reducing hyperhidrosis, hence preventing chafing and avoid developing of fissuring, erythema and maceration, as well as inhibiting fungal and bacterial infections (Qadir and Hafeez, 2012; Garg et al., 2014).

Facial masks, creams, poultices and lotions containing kaolinite (e.g., ZO® 10% sulfur cream, OFFECTS® and AIN'T misbehavin'® 10% sulfur masks, CALMA® mask for acne and psoriasis and LACTO® Calamine lotion) exhibit therapeutic activity as antiacne treatments, because these absorb surface lipids, oily secretions and exfoliated dead skin cells as well as adsorb superficial toxins (e.g., poison oak and poison ivy), bacteria and viruses that could cause acne infection, and therefore, preventing blemishes, blackheads and reducing acne spread (Lee et al., 2007; Guerrero, 2010; Otto and Haydel, 2013; Pura et al., 2014). Other interesting application of kaolinite includes its use to relieve insect bites (bed bugs or mosquitoes) allowing the bite soothes, dry and helps it to heal besides the insecticidal activity (Marcotegui et al., 2015).

6.3. As anti-inflammatory and topical analgesic agent

Inflammation is an adaptive response to infection of any body organ with foreign organisms (e.g., bacteria and viruses) and tissue injury. With this induction, white blood cells (leukocytes) and inflammatory mediators (including chemokines, cytokines, vasoactive amines, eicosanoids and proteolytic enzymes) are produced and delivered to the site of infection or injury with increasing blood flow to protect the organ against the foreign substances, that may result in redness and heat. Some of these fluids are leaked into the tissues (*i.e.,* edema), resulting in swelling and may stimulate nerves and cause pain, stiffness and loss of mobility (Medzhitov, 2008).

Joint inflammations that occurred by the increase of inflammatory substances due to autoimmune response are termed as arthritis diseases (rheumatoid, psoriatic and gouty arthritis). In this case, the immune system damages its own tissues and causes joint irritation and pain, loss of joint function and stiffness, cartilage wearing down and swelling of joint lining forming cushions at the end of bones (Choy, 2012).

Kaolinite poultices or cataplasms (e.g., Caloplast®, One Minute® and KL® kaolin B.P) can be used as topical anti-inflammatory and analgesic agent, as mention by López-Galindo and Viseras, (2004). The bases of kaolin and clay therapeutic action to this purpose are mainly depending on their surface properties, which help on inhibiting edema (i.e., the excess of biochemical fluids accumulated and collected within the swelled tissues) in the inflammation site and hence alleviate pain and congestion, as well as their high adsorption and heat-retention capacity that assisting in skin cooling (Cornejo-Garrido et al., 2012; Caglar, 2012; Cervini-Silva et al., 2015, 2016). It is worth to mention that temperature of the applied kaolinite poultices should be considered carefully. Normally, a hot poultice causes vasodilation and increases the skin blood flow to the infected site, leading to heat dissipation (Charkoudian, 2010), but in case of inflammations, the hot poultices could also increases edemas, which in turn influence the coagulability and increase of the pain intensity, particularly in cases of inflammations triggered by bacterial infections.

6.4. As gastrointestinal protector and antidiarrheal agents

Kaolinite has beneficial effects in alleviation and treating of some digestive tract disorders such as stomachaches, gastric ulcer, acid indigestion, vomiting (pica) and nausea (Finkelman, 2006; Young et al., 2010; Voinot et al., 2014). Therefore, kaolinite appears as an essential active ingredient in some commonly used oral gastrointestinal products such as ASDA® upset stomach tablets, Entrocalm® or Boots Kaolin & Morphine Mixture B.P. The gastric hyperacidity can be relieved by interaction of excessive gastric acid with the ingested kaolinite. This may be accompanied by leaching and releasing of Al^{+3} cations and leading to therapeutic implications in acceptable limits of concentrations (Hollander et al., 1986; Tateo et al., 2001; Kikouama et al., 2009; Constancio et al., 2011).

In the case of peptic ulcer, the orally administrated kaolinitic products can adhere to the gastrointestinal mucous membrane for adsorbing mucus secretions, reducing the activity of the gastric enzymes (e.g., pepsin) and protecting the wall membranes of stomach and bowels from biodegradation and damage. In such conditions, where the pH of the gastric acid is less than 3, kaolinite is kinetically more stable, exhibits lower dissolution rate and is more resistant to acid attach than montmorillonite at the same pH and temperature conditions (Huertas et al., 1999; Schubert and Peura, 2008; Rozalen et al., 2009; Lavkulich et al., 2014).

On the other hand, oral administration of kaolinite can facilitate the lipid digestion and absorption to avoid gastrointestinal disorders. These are occurred by enhancing the triacylglycerol hydrolysis and stimulating the uptake of non-esterified fatty acid and glucose through the intestinal mucosa. These activities can be attributed to the sorptive properties of kaolinite and its role in slowing down of gastric emptying and intestinal transit (Habold et al., 2009).

Kaolinite also has been orally used as antidiarrheal agent in formulation of some common products such as kaolin/pectin (Kaopectate®) and Kaomix® suspensions, kaolin Antacil®, Sainsbury's Diarrhoea relief® and Treda® tablets. The activity of kaolinite to heal diarrhea depends on the sorption capacities of excessive fluids and secretions besides bacterial and viral inactivation in gastrointestinal tract (e.g., Norwalk and rotavirus, *salmonella, Shigella* and *Escherichia coli* bacteria, Clark and Ede, 2011). These are attributed to the hydrophilicity, surface area, microporosity, water osmotic and retention properties of the kaolinite, as well as its antibacterial and antiviral effect (Primandini et al., 2012; Wardhana et al., 2014; Pieszka et al., 2016).

6.5. As antibacterial agent

Kaolinite has been reported as bactericidal material (Lafi and Al-Dulaimy 2011; Otto and Hydel, 2013), interestingly with antibiotic drug-resistant bacterial pathogens (e.g., *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* and *Bacillus subtilis*). Antibacterial activities of natural clays are attributed to their physical and/or chemical properties. Physical bactericidal processes are occurred by surface adsorption between clay particles and bacterial cell wall, due to their electrostatic attraction; for instance, *Pseudomonas putida* and *Staphylococcus gallinarum* bacteria exhibit high adsorption affinity to

kaolinite surface (Vasiliadoua et al., 2011; Abdel-Khalek et al., 2014). This surface attraction leads to envelope the bacterial cells and hence interrupts their uptake of metabolic nutrients (Williams et al., 2011).

The chemical mechanisms of bacterial inhibition by kaolinite depend on the presence of bacterial toxic elements, such as Fe, Cu, P, V or Pb, in addition to the pH and oxidation state of the aqueous formulation medium. In such case, the capacity of kaolinite to buffer solution to the healthy pH and Eh at low oxidation conditions can lead to metal leaching and stable Fe^{+2} < /xps:span > and Cu^{+2} cations. These divalent cations can be transferred easily from the clay surface to the bacterial cell membrane to be oxidized, precipitating Fe^{+3} and Cu^{+3} oxides, and producing lethal intercellular hydroxyl radicals that attach and damage the biomolecules and hence kill the bacteria. Leached Al^{+3} and other tri- or tetravalent cations are usually prevented to pass through the cell membrane and might be precipitated on the bacterial cell wall, inhibiting the nutrients influx or the waste efflux (Williams et al., 2011; Morrison et al., 2014, 2016).

TiO_2/kaolinite and ZnO/kaolinite nanocomposites were found to have antibacterial activity to *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis* and *Pseudomonas aeruginosa*. This potentiality is due to photocatalytic activity of titanium and zinc oxides and their biological interaction with bacterial cells (Dědková et al., 2014,2015). Kaolinite modified with cetyltrimethylammonium bromide and copper have been confirmed to have powerful antibacterial activity against *Pseudomonas aeruginosa* (Malek et al., 2013). Moreover, kaolinite modification with cetylpyridinium bromide affected the total charge of kaolinite and their antibacterial activity against *Escherichia coli* (Malek and Ramli, 2015). Fe-porphyrins/kaolinite hybrid materials have been demonstrated as excellent antibacterial agents against oral pathogens *Bacillus subtilis*, *Klebsiella pneumonia*, and *Escherichia coli* (Carvalho et al., 2014). Nanocomposites including kaolinite have been also proposed as antibacterial materials (Holešová et al., 2016). Antibacterial activity of chlorhexidine loaded silver-kaolinite has been recently also studied (Jou and Malek, 2016).

6.6. As antiviral agent

During the second half of the 20th century, a few trials have been attempted to study the interactions between the human enteric and pathogenic viruses and phages (e.g. polioviruses, reoviruses, rotaviruses, Norwalk virus, bacteriophages, actinophages and coliphages) and clay surfaces. These earlier investigations considered that viruses, in wastewater, estuarine and freshwater ecosystems, can be inactivated by their adsorption onto clay particles due to their electrostatic interactions. Moreover, they attributed the efficiency of adsorption capacity and antiviral effect of kaolinite and other clay minerals to the presence, concentration and valency of associated cations, as well as controlled by cation exchange capacity and surface area (Carlson et al., 1968; Sykes and Williams, 1978; Schiffenbauer and Stotzky, 1983; Lipson and Stotzky, 1986; Meschke and Sobsey, 1998; Vettori et al., 1999).

In the recent decade, studies have demonstrated that the net charge of the viral protein coat is due to the type of the composing amino acid residues of carboxylic and amino groups (e.g., glutamic acid, aspartic acid, histidine and tyrosine). The adsorption affinity between the virus particle and the adsorbents (e.g., kaolinite, montmorillonite, etc) is a function of pH, isoelectric point of the virus and clay particles, hydrophobicity, flow rate and ionic strength. Most viruses possess a net negative charge at a pH above 5 which may vary to net positive charge below pH 5. High flow rate may influence the viruses' adsorption sites and reducing their contacts. Dilution of the ionic concentration enables the reversible desorption (Okoh et al., 2010; Syngouna and Chrysikopoulos 2010, 2013).

The electrokinetic study done by Chrysikopoulos and Syngouna (2012) showed that bacteriophages MS2 and Φ;×174 have greater affinity to be adsorbed onto well-crystallized kaolinite surfaces, mostly caused by hydrophobic interaction. The sorption in this batch experiment is described by the Freundlich isotherm, and the total energy of the virus-clay interaction is strongly governed by Lewis acid–base interactions. *In vitro* Huh-7 cell line study by Ali et al. (2014) on the inhibitory effect of kaolinite derivatives against hepatitis C virus (HCV) concluded that kaolinite is a promising material that could be applied as excellent therapeutic agent for treatment of HCV. Static and dynamic interaction *in vitro* experimental studies conducted by Bellou et al. (2015) and Syngouna and Chrysikopoulos (2015) showed that human enteric pathogenic adenoviruses (hAdVs) and coliphages (MS2 and ΦX174) can be removed from diluted aqueous solutions by adsorption on kaolinite surfaces. Silva et al. (2015) demonstrated that kaolinite particles suspended in water reduced viral genome copy numbers and infectivity of the adenovirus (HAdV-5).

6.7. As detoxification and antitumor activity

Kaolinite derivatives and products (e.g., ToxiBan®) have been used for internal detoxifications by adsorption from gastrointestinal tract of ingested noxious substances or organisms, such as heavy metals, mycotoxins or toxic antibiotic compounds, as well as to control the release of some trace elements (Fe and Zn) in the oral delivery in order to optimize their gastrointestinal absorption (Tiwary et al., 2009; Kikouama and Balde 2010; Carraro et al., 2014; Wardhana et al., 2014). Recently, Misyak et al. (2016) have discovered a new pharmacological antitumor activity of kaolinite, reducing metastases and tumor mass in animals. Kaolinite exhibits an ability to influence electron transport during superoxide radical generation by hepatocyte mitochondria and immunocompetent blood cells of mice inoculated with Lewis lung carcinoma cells. They considered the kaolinite derivatives as promising compounds for use in restorative procedures for cancer patients.

7. Pelotherapy

Medicinal thermal muds (peloids) are hydrothermalized semisolid products (pastes or poultices) formulated by the mixing of geomaterials (clay, silt and sand sized sediments composed of clay and non-clay minerals) with sea, lake saline or spring thermo-mineral medicinal water (45–50 °C) and subjected to the so-called "maturation" process (Veniale et al., 2004).

Pelotherapy is the application of peloids (either naturally, manipulated or dressed) to be administrated topically by means of facial masks or body bathing for healing of muscles, bones and rheumatic (arthrosis, arthritis and fibromyalgia) and skin diseases (acne, psoriasis and seborrhea), besides skin pathologies prevention and care purposes. Their biophysical and/or biochemical therapeutical actions are based on the original physical and chemical characteristics of the mineral fraction, as well as those acquired after the thermal water treatment, allowing heat treatments and transdermal delivery of element (Veniale et al., 2007; Tateo and Summa, 2007; Tateo et al., 2009; Carretero et al., 2010; Gomes et al., 2013).

Peloids quality and healing activity are influenced by specific heat, heat capacity, thermal conductivity, heat diffusiveness and cooling kinetics (low cooling rate), maturation time, chemical compositions of solid (minerals and organic matter) and fluid phases, particle size distribution, viscosity, plasticity, adhesivity, abrasivity, solid/liquid ratio, ion exchange capacity, molecule absorption capacity, ion and molecule adsorption/desorption capacity (Quintela et al., 2012; Gomes et al., 2015).

Kaolinite is a main component in both naturally occurred (virgin) and artificial (dressed) polymineralic medicinal peloids, that are frequently associated or formulated with smectite and illite clay minerals and subordinary non-clay minerals such as quartz, micas, feldspars, carbonate and iron oxide minerals (Veniale et al., 2004; Tateo et al., 2010; Rebelo et al., 2011; Gomes, 2013).

Depending on the chemical composition and properties of the different medicinal mineral waters, some small mineralogical changes can

be occurred during the maturation process (Veniale et al., 2004, 2007). In this regard, the kaolinite crystallinity could be decreased with peloids maturation (Fernández-González et al., 2013).

8. Conclusion

Kaolinite may be considered as a suitable inexpensive excipient and the interaction of kaolinite with drugs may be useful in the design of modified drug delivery systems. Future applications of kaolinite and derivatives in biomedicine will include also the design and development of platforms for optimization of diagnostics and treatment of relevant pathologies as cancer and immunological diseases. The use of kaolinite in modified drug delivery as well as modulation and control of the immune response to treat a variety of disease conditions is the new frontier in the use of kaolinite in biomedicine.

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4. CHARACTERIZATION OF EGYPTIAN KAOLINS FOR HEALTH-CARE USES

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Characterization of Egyptian kaolins for health-care uses

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ABSTRACT

This work aimed to evaluate by first time the suitability of the Egyptian Abu Zenima (Sinai Peninsula) kaolins to be used in pharmaceutical and cosmetic applications. Sixty five kaolin samples were collected from six stratigraphic sections: Wadi Khaboba, Gabal Hazbar and Wadi Abu Natash sections, belonging to the Abu Thora Formation (Carboniferous age), and Gabal El Dehessa, Gabal Farsh El Ghozlan and Wadi Budra sections, belonging to the Malha Formation (Lower Cretaceous), and characterized by mean of X-ray diffraction and fluorescence, electron microscopy, spectrophotometry and rheometry.

Most of the samples were dominated by kaolinite, and half of the samples contained >75% of this mineral, reaching up to 96%. Quartz was the main impurity, with very variables quantities; it was always present except in some parts of the Wadi Abu Natash and Wadi Budra sections. Mica, anatase and hematite were frequently present, but they normally did not exceed 10%. Other detected impurities were carbonates (calcite, dolomite, ankerite), sulfates (gypsum, alunite), smectite, feldspars, magnetite, pyrite, halite and heulandite, but in lesser amounts and only in some samples.

Carboniferous kaolinites exhibited a high crystallinity (Hinckley Index >1), while most of Cretaceous kaolinites were medium to poorly crystallized (Hinckley Index normally <1). CIELAB colorimetric parameters put into evidence the general grayish color of the samples, some of which showing light tints of redness and yellowness in correlation with their iron content.

The rheological characterization of the 31 purest kaolin samples revealed that their dispersion exhibited similar and good pseudoplastic flow behavior at 50% W/W solid concentrations. The apparent viscosity and yield stress values of Carboniferous samples showed a widest range of variations when compared to Cretaceous ones. The observed variations were interpreted to be correlated with both, the kaolinite content as well as microtexture and the dimensions of kaolinite particles.

With these premises, some of the studied kaolins are considered to have a very high economic potential, once the detected impurities are removed easily by the appropriate process, and then suitable for pharmaceutical and cosmetic purposes. Even if there were zones rich in kaolinite in all the studied sections, the highest quality for the target purposes is found at the lower part of the Wadi Abu Natash section, where quartz was absent and include the samples with the highest viscosities.

1. Introduction

Kaolinite is a planar hydrous 1:1 dioctahedral clay mineral with an ideal structural formula of $Al_2Si_2O_5(OH)_4$. It is the most common mineral of the kaolin-group, which includes other members as halloysite, nacrite and dickite. These minerals exhibit many excellent physical, chemical, mechanical and structural properties (rather simple structure, plasticity, alkaline pH, thixotropic and colloidal properties, influence on the viscosity of organic polymer dispersions, relatively low specific surface area and low sorption capacity) that make them very useful for many pharmaceutical applications, like drug excipients (e.g., diluent and binder, emulsifying, thickening and anticaking agent, flavor corrector and carrier-releaser) or active ingredient in many solid and semisolid drug products administered orally or topically such as gastrointestinal protector, antidiarrhoeaic product, dermatological protector, anti-inflammatory and local anesthetic, cosmetic creams, powders and emulsions (Braun, 1994; Bolger, 1995; Wenninger et al., 2000; Carretero, 2002; López-Galindo and Viseras, 2004; Carretero et al., 2006, 2013; Droy-Lefaix and Tateo, 2006; Sweetman, 2007; Ferrell, 2008; Carretero and Pozo, 2009, 2010; Rowe et al., 2009).

In addition to the classic pharmaceutical uses, new advanced biopharmaceutical strategies are focusing on applying clay nanoparticles

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as vectors for drug and gene delivery, based on their interactions with drugs and biochemical molecules, bioadhesion and cellular uptake (Aguzzi et al., 2007). Moreover, modified clays and clay-biopolymer nanocomposites offer further capabilities for improvement of drug loading and release properties and also the specificity of targeted drug delivery, and minimize toxicity (Viseras et al., 2010).These interesting advancements have also paid attention to apply kaolinite in many biomedical innovation areas, such as development of products used for treating antibiotic-resistant bacteria, antiviral activity against hepatitis C virus and anticancer activity (Shi et al., 2011; Vergaro et al., 2012; Cervini-Silva et al., 2013; Ali et al., 2014; Pasbakhsh and Churchman, 2015).

Egypt has numerous and big sedimentary kaolin deposits, ranging in age from Carboniferous to Neogene (Zaghloul et al., 1982; Saied, 1990; Boulis and Attia, 1994; Baioumy and Gilg, 2011; Baioumy, 2014). The most important deposits are located at Abu Zenima and El Tih plateau (West-Central Sinai), Abu El Darag area (approximately 85 km south of Suez city), Wadi Qiseib area (about 90 km south of Suez city), Wadi Abu Sanduk area (94 km south of Suez city), Wadi Abu Had area (at 80 km west of Ras Gharib city), Wadi Abu Sobeira area (15 km north east of Aswan city), and Wadi Kalabsha area (105 km southwest of Aswan city). The reserves are estimated to be around 120 million tons in west central Sinai deposits (Abd El-Razik, 1972), about 17 million tons in the Wadi Kalabsha area, and 5 million tons in the Wadi Abu Sobeira area (Qusa, 1986). The exploited Egyptian kaolins are used in ceramics, refractories, white ware, heavy-clay products, Portland cement, paints and paper on the basis of the great demand and importance of such industries in Egypt (Abdel Shafy, 1967; Soliman and El Fetouh, 1969; Amer et al., 1971; Abd El-Razik, 1972; Hegab et al., 1992; Abdel Razek, 1994; Boulis and Attia, 1994; Rashed and Amer, 1994; Kamel et al., 1997). However, these kaolins have never been submitted to special characterizations to evaluate their suitability for pharmaceuticals, cosmetics and other health care applications, even if the output value of kaolinite in pharmaceutical industries is enormous, because the price of pharmaceutical grade quality may be up to ten times that of the same grade dedicated to the above mentioned uses. The kaolinite materials have to completely correspond to stringent and precise chemical, physical, toxicological and microbiological specifications regulated by the Pharmacopoeias (EP. 8.0, 2014; USP 39-NF34, 2015).

The quality of industrial kaolinite is influenced, among other factors, by the quantities of mineral impurities such as quartz, anatase, rutile, mica, feldspar, calcite, dolomite, magnetite, hematite, illite, smectite or pyrite. The economic value of kaolinite upgrades as the purity increases, because this minimizes the processing cost. Pharmaceutical grade kaolin is mined, powdered and freed of coarse gritty particles either by elutriation or by screening. Impurities such as ferric oxide, calcium carbonate, and magnesium carbonate, that usually accompany kaolinite, are removed easily with an electromagnet and by treatment with hydrochloric acid and/or sulfuric acids.

This study aims to characterize samples from Abu Zenima kaolin deposits, located at West Central Sinai, with the highest reserves and purist grade amongst all the Egyptian kaolin deposits (Rashed and Amer, 1994), in order to evaluate their general potentialities in pharmaceutical and/or cosmetic industries and other health care applications. The results will be used to propose those samples that could be exploited for health care application, to increase the market of Egyptian kaolinites and to call attention of the Egyptian Mineral Resources, Industry and Investment authorities for the high quality of the selected samples.

2. Geological context

The studied kaolin deposits are located in the Abu Zenima district (Eastern coast of the Gulf of Suez, West Central Sinai Peninsula), in an area of around 333 Km^2. They belong to both Carboniferous and Lower Cretaceous sedimentary units. The Carboniferous (Upper Visean) kaolin deposits occur within the Abu Thora Formation (Kora, 1989), and the Lower Cretaceous (Albian) kaolin deposits occur within the fluvial-continental Malha Formation (Abdallah et al., 1963).

As regards to the studied sections, the Abu Thora Formation is a siliciclastic sequence with a thickness ranging from 65 to 188 m, made up of pinkish white sandstones intercalated by multicolored siltstones and mudstones. The "Wadi Khaboba" section (named K, at 29°05′01″ N and 33°14′46″ E) includes three dark grey to yellowish grey kaolinitic horizons each one of around 5 m thickness, alternating with three multicolored cross bedded medium to coarse grained sandstone beds. The "Gabal Hazbar" section (named H, at 29°04′45″ N and 33°22′05″ E) includes two light to dark grey laminated kaolin horizons intercalated by a yellow fine-grained sandstone bed and overlaid by a white and laminated sandstone bed. In "Wadi Abu Natash" section (named N, at 28°56′45″ N and 33°19′24″ E) there are three light gray, grey and reddish brown kaolinitic claystone beds intercalated with four ferruginous laminated and cross-bedded sandstone layers.

The Malha Formation, which ranges between 70 and 130 m in thickness, is composed mainly of thin cross-bedded, very fine to coarse-grained "Nubian-type" sandstones with intercalations of red to grey, fine-grained claystones and siltstone beds, and sporadic thin kaolinitic lenses. The "Gabal El Dehessa" section (named D, at 28°55′55″ N and 33°17′59″ E) exhibit three grey and pinkish grey massive kaolinitic siltstone and claystone intercalated with cross-bedded white and ferruginous sandstone layers. In "Gabal Farsh El Ghozlan" section (named F, at 28°55′40″ N and 33°18′10″ E), the kaolin deposits occur in the form of white, pinkish grey and reddish brown lenticular beds intercalated within the sandstone. The "Wadi Budra" section area (named B, at 28°55′06″ N and 33°19′16″ E) is characterized by its varicolored sandstones intercalated by lenses of massive kaolin, kaolinitic clays and siltstone beds.

3. Materials and methods

3.1. Mineralogy and chemistry

Sixty five samples (dried, milled and sieved under 125 μm) were studied by means of X-ray diffraction (XRD), using a PANalytical X'Pert Pro diffractometer (CuKα radiation, 45 kV, 40 mA) equipped with an X'Celerator solid-state linear detector, using a step increment of 0.008° 2θ and a counting time of 10 s/step. The diffraction data were analyzed using the XPOWDER® computer program (Martín-Ramos, 2004). Semi-quantitative analysis were performed following Moore and Reynolds (1989), and the final contents of the different mineral phases were calculated by combining XRD and chemical analytical data, following Torres-Ruiz et al. (1994) and López-Galindo et al. (1996).

The Hinckley Index (Hinckley, 1963) was measured by using the reflections (02l) and (11l) in the range from 19° to 24° 2θ in random oriented powdered samples, that are very sensitive to the structural defects (random and interlayer displacements) in kaolinite structure. The maximum intensity ratio of (020), (0-10) and (11-1) reflections were determined using the XPOWDER® software.

Elements were analyzed using a commercial wavelength dispersive X-ray fluorescence instrument (Bruker S4 Pioneer) equipped with an Rh anode X-ray tube (60 kV, 150 mA); three analyzer crystals (OVO-55, LiF 200 and PET) and a flow proportional counter for light element detection and a scintillation counter for heavy elements. Quantification was made by the fundamental parameters method using the software linked to the equipment (SpectraPlus). Five grams of each powdered sample was mixed with 0.5 g of a binder (Hoechst wax C micropowder) and homogenized in agate mortar. To obtain a XRF-pellet, a small metallic sample holder made of aluminum with a diameter of about 4 cm was used. The pellets were pressed at 90 bars in a Nannetti hydraulic press for 30 s. To determine loss on ignition (LOI), samples were heated to 900 °C for 1 h.

Table 1
Mineralogical composition, Hinckley Index of kaolinite and CIELAB spectrocolorimetric data of the studied Abu Zenima samples.

			Kaolinite	Muscovite-Illite	Smectite	Quartz	K-feldspar	Anatase	Hematite	Magnetite	Pyrite	Calcite
Carboniferous	Wadi Khaboba	K1	88	3		7		1				
		K2	84	5		1		1	9			
		K3	89	4		5		1				
		K4	65	4		23		1				
		K5	80	3		13	1	2	1			
		K6	65	5		24		1	1			
		K7	64	7		26		2	tr			
		K8	63	4		24	2	1				
		K9	67	5		22	2	2				
		K10	57	11		28	2	2				
		K11	40	4		48	1	2				
		K12	72	4		17	2	2	3			
	Gabal Hazbar	H1	55	8		36		1				
		H2	58	8		32		1	1			
		H3	43	8		48		1				
		H4	57	3		31		1				
		H5	81	2		14	1	2				
	Wadi Abu Natash	N1	93					3	2			
		N2	96					3	tr			
		N3	93					4	tr			
		N4	95					3	1		tr	
		N5	92					3	2	2		
		N6	94					3		1		
		N7	69	5		22		1	1			
		N8	68	3		25		1	1	2		
		N9	68	5		23		2	1			
		N10	17	42		20			21			
		N11	89					3	1			
		N12	92			1				2		
Cretaceous	Dehessa	D1	78			18		2	1			
		D2	77			20		2	1			
		D3	79			18		2	1			
		D4	71			24		3	2			
		D5	83			14		2	1			
		D6	93			3		3	1			
		D7	92			3	1	3	1			
		D8	77			20		2	1			
		D9	93			4		3	tr			
		D10	78			18		3	1			
	Farsh El Ghozlan	F1	89			9	tr	2	tr			
		F2	95			2		3				
		F3	94			3		2	1			
		F4	79			17		2	2			
		F5	84			12		2	2			
		F6	67			28		3	1			
		F7	78			18		2	2			
		F8	88	1		7		2	2			
		F9	85			11		3	1			
		F10	78	2		13		2	4			
		F11	55	12		21	4	1	5			
		F12	23	20	8	17		1	4			
		F13	9			4			2			77
	Wadi Budra	B1	65	3		18		2	10			
		B2	60	5		21		2	10			
		B3	86			3		2	5			
		B4	67			20	3	2	5			
		B5	65			13		2	17			
		B6	53		20	15		1	4			
		B7	22		41		26	2	3			
		B8	32	3	40			1	11			
		B9	60	5	tr	16		1	13			
		B10	65		10			2	19			
		B11	44	25		15	1	1	5			
		B12	53	8		37		1				
		B13	51			24	2	1	5			
Guinama Kaolin[a]			86	7		6						

[a] Internet link (only for mineralogical data): http://www.guinama.com/media/tecnico/91694_FT%20Kaolin%20v02.pdf.

3.2. Color

Chromatic coordinates of kaolin samples were measured in a Konica-Minolta CM-700d spectrophotometer. A pulsed xenon lamp with UV cut filter provided the illumination for the surface of the samples. A silicon photodiode array detected and measured both incident and reflected light. The measurements were performed by selecting CIE illuminant D65, which simulates daylight with a temperature color of 6504 K. According to the UNE-EN 15886 (2011) standard, air dried samples were placed on 4 cm^2, 2 mm thick

Dolomite	Ankerite	Halite	Gypsum	Alunite	Heulandite	Hinckley Index	L* (D65)	a* (D65)	b* (D65)	WI (Stensby)	WI (CIE)
		tr		1		1.28	72.68	1.93	3.24	62.11	26.43
		tr				1.30	61.60	12.83	8.54	66.54	−22.81
		1				1.33	77.32	1.78	3.77	65.28	31.87
				7		1.26	82.91	1.50	4.53	68.58	39.05
						1.38	77.47	2.65	5.45	62.91	23.25
				4		1.19	79.23	2.03	4.60	65.81	31.16
				1		1.26	78.69	2.07	5.26	63.27	26.62
				6		1.35	79.78	1.73	5.12	63.90	29.53
				2		1.23	80.41	1.57	4.07	67.53	36.30
						1.08	78.58	1.42	4.72	62.94	29.22
				5		1.17	79.75	2.00	5.82	62.51	25.86
						1.35	76.66	4.26	13.67	42.31	−22.30
						1.27	80.96	0.12	1.45	72.12	50.89
						1.17	78.63	0.75	1.94	69.64	44.02
						1.02	82.35	2.11	5.39	67.03	33.57
				8		0.99	74.73	1.76	5.10	58.46	19.73
						1.33	67.05	3.87	6.89	50.86	−4.52
		2				1.46	82.67	1.82	5.51	66.26	33.61
		1				1.50	86.72	0.85	7.74	60.75	31.60
		2	1			1.42	88.75	0.64	5.71	69.01	46.23
		1				1.48	79.39	8.19	12.25	61.00	−7.46
		1				1.46	65.52	16.48	22.58	46.31	−95.66
		1		1		1.39	88.03	0.72	8.47	59.65	31.23
		2				1.35	72.68	2.21	4.64	58.78	18.56
		tr				1.44	69.83	4.06	6.63	55.00	2.15
		1				1.26	67.36	1.80	4.57	52.28	9.69
						n.d.	43.91	16.44	17.74	38.04	−122.34
		5	2			1.50	86.51	0.39	6.85	62.40	35.42
				5		1.29	82.13	5.13	3.27	82.57	44.14
		1				0.54	84.91	3.04	7.19	67.14	30.30
		tr				0.55	86.40	1.24	6.96	64.15	34.66
						0.50	83.08	4.38	7.64	67.88	24.01
						0.50	80.01	5.69	7.78	67.97	16.62
						0.82	86.70	1.30	7.96	61.57	30.48
						0.27	87.10	1.33	8.22	61.46	30.22
						0.47	82.81	4.18	8.31	65.14	20.01
						0.80	85.39	2.50	7.08	66.58	31.90
						0.63	89.20	0.57	7.14	64.74	40.46
						0.82	84.10	2.73	7.93	63.28	24.71
						0.53	87.50	0.75	7.37	62.63	35.25
						0.45	88.25	1.00	7.58	63.66	36.10
						0.59	82.26	5.23	6.34	73.85	28.85
						0.68	79.56	7.18	9.80	65.74	5.39
						0.52	77.36	9.07	12.77	60.09	−14.80
		1				0.54	84.83	2.25	8.45	60.58	23.75
						0.66	80.19	0.20	3.61	64.67	38.15
						0.72	77.66	7.56	11.92	58.22	−9.94
						0.61	84.89	1.32	9.22	55.80	19.96
		1				0.95	66.44	5.37	6.68	55.28	−4.08
		2				0.68	66.57	7.06	8.82	54.23	−16.37
25		2				1.18	72.23	2.41	19.53	17.83	−66.10
	5		3			0.94	79.29	2.30	14.84	36.10	−22.36
		2				1.03	74.86	7.86	28.67	12.74	−104.85
		2				1.36	58.16	13.89	21.78	34.45	−112.42
		1			3	0.99	70.48	4.91	4.45	64.59	16.03
		3				0.49	60.40	10.08	12.73	46.54	−52.11
		3				0.84	41.54	19.58	20.12	40.62	−144.11
		5			2	0.51	69.22	8.46	13.64	47.69	−38.61
		6				0.65	76.79	1.41	14.62	32.44	−27.75
		9	4			1.10	47.13	16.75	19.80	37.67	−128.09
		5				1.50	52.06	13.15	19.14	32.97	−112.47
		4				0.96	42.60	18.97	18.00	43.41	−126.03
		7	1		1	1.01	62.18	6.24	24.32	10.31	−120.49
		1				1.00	85.09	1.94	6.43	66.25	34.34
		10		7		1.23	73.80	5.21	21.27	22.69	−70.28
						1.32	93.32	0.47	3.75	80.08	66.45

plaques with a flattened surface. After calibration by the reference sample and adjustment, the aperture of the equipment was focused vertically on the surface of each sample to get the normal position that was fixed to press on the flash scanning button. Lightness parameter L* (0 = black, 100 = white), chromatic parameters a* (+100 = red and −100 = green), and b* (+100 = yellow and −100 = blue), and Stensby Whiteness Index (WI) were used for color characterization.

Table 2
Chemical composition (major and trace elements) of the studied Abu Zenima samples. Trace elements are ordered according to ICH guidelines.

			Major oxides (%)												Trace elements (ppm)			
																Class 1		
			SiO_2	Al_2O_3	Fe_2O_3	MgO	CaO	Na_2O	K_2O	TiO_2	MnO	P_2O_5	SO^{-3}	L.O.I	Cl	Cd	Pb	As
Carboniferous	Wadi Khaboba	K1	47.04	35.00	0.53	0.11	0.05	0.51	0.52	1.33	0.00	0.05	0.53	13.80	3700		112	–
		K2	41.16	34.21	8.91	0.10	0.03	0.39	0.52	1.15	0.00	0.05	0.19	12.80	2000		61	59
		K3	47.04	36.01	0.52	0.14	0.04	0.46	0.49	1.30	0.00	0.06	0.06	13.40	4100		–	–
		K3[a]	46.98	35.28	0.54	0.18	0.04	0.26	0.44	1.20	<0.01	0.05	0.01	15.07	100	<0.5	31	6.6
		K4	54.06	28.79	0.58	0.14	0.06	0.29	1.18	1.59	0.00	0.07	2.41	10.60	400		–	–
		K5	52.62	32.74	1.11	0.11	0.09	0.13	0.75	1.83	0.00	0.06	0.05	10.30	300		–	55
		K6	54.46	28.39	1.17	0.16	0.07	0.29	1.07	1.53	0.01	0.05	1.64	10.90	700		–	–
		K7	58.12	28.18	0.80	0.18	0.07	0.16	0.93	1.61	0.00	0.05	0.46	9.23	100		–	25
		K8	54.92	28.01	0.63	0.16	0.06	0.25	1.19	1.55	0.00	0.07	2.30	10.70	200		–	–
		K9	57.91	29.32	0.66	0.13	0.06	0.20	0.88	1.92	0.01	0.10	0.59	7.98	300		–	–
		K10	62.27	24.35	0.61	0.20	0.13	0.33	1.36	1.81	0.00	0.10	0.27	8.24	2000		–	35
		K11	69.60	18.61	0.41	0.15	0.08	0.21	1.26	1.78	0.00	0.11	1.93	5.66	400		–	26
		K12	52.93	29.55	3.43	0.13	0.25	0.30	0.67	1.73	0.00	0.09	0.07	10.40	3600		–	41
	Gabal Hazbar	H1	64.81	24.06	0.49	0.21	0.10	0.37	0.70	1.33	0.03	0.06	0.14	7.38	1800		–	35
		H2	61.29	25.49	1.06	0.26	0.15	0.52	0.71	1.41	0.00	0.11	0.37	8.22	2800		126	47
		H3	70.79	18.76	0.64	0.11	0.04	0.63	0.80	1.57	0.00	0.09	0.26	5.85	3900		–	–
		H4	72.61	15.12	0.37	0.09	0.03	0.25	1.02	1.23	0.01	0.06	2.98	6.11	100		–	–
		H5	52.35	31.82	0.60	0.09	0.34	0.07	0.51	1.79	0.00	0.08	0.13	12.00	200		–	–
	Wadi Abu Natash	N1	40.80	36.20	1.76	0.52	0.09	0.66	0.01	3.29	0.00	0.08	0.07	15.06	14,600		95	–
		N2	42.70	37.35	0.81	0.13	0.05	0.69	0.02	3.36	0.01	0.02	0.03	14.10	7500		–	–
		N2[a]	43.11	36.82	0.60	0.13	0.04	0.26	< 0.01	1.31	<0.01	0.01	0.01	17.59	100	<0.5	8	5.8
		N3	42.17	37.01	0.84	0.17	0.21	0.63	0.02	3.42	0.01	0.04	0.29	14.30	8500		–	–
		N4	41.93	36.99	1.01	0.16	0.15	0.42	0.03	3.32	0.00	0.05	0.24	14.90	7800		–	40
		N5	40.90	36.27	3.00	0.10	0.11	0.38	0.06	3.57	0.00	0.09	0.49	14.30	5800		–	–
		N6	40.72	36.64	0.60	0.27	0.32	0.46	0.10	3.15	0.00	0.09	0.65	15.90	12,200		–	32
		N7	56.70	26.33	1.46	0.44	0.48	0.49	0.46	1.47	0.00	0.25	0.43	9.98	15,800		91	33
		N8	61.34	25.14	2.83	0.08	0.11	0.38	0.40	1.48	0.00	0.09	0.15	7.50	3600		–	53
		N9	54.69	27.96	1.18	0.59	0.64	0.28	0.55	1.91	0.01	0.17	0.11	10.30	17,600		108	–
		N10	45.96	16.49	21.34	2.35	0.54	0.18	4.46	0.89	0.20	0.28	0.07	6.51	100		66	148
		N11	37.85	33.79	0.95	1.32	0.42	1.22	0.03	3.29	0.00	0.07	0.53	17.70	34,300		94	–
		N12	39.49	36.28	1.97	0.28	0.11	0.62	1.01	0.19	0.00	0.05	2.12	17.30	2500		837	–
Cretaceous	Dehessa	D1	54.92	31.15	1.31	0.09	0.08	0.46	0.09	2.31	0.00	0.12	0.10	8.82	4500		–	–
		D2	56.99	31.12	1.03	0.08	0.11	0.50	0.03	2.74	0.02	0.05	0.08	6.47	5700		–	70
		D3	54.22	31.17	1.56	0.04	0.07	0.14	0.03	2.57	0.01	0.06	0.05	9.68	1100		74	86
		D4	58.42	28.50	1.81	0.02	0.05	0.06	0.03	2.70	0.01	0.07	0.03	7.91	100		69	87
		D5	53.30	33.14	0.94	0.03	0.04	0.17	0.10	2.48	0.01	0.11	0.00	9.27	500		68	26
		D6	43.92	37.19	1.36	0.03	0.06	0.10	0.04	3.13	0.00	0.10	0.03	13.60	100		155	91
		D6[a]	42.86	36.41	1.11	0.06	0.04	0.08	0.02	2.26	<0.01	0.11	0.01	16.83	100	<0.5	83	3
		D7	43.65	36.81	1.78	0.03	0.04	0.16	0.04	3.51	0.00	0.09	0.05	13.40	300		123	–
		D8	58.78	30.68	0.90	0.04	0.05	0.09	0.09	2.28	0.01	0.13	0.04	6.56	200		–	–
		D9	46.80	36.75	0.85	0.03	0.13	0.06	0.03	2.78	0.01	0.09	0.06	12.10	500		–	61
		D10	54.63	31.23	0.97	0.04	0.06	0.08	0.08	3.22	0.01	0.08	0.04	9.18	200		69	58
	Farsh El Ghozlan	F1	51.47	36.22	0.96	0.03	0.07	0.04	0.02	2.50	0.01	0.06	0.02	8.30	100		–	52
		F2	43.91	37.93	0.87	0.04	0.09	0.05	0.02	2.87	0.00	0.04	0.00	13.80	100		56	55
		F2[a]	43.04	36.84	0.74	0.06	0.06	0.04	0.01	2.15	<0.01	0.05	0.03	16.81	100	<0.5	32	< 0.5
		F3	45.94	36.45	1.52	0.05	0.09	0.06	0.03	2.33	0.00	0.08	0.00	13.10	100		77	30
		F4	53.78	31.36	2.05	0.10	0.49	0.05	0.13	2.23	0.01	0.16	0.05	9.23	300		92	–
		F5	49.68	32.92	2.27	0.07	0.15	0.31	0.06	2.28	0.01	0.08	0.12	11.50	2800		66	–
		F6	59.99	26.98	0.97	0.08	0.27	0.43	0.05	3.42	0.01	0.09	0.18	6.68	5700		51	53
		F7	53.76	30.69	1.98	0.09	0.27	0.29	0.07	2.54	0.01	0.06	0.23	9.45	2900		–	38
		F8	46.66	35.31	2.43	0.11	0.34	0.04	0.10	2.42	0.01	0.06	0.11	12.00	200		–	39
		F9	51.05	33.92	0.95	0.06	0.26	0.03	0.04	3.55	0.01	0.09	0.04	9.65	100		72	54
		F10	49.51	31.12	4.75	0.17	0.22	0.37	0.26	1.82	0.01	0.10	0.22	10.80	3600		50	77
		F11	54.37	22.38	5.74	1.42	0.69	1.12	2.69	1.09	0.01	0.05	0.19	9.09	12,700		–	–
		F12	37.71	17.02	4.68	3.22	7.73	0.77	2.40	0.90	0.10	0.17	0.29	22.70	28,000		–	–
		F13	8.77	3.69	2.30	1.55	43.34	0.13	0.54	0.20	0.16	0.18	1.21	37.70	2700		–	–
	Wadi Budra	B1	47.78	25.07	10.45	0.26	0.26	0.99	0.20	1.65	0.00	0.02	0.04	12.10	13,200		–	–
		B2	51.86	24.02	9.74	0.37	0.39	0.76	0.50	2.07	0.02	0.03	0.13	8.70	15,300		–	22
		B3	44.33	34.16	5.00	0.11	0.24	0.60	0.07	1.62	0.00	0.07	0.31	12.60	6400		109	52
		B4	48.22	26.21	5.21	0.73	1.03	0.93	0.39	2.35	0.00	0.03	0.14	12.80	22,100		–	–
		B5	37.43	25.84	16.71	0.60	1.00	0.62	0.23	1.98	0.01	0.03	0.01	13.70	21,500		–	–
		B6	46.50	23.76	4.01	1.60	1.35	1.25	2.57	1.50	0.00	0.03	0.12	14.80	30,200		–	–
		B7	42.93	20.11	2.95	3.28	3.00	1.46	3.74	1.72	0.03	0.31	0.03	17.30	35,200		–	44
		B8	32.90	18.73	10.76	2.57	1.10	4.82	1.78	1.40	0.01	0.26	1.72	19.10	56,100		–	–
		B9	39.85	23.81	13.19	0.63	0.24	3.39	0.94	1.15	0.01	0.10	1.32	12.80	31,500		–	–
		B10	29.92	25.58	19.56	1.37	0.81	0.80	0.24	2.14	0.03	0.04	0.10	17.20	27,100		–	–
		B11	44.57	20.36	5.40	2.21	1.91	0.81	2.33	1.09	0.00	0.07	0.32	17.40	43,200		–	–
		B12	67.50	22.72	0.62	0.24	0.05	0.60	0.81	1.22	0.00	0.04	0.06	5.64	4900		–	–
		B13	46.28	20.21	5.17	0.71	0.07	5.44	0.35	1.35	0.00	0.02	2.51	14.10	47,700		–	–
Guinama kaolin[b]	49.00	36.50	0.50	0.00	0.10	0.00	0.60	0.15	0.00	0.00	0.00	12.80			<30			

[a] Actlabs, Canada (ICP-OES, INAA).
[b] Internet link: http://www.guinama.com/media/tecnico/91694_FT%20Kaolin%20v02.pdf.

Trace elements (ppm)																			
Class 2A			Class 2B				Class 3					Other elements							
Co	V	Ni	Au	Ir	Se	Ag	Sb	Ba	Mo	Cu	Cr	Sc	Zn	Ga	Rb	Sr	Y	Zr	Nb
–	–	–						91		109	153	–	37	71	25	152	35	541	108
40	711	17						54		41	133	33	26	53	22	110	34	432	77
14	–	25						–		80	120	–	32	66	24	150	43	538	104
4	151	10	<2	<5	<3	<0.5	0.5	111	<0.5	32	134	16	22		< 20	125	23	430	
–	173	32						–		56	146	–	56	46	52	167	54	537	56
16	171	27						–		80	173	41	27	56	45	126	–	584	65
27	–	41						–		54	211	40	40	56	58	114	–	473	69
7	–	32						–		68	188	–	40	45	51	107	–	504	69
–	–	30						–		49	152	40	36	–	61	135	–	492	61
–	167	12						–		64	224	37	5	–	44	146	–	760	72
17	135	22						–		69	117	–	38	31	81	373	–	379	73
–	–	36						–		63	128	37	47	–	40	249	–	590	60
–	–	23						–		110	147	–	74	37	33	221	–	563	64
–	–	–						–		45	123	–	44	37	28	105	90	677	90
–	–	–						–		50	122	36	26	42	28	222	93	700	95
–	–	–						–		–	123	–	16	–	26	172	74	542	63
–	–	11						–		69	94	–	47	–	34	187	31	433	33
–	142	39						–		90	196	–	36	35	–	210	68	542	70
–	298	39						–		54	359	65	39	47	–	332	–	201	57
5	272	19						–		49	367	47	35	58	–	35	–	209	44
4	191	11	<2	<5	<3	<0.5	<0.2	7	<0.5	6	435	22	58		< 20	17	4	103	
–	260	31						–		53	460	–	29	64	6	106	–	220	45
–	203	94						–		47	329	49	29	60	–	252	–	175	47
2	323	55						–		49	493	67	28	42	–	437	–	215	51
–	220	22						–		34	458	38	23	42	–	465	–	193	48
17	–	43						–		65	234	38	27	41	–	740	–	823	111
–	–	25						–		75	173	46	–	47	–	181	–	779	108
–	–	29						–		98	178	–	28	48	–	398	–	970	116
–	338	224						678		47	968	–	1209	–	107	226	278	818	52
16	145	55						–		66	300	47	–	56	–	237	–	209	43
–	274	232						–		75	–	–	1424	2	26	353	3	77	–
–	–	–						45		62	251	48	47	–	–	146	39	763	77
–	–	46						45		59	221	–	46	34	6	79	51	1162	71
11	158	54						89		48	239	–	84	47	9	75	69	982	104
41	–	81						35		63	301	39	109	45	5	98	78	1048	95
–	–	38						69		46	264	41	18	48	9	129	83	1052	93
–	158	76						–		56	368	51	79	81	2	160	135	1126	161
14	126	48	8	<5	<3	0.8	0.6	73	<0.5	8	292	27	88		< 20	125	97	640	
–	189	71						–		46	327	42	95	73	6	149	149	1218	164
12	125	27						111		66	209	41	8	36	5	132	56	949	76
3	–	44						73		63	228	–	60	60	1	169	86	918	119
1	180	51						62		63	212	–	2	36	17	165	69	1120	109
28	146	52						33		47	205	–	33	44	10	72	50	937	86
6	134	85						–		66	271	–	43	59	9	88	64	906	142
9	122	58	<2	<5	3	0.7	0.4	41	<0.5	14	209	22	65		< 20	68	44	550	
17	–	77						–		66	257	–	65	73	–	136	99	864	137
–	–	28						67		35	308	–	36	35	17	162	78	1028	104
16	120	113						17		66	236	39	154	53	16	112	104	990	118
32	128	55						15		45	220	–	34	34	2	122	66	1417	101
–	158	72						63		53	169	–	93	45	5	112	61	891	96
–	–	135						52		59	258	–	311	63	12	165	71	857	104
–	–	58						–		57	279	–	60	56	10	138	82	1516	146
–	132	35						118		84	197	35	21	63	14	193	88	971	123
–	–	34						71		43	118	–	149	23	77	107	27	543	22
11	–	31						63		42	92	–	42	16	69	76	20	160	–
–	–	17						–		38	63	–	17	–	15	281	10	46	–
78	205	105						–		45	319	36	53	36	7	38	33	354	46
–	153	59						14		44	317	–	36	28	16	61	50	604	48
–	192	74						–		105	223	–	51	77	5	157	110	1050	160
–	274	93						29		40	465	–	41	30	–	71	85	416	28
35	245	118						–		46	530	–	30	31	4	90	42	247	–
30	150	115						13		37	608	–	59	35	66	126	–	226	–
143	279	320						1070		832	304	–	69	–	50	186	27	117	32
124	362	1124						–		72	1397	–	332	24	36	55	–	91	–
–	117	–						–		57	111	–	40	24	40	43	43	312	33
49	155	65						15		142	115	60	28	30	–	128	–	118	–
18	113	70						–		44	120	–	60	22	95	366	40	347	33
0	–	–						–		–	94	–	–	–	41	50	54	633	45
18	–	36						13		40	114	–	20	22	8	16	35	399	34

3.3. Rheology

Thirty one high purity kaolin powdered samples (>75% kaolinite) were selected for rheological characterization, and results were compared with a pharmaceutical grade kaolinite purchased from Guinama S.L. (Valencia, Spain). Each sample was sieved to obtain particle aggregates below 125 μm. 50% W/W kaolinite dispersions were prepared with purified water using a Power Sonic 405 ultrasonic equipment for 10 min. Rheological analysis was carried out by a computerized controlled rate viscometer (Thermo Scientific HAAKE, RotoVisco 1 equipment and RheoWin software) as a triple measure of the shear rate ($\gamma' = d\gamma / dt$ in s^{-1}), shear stress (τ in Pa) and apparent viscosity (η in Pa·s) at controlled temperature (25 °C) after a rest time of 90 s in the shear rate range 10–800 s^{-1}.

3.4. Granulometry and textural analysis

A granulometric analysis of these selected samples was carried out by using a laser diffraction particle size analyzer in a range between 0.02 and 1500 μm. The equipment (Mastersizer 2000LF, Malvern Instruments) consists of a wet sample dispersion unit (Hydromu, Malvern) and a microvolume wet sampler (Hydro 200Up, Malvern). Prior to the analysis, a few milligrams of powder sample were dispersed in purified water and sonified for 30 s.

Micromorphology of kaolinite particles was investigated by field emission scanning electron microscopy (FESEM) by using a Zeiss SUPRA40VP equipment with microanalysis EDX Aztec, working at 5 to 10 kV.

3.5. pH

The pH of these selected samples has been measured in 20% W/V water dispersions, by using a Crison ph-meter Basic 20+, calibrated by pH standard solutions pH 7, 4 and 9. Three replicates were carried out for each measurement and results averaged (±0.1 standard deviation).

3.6. Specific studies

On the basis of their purity, color and rheological behavior, four samples (two Carboniferous, K3 and N2, and two Cretaceous ones, D6 and F2) were selected for additional studies. A sedimentation process was carried out trying to eliminate from them some impurities such as quartz or anatase.

3.6.1. Chemical analysis

Complementary chemical analysis (major elements and Ag, As, Au, Ba, Cd, Co, Cr, Cu, Ir, Mo, Ni, Pb, Rb, Sb, Sc, Se, Sr, V, Y and Zn measured by Inductively Coupled Plasma Optical Emission Spectrometry and Instrumental Neutron Activation Analysis, Actlabs Ltd., Canada; accuracy was in 1–3% range, depending on the element amount) were performed on these samples (K3*, N2*, D6*, F2*).

3.6.2. Microcomposition

The chemical composition of the kaolinite particles on these selected samples was quantitatively determined using a FEI Titan G2 60-300 electron microscope operated at 300 kV and equipped with a SUPER-X silicon-drift window-less EDX detector. The spectra were collected in STEM (Scaning Transmission Electron Microscopy) mode using a HAADF (High Angle Annular Dark Field) detector. EDX data were corrected by the thin-film method. The K-factors were determined using mineral standards. Atomic concentration ratios were converted into formulae according to stoichiometry (number of O atoms in theoretical formulae). TEM microanalyses were performed on 10 individual kaolinite microparticles for each sample.

3.6.3. Pharmacopoeial tests

Additional specific tests described in "Heavy Kaolin" monograph of European Pharmacopoeia (EP 8.0, 2014) were also done in these selected samples, including buffer capacity (phenolphthalein method), organic content (by calcination), adsorption power (methylene blue method) and swelling power (flow method).

Identification and compositional assays described in EP 8.0 (chlorides, sulfates, calcium and extractable heavy metals) were redundant after the complete mineralogical and chemical characterization of the samples.

Microbiological test were carried out including Total Aerobic Microbial Count (TAMC) and Total Combined Yeast and Mould Count (TYMC).

4. Results

4.1. Mineralogy and chemistry

The mineralogy and chemical analyses of the studied samples (Tables 1 and 2), as well as some representative diffractograms of samples (Fig. 1), showed that: A) in the Carboniferous Wadi Khaboba section, samples were mainly made up of kaolinite (normally >50%), quartz (very variable, from 1% to 48%) and mica (up to 11% but normally below 5%). The highest contents in kaolinite (65–89%) were found in the lower 7 m of the section, where one hematite-rich sample was detected; anatase was present in all samples but in small quantities (<2%); alunite (up to 7%), feldspars, hematite and halite were also present as minor phases in some samples; B) Gabal Hazbar section exhibited lower kaolinite contents (only sample 5H was very rich in this mineral) and higher quartz contents; mica (up to 8%) and anatase (up to 2%) were always present; alunite, hematite and feldspars were only sporadically found, but in lesser quantities; C) meanwhile, almost of kaolin samples collected from Wadi Abu Natash section represented the highest kaolinite contents amongst all the Carboniferous sections. The majority of these purest samples contained 92% to 96% kaolinite without or very low quantities of quartz, mica and hematite contents; anatase and halite were also associated, in average contents 3% and 2%, respectively; some other samples were composed of 69% to 87% kaolinite and <25% quartz contents, whereas hematite and magnetite contents did not exceed 2%; two samples showed some alunite (<5%, N6 and N12), and one sample exhibited very low kaolinite content (10 N); D) samples from the Dehessa Cretaceous section were made up almost exclusively of kaolinite and quartz, with lesser amounts (<3%) of anatase and hematite; the majority of these samples contained 71% to 84% kaolinite, and only three samples, located in the upper part of the section, exhibited kaolinite contents over 90%; E) the mineralogy of Farsh El Ghozlan section was rather similar to that found in Dehessa section: kaolinite was the main mineral phase, and quartz was the main accessory mineral; hematite and anatase appeared as traces; most of these samples exhibited kaolinite contents in the range 78 to 89%, and two samples, located in the lower 5 m, exceeded 90%; other identified minor mineral phases, but only detected in the three upper samples, included mica, feldspar, halite, gypsum and smectite; remarkably, noticeable amount of carbonates were also found in the top of the section, which included dolomite (25%), calcite (77%), and ankerite (5%); F) when compared with the other two Lower Cretaceous sections, the majority of samples collected from Wadi Budra section showed lower kaolinite contents (22% to 65%), except sample B3, which contained 86% kaolinite; other important mineral phases were quartz, hematite and halite, with contents reaching up to 37%, 19% and 10%, respectively, anatase was present, but in small quantities (<2%); it is worth mention that noticeable amount of smectites (up to 40%) were recorded in the middle part of this section, as well as some samples contained significant mica, feldspar, heulandite and/or gypsum contents.

The major elements content correlate with the mineralogical characteristics observed. Globally, the chemical analysis showed high silica

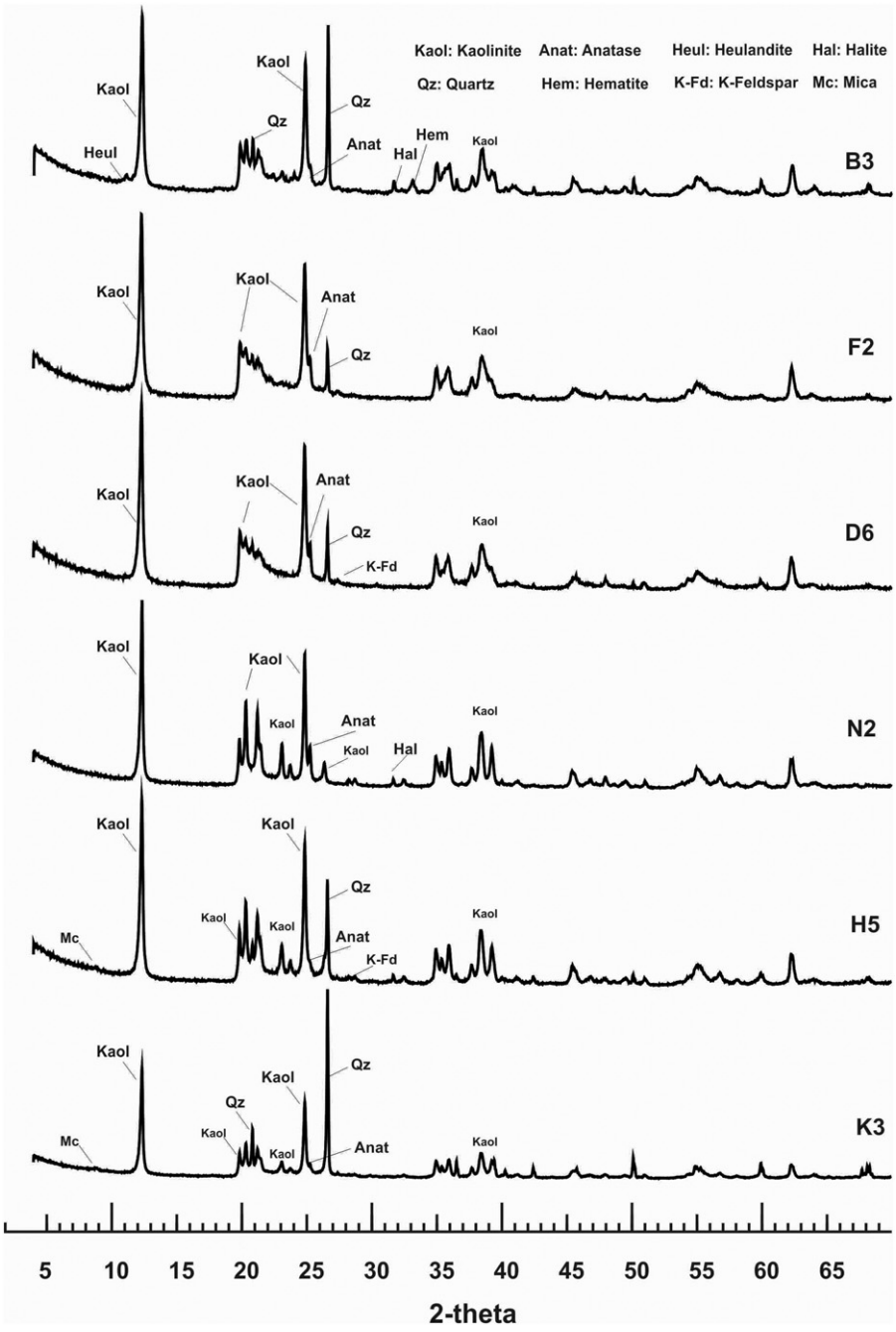

Fig. 1. XRD diffractograms of representative bulk samples from the studied kaolin deposits.

and alumina contents, iron content in most samples is low and linked to the presence of hematite (and few magnetite) and titanium content is due to anatase. With regards to alkaline oxides, sodium is due to halite and most of the potassium to mica (only a small number of samples contain felspars or smectite). Minor amounts of CaO and MgO content reflect the absence of carbonate minerals in almost all of the samples.

Purification of the selected samples induced minor changes in the major element composition of K3*, N2*, D6* and F2*, and only a decrease in TiO_2 (anatase) was observed. On the contrary, a general decrease of the trace element contents is observed (Table 2), but this could be due to the different analytical techniques involved.

The structural formula of the kaolinite, measured by TEM on the purified samples, exhibit only small differences between Cretaceous and Carboniferous kaolinites: some Al (0.01 atoms by unit cell) in the octahedral sheet of the Cretaceous samples, and some Mg (around 0.04 atoms by unit cell) in the octahedral sheet of the Carboniferous samples; both types contain around 0.02 Fe atoms by unit cell.

Trace element composition of the samples was also measured and the results used to determine possible safety concerns. By considering the use of mineral substances in pharmaceutics, variability of elemental impurities must be included in the datasheet as well as the analytical method used, given that some variability could be derived from the technique (ICH-Q3D, 2014). With this premise, Table 2 also includes the analytical data obtained by using two different techniques for selected samples. The presence of elevate amounts of metallic impurities of Class 1 and 2 in some samples, even if they are very rich in kaolinite,

could compromise their possibilities. By using complementary analytical methodologies, these elements were determined with higher precision in the 4 selected samples.

4.2. Kaolinite crystallinity

All Carboniferous kaolinites showed Hinckley Index higher than 1 (Table 1), with a maximum value of 1.50; on the contrary, Cretaceous kaolinites normally exhibited values below 0.8, with the exception of some samples of Farsh El Ghozlan and Wadi Budra sections, which reached up to 1.3.

4.3. Color

The only general clear correlation found between the color parameters (Table 1) versus mineralogy and/or chemistry was with the iron content (Fig. 2, R = −0.86 for L* and Fe_2O_3; R = 0.85 for a* and Fe_2O_3) and, consequently, with the hematite and/or magnetite content.

In Carboniferous samples, L* values were normally >75, a* values were normally below 4, and b* were normally below 6; Whiteness Index (WI)-Stensby was more variable, but in general it was comprised in the range 55–65; with regards to WI-CIE, only samples having some noticeable hematite and/or magnetite contents showed clearly different values (as in such cases of samples K2, K12, N5 and N10).

In the Cretaceous Dehessa deposit, the measured color parameters were rather homogeneous, and no significant changes were observed for these along the stratigraphic sequence. However, in Farsh El Ghozlan and Wadi Budra deposits, the drastic variations observed in the color parameters could be related to the presence of iron oxide minerals, calcite or dolomite in different proportions that may influence the L*, a*, b* and WI parameters.

4.4. Rheological characterization

Apparent viscosity, Bingham yield stress and flow index (varied between 0.22 and 0.55) of the samples allowed to classify them as pseudoplastic non-Newtonian systems. There was a very strong positive correlation between yield stress and apparent viscosity (Fig. 3).

The yield stress and the apparent viscosity showed a widest range of variations in Carboniferous samples when compared to Cretaceous ones. So, the obtained yield stress values for the former samples varied from 16.77 to 188.5 Pa, while for the later, the range was narrowest (8.67 to 64.25 Pa). Apparent viscosities showed the same trend (0.09 to 0.91 Pa·s for Carboniferous samples, and 0.04 to 0.32 Pa·s for Cretaceous ones). For Guinama kaolin, the obtained values were 134.2 Pa and 0.69 Pa·s, respectively.

As discussed earlier, samples exhibit a pseudoplastic flow character (Fig. 4A). All Cretaceous samples had shear stress values under 100 Pa, the lowest ones found in Farsh El Ghozlan samples, while the highest belonged to Wadi Budra deposit. On the contrary, several Carboniferous samples (particularly, samples N2 and K3) showed higher values (up to 250 Pa at 800 s^{-1}). The thixotropy of the studied samples (area of the hysteresis loop of the flow curves) was normally very small, but some samples (particularly N2, and to a lesser extend N4, K1, K2, K3, F2 and F3) exhibited a higher thixotropy. The pseudoplastic behavior of all kaolin dispersions was considered as shear thinning, indicated by a decrease in the apparent viscosity with the increase of the shear rate (Fig. 4B).

4.5. Granulometry and textural analysis

All the studied samples showed similar particle size distributions, with values of D10 around 0.4 μm, D50 around 1.2 μm and D90 in the interval 5–7 μm (Table 3). They are made up of aggregates (up to 40 μm in size) of smallest anhedral to subhedral kaolinite platelets, with face-face contacts and few pseudo-hexagonal edges. Carboniferous samples show well sorting, open packing and very small particle dimensions (<2 μm on average, Fig. 5A and C) that rarely form booklets-like aggregates (Fig. 5C). Cretaceous samples exhibited, on the contrary, a heterogeneous size distribution, closed packing texture and individual kaolinite platelets can reach up to 5 μm in size (Fig. 5D, E and F).

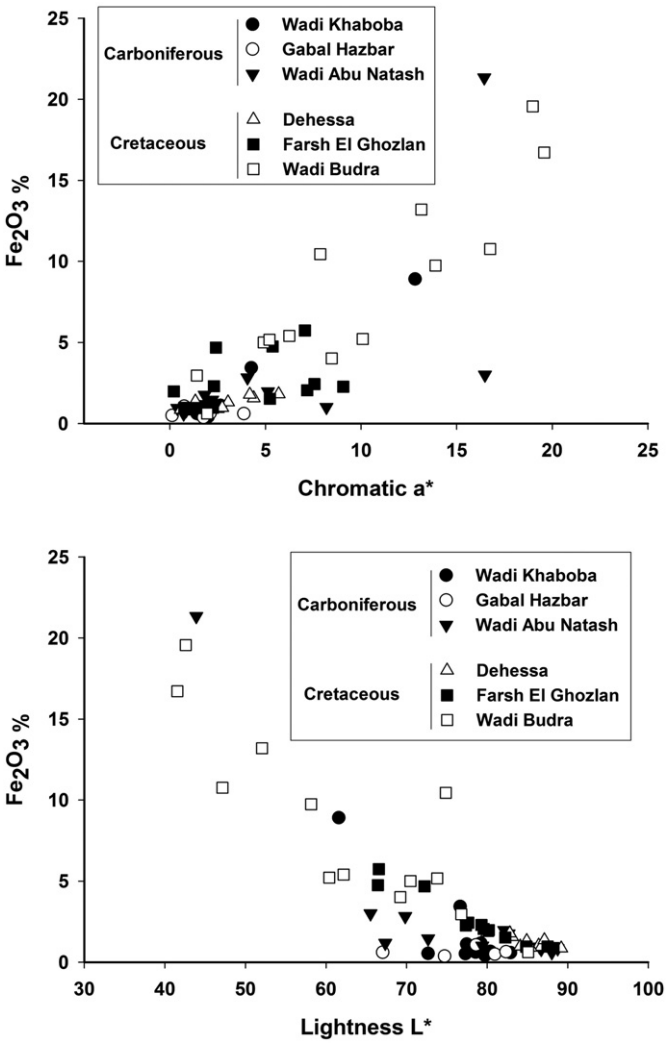

Fig. 2. Effects of Fe_2O_3 on the Lightness L* and chromatic a* parameters of selected high purity kaolin samples.

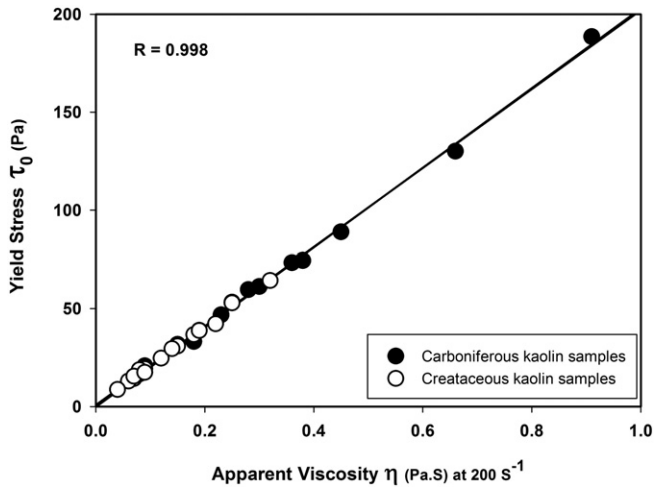

Fig. 3. Correlation between yield stress and apparent viscosity of the kaolin dispersions.

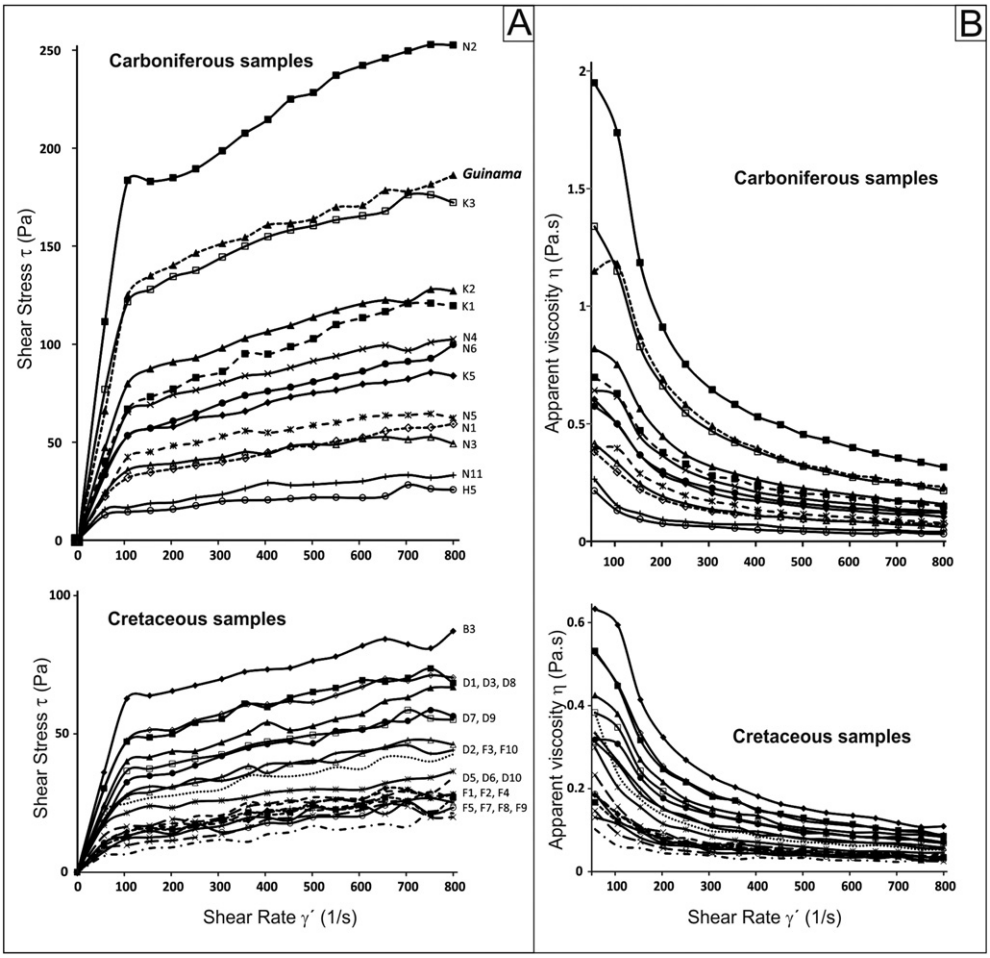

Fig. 4. Flow curves showing (A) shear rate vs. shear stress; and (B) shear rate vs. viscosity in the Egyptian kaolin dispersions.

4.6. pH

The pH values of Carboniferous kaolinite dispersions laid between 4.75 and 6.87, within the weakly acidic range, except for sample N11, which exhibited a pH value of 9.34 (weakly alkaline). On the contrary, the pH values of the Cretaceous dispersions varied from weakly acidic (5.98) to weakly alkaline (8.36, Table 3). The variable positive charges on the edge surface of kaolinite crystals determine the interaction between the particles. Accordingly, samples with higher pH values showed lower apparent viscosities.

4.7. Pharmacopoeial tests

Samples N2, F2, D6 and K3 complied with the specific tests for organic impurities (after heating in a calcination tube, the residue was not more colored that the original substance) as well as those for adsorption power (after reaction with methylene blue, the resultant solution was not more intensely colored that the 0.03 g/L reagent solution) and swelling power (the 2 g/2 mL water suspensions did not flow).

Microbiological studies revealed that the samples contained <1000 CFU/g of total viable aerobics and <10 CFU/g of contaminating fungi (yeast and mold). Consequently, they complied with both the TAMC and TYMC limits (10^3 and 10^2 CFU/g, respectively).

5. Discussion

Flow behavior of kaolin dispersions strongly depends on the purity, nature and quantity of the existing impurities, kaolinite crystallinity, pH, particle morphology, aggregation, and size distribution (Langston et al., 1964; Beazley, 1972; Prasad et al., 1991; Yuan, 1997; Nuntiya and Prasanphan, 2006; Gregorová et al., 2009; Nasser and James, 2009, Blachier et al., 2014; Ndlovu et al., 2015). Homogeneous and small platy particles exhibit higher viscosity than coarser, spherical and heterogeneous particles. All these characteristics greatly determine the suitability of clay minerals in the design and development of pharmaceutical semisolid systems (Viseras et al., 2007). The absence of clear differences in individual and/or aggregates sizes of kaolinite particles makes difficult to propose a direct relationship with the observed rheological differences. Rheological behavior comes from the aggregation of kaolinite particles and depends on several factors, including pH and ionic strength (Lagaly, 2006). This complexity usually became even more complicated as with the presence of single mineral particles, aggregates and assembly of aggregates (Bergaya and Lagaly, 2006).

In the studied Egyptian kaolins, the higher viscosities have been found in samples belonging to the Carboniferous Wadi Khaboba and Wadi Natash deposits, where occasionally the shear stress can reach up to 188.5 Pa (sample N2), even higher than the value obtained for Guinama kaolin (134.3 Pa). These Carboniferous kaolins are characterized by very small and well sorted particles with an open packing. Almost half of the studied samples contain >75% of kaolinite and the rest of the samples are very rich in this clay mineral. Nevertheless, quartz is systematically present in all samples (except in the samples from the lowest 5 m of the Wadi Abu Natash section). Other detected impurities are hematite and anatase, normally present in low quantities (<3%). According to the pharmacopeial specifications of kaolin (Rowe et al., 2009), these impurities are not considered to be dangerous to human health, as no mention to a specific limit is included in USP 39

Table 3
Apparent viscosity (n = 3; at shear rate 200 S^{-1}), yield stress, flow index and pH obtained in dispersions made with the kaolinite-richer samples (>75%), as well as for Guinama kaolinite. Granulometric data (D10, D50 and D90) are also included.

	S. no.	Apparent viscosity (Pa·S)	Yield stress (Pa)	Flow index (Pa·S)	Hinckley Index	pH (20% W/V)	Granulometry (μm)		
							D_{10}	D_{50}	D_{90}
Carboniferous	K1	0.38 ± 0.02	74.42	0.35	1.28	5.3	0.40	1.04	4.21
	K2	0.45 ± 0.03	88.88	0.28	1.30	5.4	0.37	1.14	4.66
	K3	0.66 ± 0.02	130.05	0.23	1.33	4.9	0.44	1.36	4.76
	K5	0.28 ± 0.02	59.66	0.28	1.38	6.6	0.45	1.26	4.96
	H5	0.08 ± 0.03	16.77	0.31	1.33	6.9	0.39	0.93	3.10
	N1	0.18 ± 0.04	33.15	0.35	1.46	6.0	0.38	1.33	10.03
	N2	0.91 ± 0.06	188.5	0.24	1.50	6.3	0.40	1.39	9.16
	N3	0.19 ± 0.03	38.85	0.23	1.42	5.9	0.39	1.21	6.35
	N4	0.36 ± 0.02	73.33	0.28	1.48	4.8	0.34	1.25	5.67
	N5	0.23 ± 0.10	46.78	0.27	1.46	5.1	0.33	1.19	4.05
	N6	0.30 ± 0.02	61.23	0.34	1.39	4.9	0.37	1.30	5.62
	N11	0.09 ± 0.01	20.74	0.34	1.50	9.3	0.38	1.35	6.95
Cretaceous	D1	0.25 ± 0.01	53.2	0.24	0.54	6.0	0.38	1.30	6.58
	D2	0.15 ± 0.04	31.69	0.28	0.55	6.7	0.38	1.16	5.01
	D3	0.22 ± 0.04	42.22	0.31	0.50	6.1	0.36	1.18	6.69
	D5	0.09 ± 0.05	19.24	0.3	0.82	7.3	0.38	1.31	7.83
	D6	0.12 ± 0.05	24.64	0.25	0.27	7.4	0.40	1.08	4.57
	D7	0.18 ± 0.02	36.67	0.34	0.47	6.8	0.38	1.09	4.97
	D8	0.08 ± 0.02	16.54	0.34	0.80	7.0	0.38	1.26	6.44
	D9	0.19 ± 0.02	38.78	0.28	0.63	6.6	0.38	1.16	4.54
	D10	0.07 ± 0.01	14.27	0.44	0.82	7.6	0.37	1.26	7.38
	F1	0.08 ± 0.01	16.93	0.41	0.53	7.2	0.38	1.10	5.21
	F2	0.25 ± 0.03	52.85	0.26	0.45	7.0	0.38	1.02	4.58
	F3	0.15 ± 0.01	30.87	0.32	0.59	7.6	0.38	1.03	4.80
	F4	0.06 ± 0.04	12.95	0.43	0.68	8.4	0.38	1.27	7.49
	F5	0.08 ± 0.02	18.71	0.39	0.52	6.3	0.38	1.21	6.05
	F7	0.07 ± 0.03	15.42	0.32	0.66	7.0	0.38	1.29	6.73
	F8	0.09 ± 0.02	17.44	0.34	0.72	7.8	0.45	1.47	6.54
	F9	0.04 ± 0.01	8.67	0.55	0.61	7.4	0.38	1.08	5.93
	F10	0.14 ± 0.02	29.48	0.27	0.95	7.4	0.38	1.12	4.89
	B3	0.32 ± 0.02	64.25	0.22	0.99	6.7	0.38	1.09	4.05
	Guinama kaolin	0.69 ± 0.02	134.2	0.25	1.32	8.4	0.40	1.55	6.90

or EP 8.0. Good correlation between viscosity and kaolinite content was observed in the Carboniferous samples but not in the Cretaceous kaolinite-rich samples (Fig. 6). No significant differences in the rheological behaviors of samples K3*, N2*, D6* and F2* have been observed.

As regards to crystallinity, Delgado et al. (1994) found a linear correlation between kaolinite crystallinity and drug release, and Ptáček et al. (2013) and Wardhana et al. (2014) showed the increase of the kaolinite adsorptive surface activity with increasing crystallinity after kaolinite thermal structural modifications. Kaolinite crystallinity influences the mechanical, thixotropic and rheological properties of their dispersions given that the surface area, cation exchange capacity, dispersion yield stress and viscosity increase as crystallinity decreases (Murray and Lyons, 1955, 1959; Vasilev et al., 1976; Cabrera and Eddleston, 1983; LaIglesia and Aznar, 1996; Fialips et al., 2000; Ndlovu et al., 2015). Its determination may be crucial for a good sample selection, size and structural determinations (Wardhana et al., 2014). Many authors have worked with the measurement of the kaolinite crystallinity and the different problems involved in its determination (Hinckley, 1963; Plançon et al., 1988; Plançon and Zacharie, 1990; Galán et al., 1994; Aparicio and Galán, 1999; Chmielová and Weiss, 2002; Aparicio et al., 2006). There is a clear difference in crystallinity when Carboniferous and Cretaceous Egyptian kaolinite-rich samples (>75% in kaolinite content) are compared, but except for some samples (particularly N2, K3, K2 and K1), their apparent viscosities are rather similar (Fig. 7). In general there is an increase in apparent viscosity, yield stress or flow index with decreasing crystallinities if both groups of samples are separately considered.

In agreement with the observations made by Nasser and James (2009), which found changes in the rheological behavior of kaolinite dispersions with pH, a negative correlation between this parameter and the apparent viscosity exists in the Egyptian kaolins, more evident for Cretaceous samples (Fig. 8). It is worth noting that most of the purest Egyptian kaolinite samples exhibit a pH within the range of the pharmaceutical grade kaolinite (4.0–7.5 for a 20% W/V dispersion, Rowe et al., 2009).

With regard to color, pure kaolinite powder must be white to grayish-white colored, but it could exhibit some variations in color as reddish, brownish, or greenish when some transition elements (e.g. Fe, Cu, Ni or Co) are present as adsorbed cations or in the kaolinite structure, or when colored mineral or organic impurities are associated (Deer et al., 1992). In the studied samples, the color, and therefore, whiteness of kaolins is strongly influenced by their iron content (Fig. 2). Given that the studied kaolins contain iron oxides, their whiteness can only be improved by eliminating these impurities by magnetic separation and/or reduced acid leaching (Prasad et al., 1991). The obtained CIELAB colorimetric data are not only qualitative indicators and diagnostic criterions of quality and purity but also could be used as quality control parameters in future beneficiations and processing (Soriano et al., 1998; Gámiz et al., 2005, 2011).

Control of elemental impurities is one part of the overall control strategy for a drug product that assures that these do not exceed the Permitted Daily Exposure (the maximum acceptable intake of elemental impurity in pharmaceutical products per day), and they should be reflected in the risk assessment of any medicinal product including these materials in their composition (ICH-Q3D, 2014). In particular, As, Cd, Hg and Pb are the considered class 1 elements, and require evaluation during the risk assessment as they are commonly present in drug products due to their high natural abundance in the environment. They typically come from commonly used materials (*e.g.*, mined excipients). Nevertheless, current normative for kaolin to be used as excipient only include Pb limit for topical (<50 ppm) or oral use (<25 ppm) (EP 8.0, 2014). Class 2A (Co, Ni and V; high probability of occurrence) and 2B (Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl; reduced probability of occurrence) elements also requires control. Elements belonging to Class 3

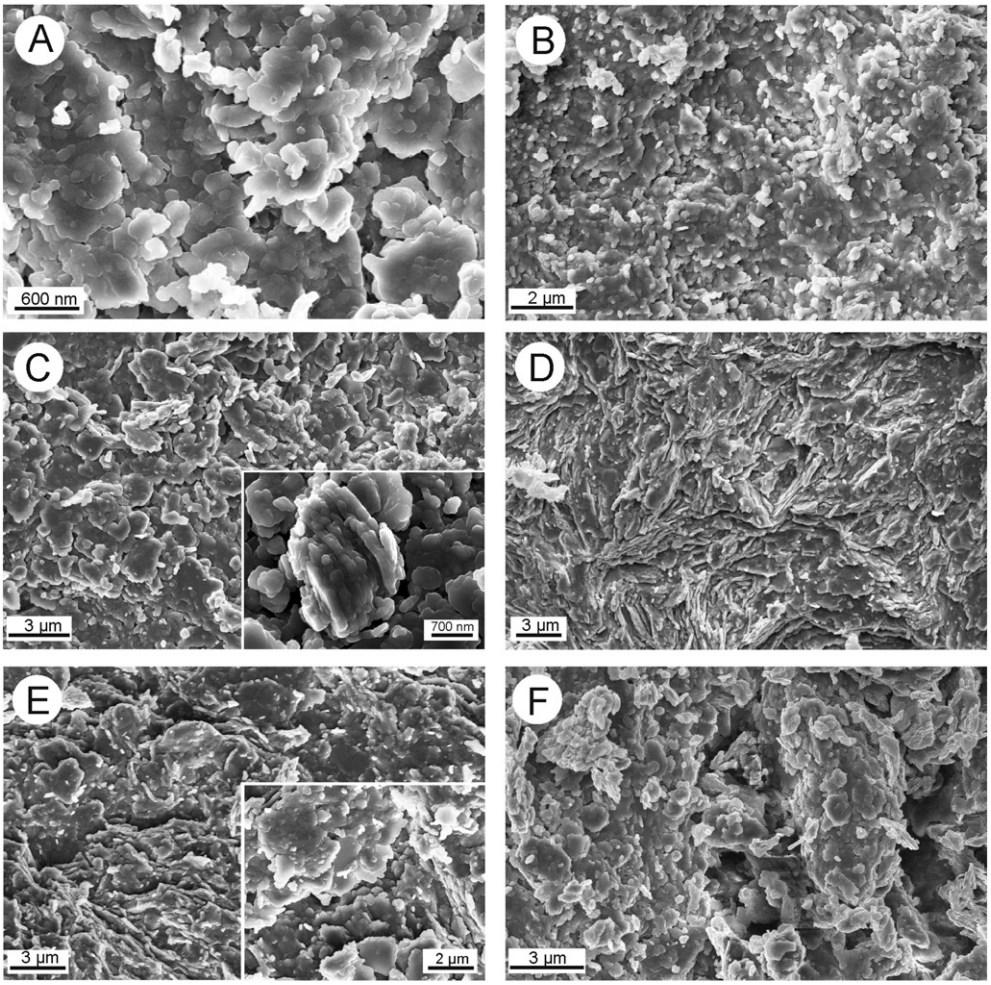

Fig. 5. Selected scanning electron microscopy (SEM) images showing the micromorphology of representative kaolinite samples (A: K3; B: N2; C: H5; D: D6; E: F2; and F: B3).

(Ba, Cr, Cu, Li, Mo, Sb, and Sn) show low oral toxicities and only require consideration in the risk assessment for inhalation and parenteral routes.

According with the EP 8.0 (2014), 3 of the selected samples complied with the topical Pb limit, whereas one of them (N2) also could be used in oral formulations. As regards of the other elemental impurities, the selected samples showed low values.

6. Conclusions

Almost half of the studied samples of the Egyptian Abu Zenima district are mainly made up of kaolinite (>75% and reach up to >90%), particularly those taken at Wadi Abu Natash, Wadi Khaboba, Gabal El Dehessa and Farsh El Ghozlan deposits. The main detected mineral impurities are quartz, mica, anatase and hematite.

The Hinckley Index of the Carboniferous kaolinites is high (1.3 to 1.5 in the richest samples), and medium to low in the Cretaceous ones (0.3 to 1).

The kaolin dispersions exhibit a rather similar pseudoplastic flow character, and some of the studied samples (particularly N2 and K3) are comparable with pharmaceutical grade kaolinite of Guinama S.L. (Valencia, Spain). The Carboniferous kaolins show higher apparent viscosity and yield stress than Lower Cretaceous ones, as results of the observed differences in crystallinity, particle size and texture.

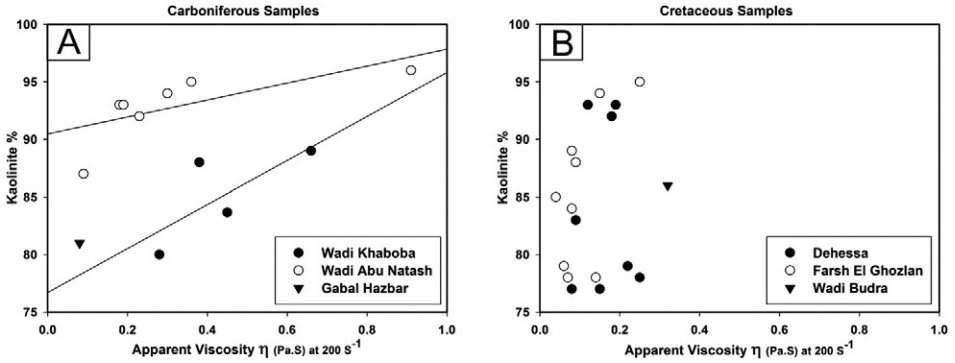

Fig. 6. (A) Correlation between kaolinite content and apparent viscosity in Carboniferous kaolin dispersions; (B) Idem for Cretaceous kaolin dispersions.

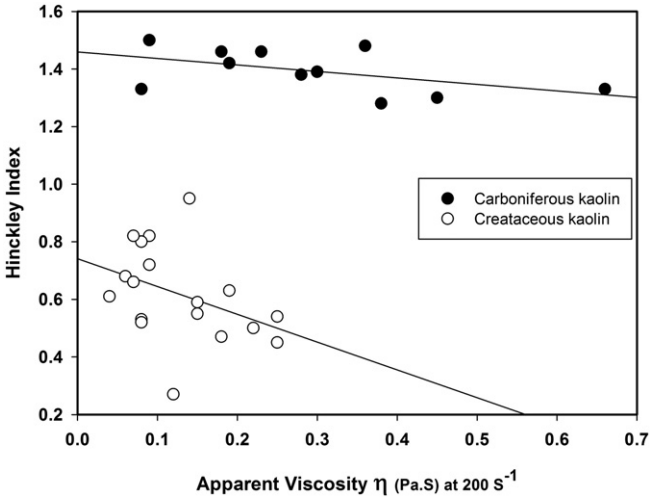

Fig. 7. Correlations between Hinckley Index and apparent viscosity of both Carboniferous and Cretaceous kaolin dispersions.

Metal impurities limit the health care use of kaolinite-rich samples. With this premise, only 4 of the initially 31 selected samples of the Egyptian kaolins located at the Abu Zenima district were finally considered. The presence of Class 1 and 2 elements in high amounts was used as selection criteria, and the content of Pb (the only required metal impurity in European Pharmacopoeia for kaolin) discriminate the 3 samples (K3, N2 and F2) that satisfy the limit for topical use (50 ppm). Sample N2 also comply with the limit for oral use (25 ppm). On the other hand, water suspensions prepared with samples N2 and K3 showed rheological behaviors similar or even better than commercial kaolin suspensions. It can be concluded that the selected kaolins would merit further experimental studies to test their advanced biopharmaceutical efficiency and activity.

Acknowledgement

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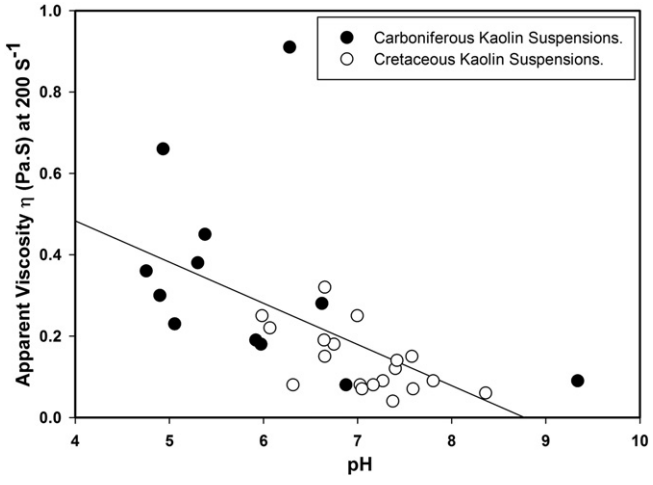

Fig. 8. Correlation between pH and apparent viscosity of both Carboniferous and Cretaceous kaolin dispersions.

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5. THERMAL PROPERTIES OF SOME EGYPTIAN KAOLIN PASTES FOR PELOTHERAPEUTIC APPLICATIONS

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Research paper

Thermal properties of some Egyptian kaolin pastes for pelotherapeutic applications: Influence of particle geometry on thermal dosage release

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ABSTRACT

The present study aims to evaluate the potentiality of 7 selected structural highly ordered kaolinite-rich samples from Egyptian Carboniferous sedimentary deposits (located at Abu Zenima district, west central Sinai peninsula) to use them in medicinal semisolid formulations as peloids. The effect of particle geometry and kaolinite crystallite size are studied to check their influence on thermal dosage performance.

The studied samples exhibit a variable mineralogy. Kaolinite is the main constituent (ranging from 81 to 94%), followed by quartz (up to 14%), lesser amounts of anatase and halite, and traces of hematite, magnetite, alunite and gypsum. The kaolinite order "Hinckley Index" varies from 1.28 to 1.50. 1:1 (w/w) kaolin mud pastes were prepared with purified water in Eppendorf tubes using a touch vibration vortex mixer for 2 min. The cooling kinetics of pastes were measured by using a differential scanning calorimetry equipment (Shimadzu DSC-50Q). Specific heats were calculated, following Cara et al. (2000). The granulometry and geometric surface area were measured by laser diffraction (Mastersizer 2000LF, Malvern Instruments) in the range 0.02 and 1500 μm.

All analyzed samples showed a clear predominance of particles under 4 μm (ranging from 82 to 94%), with median size (D_{50}) ranging from 0.93 to 1.35 μm. The heat retention time during cooling from 50 °C to 32 °C reached up to 30.82 min, oscillating around an average of 28.72 min, and the temperature corresponding to the minimal dosage time (T_{20}) was not exceed below 34.7 °C. A good correlation (R^2 = 0.875) was found between heat retention time and specific heats. There is no correlation between kaolinite content and thermal properties, but R^2 values around 0.6 are found with granulometry (finer the particles, greater the heat retention time t_{32} and the specific heat). Even if sample H5 (Gabal Hazbar deposit) is not the richest in kaolinite, it exhibits the best thermal dosage performance, in accordance with the granulometry (D_{50} = 0.93 μm), and geometric surface area (3.73 m^2/g).

1. Introduction

Thermotherapy is a recognized medicinal strategy based on the analgesic and anti-inflammatory effects that heat application produces on the human body. Clearly, the treatment route is attempted by applying exogenous local or whole changes in the heat content of body tissues for a certain time to alleviate inflammations and pains associated with rheumatic and skeletomuscular disease, or also to stimulate other therapies. In such method, the intensity of the heat that applied directly to the skin on the painful site is limited by about 44 °C with gradient of < 10 °C; that is available for heating deeper subcutaneous tissue layers from the outside. Subsequently, there are essentially three different physiological modes of temperature action: (1) beneficial increase of blood flow and control of nervous signal transduction; that could be attained by biophysical properties and biochemical processes influence local cellular activities, (2) elicit reflex responses of complexity that feedback from the central nervous system through the skeletomuscular strains by producing specific nervous signals or altering hormone levels, or (3) maintain and regulate heat balance of the body between heat production and loss; that could change various physiological activities (Kosaka et al., 2001; Brosseau et al., 2011).

Pelotherapy, or mud therapy, has received much attention in physical therapy field because clays are ubiquitous, cheap, and exhibit good heat retention capacity (Veniale et al., 2007; Gomes et al., 2015). From

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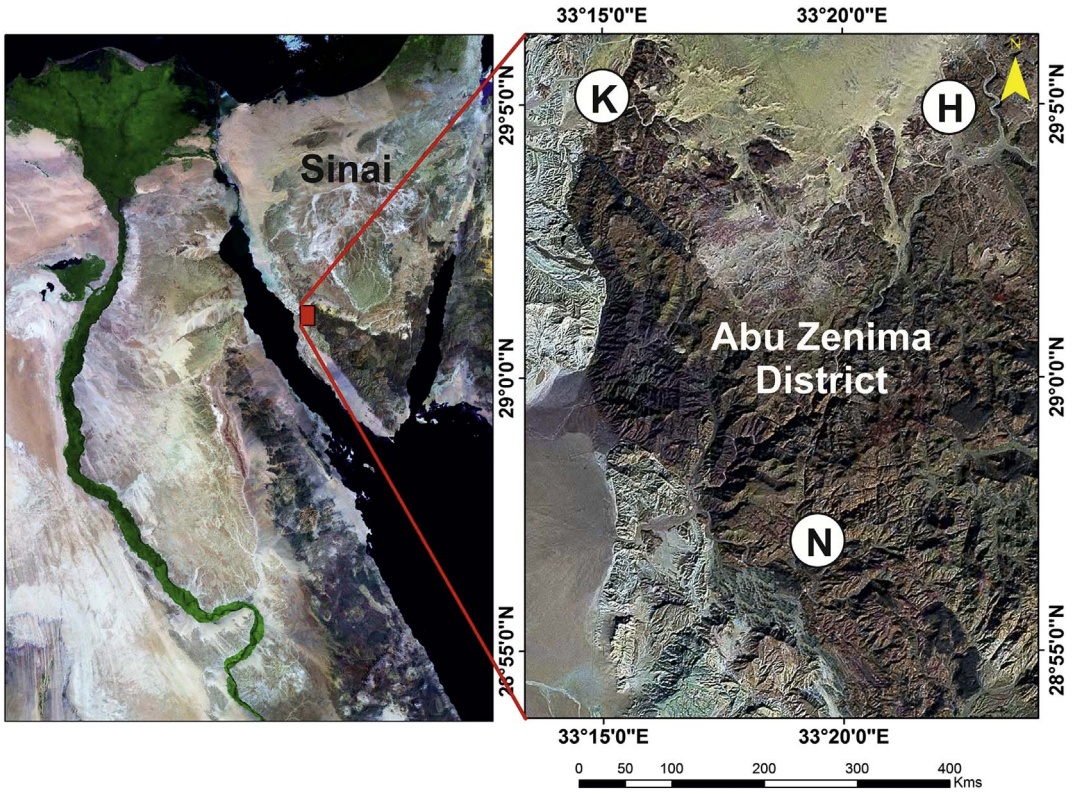

Fig. 1. Location map showing the section sites (K: Wadi Khaboba, H: Gabal Hazbar and N: wadi Abu Natash) of the collected Abu Zenima Carbonifereous kaolin samples.

pharmaceutical point of view, it has received much pioneer technological developments by Spanish and Italian scientists in the recent decades; however it was known since antique periods, hence becoming a trend of thermotherapy for competing with the other thermal methods that based on biomedical heating techniques such as microwave devices (Bird et al., 1985; Moros, 2013). In this regard, peloids or medicinal thermal mud are pharmaceutically considered as semisolid products (pastes and poultices) that can be formulated by mixing of geomaterials (mainly pure clay minerals or associated by non-clay mineral phases) of variable composition and size with saline water brought from the sea or lakes, or thermo-mineral water erupted form springs (45–50 °C) and then these mixtures are subjected to maturation (i.e., beneficial microbiological metabolic activity) process (Sánchez et al., 2002; Veniale et al., 2004; Gomes and Silva, 2007; Gomes, 2013; Gomes et al., 2013).

These medicinal products, either artificially designed mainly from clay minerals or formed in situ, can be administrated topically as facial masks or body bathing for healing pains and inflammations of skeletomuscular disorders, rheumatic (arthrosis, arthritis and fibromyalgia) and also skin diseases (acne, psoriasis and seborrhea). Hence, pelotherapy has a dual therapeutical action based on the original physical and chemical characteristics of the mineral and thermal water fractions. These agents are represented in heat treatment and/or transdermal delivery of chemical elements with other beneficial dermatological activities due to clay mineral behaviors (Grassi et al., 2003; Veniale et al., 2007; Evcik et al., 2007; Giacomino and De Michele, 2007; Tateo and Summa, 2007; Tateo et al., 2009 and 2010; Carretero et al., 2010; Fraioli et al., 2011; Rebelo et al., 2011; Beer et al., 2013; Espejo-Antúnez et al., 2013; Sánchez-Espejo et al., 2014; Suárez Muñoz et al., 2015; Awad et al., 2017b).

The quality of peloids for healing activity are mainly influenced by specific heat, heat capacity, thermal conductivity, heat diffusiveness and cooling kinetics, maturation time, chemical compositions of solid (minerals and organic matter) and fluid phases, viscosity, plasticity, adhesivity, abrasivity, solid/liquid ratio and ion exchange capacity. In the pelotherapeutic route of administration, the temperature of the paste required at the beginning of the treatment dosage is between 45 °C and 50 °C, with heat retention time in the range of 20–30 min throughout the cooling to reach 32 °C. The final temperature usually considered as 32 °C in all calculations, because the skin temperature normally reached to this degree at the equilibrium state due to the heat exchange between the skin and the sample. Therefore, the considered temperature range of 50–32 °C are used, in comparative studies, for evaluating the therapeutic performance of clay materials in hot mud-packs formulations for healing the painful chronic skeletomuscular diseases (Cara et al., 2000a,b; Legido et al., 2007; Gámiz et al., 2009; Casás et al., 2011 and 2013; Quintela et al., 2012; Fernández-González et al., 2013; Caridad et al., 2014; Khiari et al., 2014; Gomes et al., 2015; Sánchez-Espejo et al., 2015).

The water content has been attributed by Cara et al. (2000b) as a controlling factor in prolongation of heat retention time in case of using montmorillonite-formulated mud. However, the thermal behaviour of kaolin-based mud could not be significantly influenced by the formulation water content, as well as the undesirable consistency and performance are expected to the product with high water contents, because kaolinite is a non-swelling and relatively low water absorption clay mineral, if compared to montmorillonite.

In pharmacopoeia quality, the 1:1 kaolin-water system exhibits the highest clinical absorptive feature amongst other common pharmaceutical materials used in hydrophilic paste preparations (Juch et al., 1994). Technologically, the 1.0 solid/liquid ratio of the kaolin aqueous dispersions showed the optimal water content 50% in the preparations of easily molded, consistent, and desirable adhesive pastes (Ramasamy et al., 2015). Therefore, the other effects of the solid particle geometric properties of kaolin powders on the thermal behaviour translated from this hypothesized context into testing considerations.

With these premises, the present study aims to evaluate the potentiality of some highly ordered kaolinite-rich samples belong to the economic Egyptian Abu Zenima kaolin deposits, in semisolid formulations of medicinal peloids; with diagnosing the influence of granulometric characteristics (particle size distribution and geometric surface

area) as semisolid design quality control parameters, on thermal dosage release performance during pelotherapeutic administration.

2. Materials and methods

2.1. Materials and preparations of therapeutic mud

Seven representative Carboniferous sedimentary kaolin samples (collected from Abu Zenima, west central Sinai Peninsula, Egypt) of previously identified and quantified contents (Awad et al., 2017a) with highly ordered kaolinite ("Hinckley index", HI > 1) were selected for this study (Fig. 1). These samples (which coded by their localities names as Wadi Khaboba: K1, Gabal Hazbar: H5 and Wadi Abu Natash: N1, N3, N5, N6 and N11) were dried, pulverized, screened to the size below 125 μm and stocked up dry at 40 °C during this work. 1:1 (w/w) kaolin mud paste samples were prepared with purified water using vortex mixer then kept up in insulated conditions while pending to perform thermal characterization.

2.2. Thermal analysis

Thermal properties of the studied paste samples were characterized by means of cooling kinetics using differential scanning calorimetry (DSC) technique. The equipment (SHIMADZU mod. of heat flow type DSC-50Q) is calibrated and working according to ASTM and DIN standards. The system is highly sensitive with fast response and optimum signal-to-noise ratio. The sensor is capable to detect very small heat flow changes up to 10 μW and the precision of the microbalance is 0.1 μg.

Each sample was heated by 5 °C/min in the surrounding atmospheric conditions up to 60 °C then placed into a polyethylene terephthalate cylindrical cell conditioned at the same temperature, afterwards submerged in a thermostatic bath at 25 °C that equals to the room temperature and in equilibrium state with the ambient. During the cooling, temperatures and times were recorded within the interval 50 °C to 25 °C by a thermometric probe existing in the cell center. Triplicate runs of the experiments were performed and standard deviations of temperature decreasing were calculated.

Following to the method of Cara et al. (2000a,b), the obtained experimental DSC data were fitted according to the solution of Newton's differential equation of cooling described as:

$$T_t - T_{min} = (T_{max} - T_{min})e^{-k \cdot t} \quad (1)$$

where, T_t is the sample temperature at time t, T_{min} is the room temperature (25 °C), T_{max} is the initial temperature (50 °C), t is the time (in minutes) and k is a constant of the material and apparatus. For the current experiment with these minimum and maximum temperature values, the final equation can be written as:

$$\ln = (T_t - 25) = \ln(25) - k \cdot t \quad (2)$$

The constant k which governs the rate of cooling can be given by the formula:

$$k = \frac{P}{C} = \frac{P}{m \cdot C_p} \quad (3)$$

where P is the instrumental constant of the apparatus that obtained by fitting of cooling data obtained with a reference water dispersion sample of titanium dioxide (Cara et al., 2000b), C is the heat capacity of the heated sample containing m mass and exhibits specific heat C_p.

Thermal parameters of the studied therapeutic kaolin paste samples under these experimental conditions were determined by the Eqs. (2) and (3). Theoretical specific heat (*Theor.* C_p) values of the studied pastes were calculated by the formula $Cp = \sum_i w_i C_{pi}$, where (i) is the number of solid and water constitutes in the paste, (w_i) is the fractional quantity of each constituent, and (C_{pi}) is the corresponding published specific heat value (Bohmhammel and Naumann, 1987; Robie and Hemingway, 1991; Drebushchak et al., 2000; Waples and Waples, 2004).

2.3. Granulometry and geometric surface area

Granulometric analysis and geometric surface area determination of the studied samples were performed by using a laser diffraction particle size technique in the range between 0.02 and 1500 μm. The equipment (Mastersizer 2000LF, Malvern Instruments) composed of a wet sample dispersion unit (Hydro MU, Malvern) and a microvolume wet sampler (Hydro 200Up, Malvern). Prior to the measurement, a few milligrams of the powder sample (< 125 μm) were fed into the dispersion unit for stirring in purified water with sonification for 30 s.

In addition to determination of the median size (D_{50}) values instrumentally, the geometric properties of the grading curves, or grading characteristics, were determined from the particle size values D_{10}, D_{30} and D_{60} corresponding to the percentiles 10, 30 and 60% and the grading factors including the uniformity coefficient [$C_u = D_{60}/D_{10}$] and the curvature coefficient [$C_c = D_{30}^2/(D_{60}D_{10})$] were calculated.

2.4. Kaolinite crystallite size

According to Pardo et al. (2009), microstructural analysis of the X-Ray diffraction (001) basal plane reflection profiles have been used to estimate the average apparent crystallite size of kaolinite, because of their relatively high intensity without overlapped neighboring peaks. For the studied kaolinite samples, the XRD 001 reflections profiles were determined by scanning in the ranges from 11 to 13.5°2θ in random oriented powder samples using a PANalytical X'Pert Pro diffractometer (CuKα radiation, 45 kV, 40 mA) equipped with an X'Celerator solid-state linear detector, using a step increment of 0.008° 2θ and a counting time of 10 s/step.

The XPOWDER® computer program (Martín-Ramos, 2004) was used for fitting kaolinite experimental profiles of the 001 reflections and calculated the average crystallite size (D_{001}) by means of the Warren modification of the Scherrer equation: $D_{khl} = K\lambda/(\beta\cos\theta)$, that based on peak broadening analysis (Klug and Alexander, 1975). Where K is the crystallite-shape factor (0.94 for 00 l reflections), λ is the X-ray wavelength, β is the X-ray diffraction broadening (i.e., Bragg peak full width at half-maximum: FWHM, in radians), and θ is the Bragg angle (Rodriguez-Navarro et al., 2005).

2.5. Kaolin bulk and tapped density

The bulk density (d_0) was calculated in (g/ml) using the formula m/V_0, following the method (A) in the document number (QAS/11-450, 2012) of the international pharmacopoeia, by measuring the bulk volume (V_0) of approximately 100 g mass (m) of powder sample (weighted with 0.1% accuracy and passed through a sieve of aperture 1 mm to break up agglomerates that may formed during storage) into a dry graduated cylinder 100 ml (readable to 1 ml) and leveled without compacting.

The tapped density (d_c) was calculated by the formula m/V_c, where V_c is the compaction volume obtained beyond mechanical tapping of the bulk volume (V_0); achieved by raising the cylinder and allowing it from a height of 1.5 cm to drop for c = 1250 taps. Triplicate measurements were carried out for both density types for calculating median and standard deviation.

3. Results

3.1. Mineralogical composition, chemical variability and solid density

The samples were essentially composed of highly ordered kaolinite (HI > 1 and up to 1.5) in amounts ranged between 81 and 94% with

Table 1
Mineral contents, kaolinite order ("Hinckley index" HI values), index of compositional variability (ICV) and cooling kinetics parameters of the studied paste samples.

Sample code	Kaolinite %	HI	Quartz %	Total other minerals %	ICV	Exp. C_p (J/K·g)	Theor. C_p (J/K·g)	t_{32} (min)	T_{20}°C	Bulk density g/ml	Tapped density g/ml
K1	88	1.28	7	5	0.09	3.17	2.57	29.22	35.42	0.44	0.76
H5	81	1.33	14	5	0.11	3.57	2.56	30.82	35.87	0.55	1.01
N1	93	1.46	–	7	0.17	2.98	2.57	26.97	34.83	0.67	1.03
N3	93	1.42	–	7	0.14	3.30	2.57	28.93	35.46	0.54	0.99
N5	92	1.46	–	8	0.20	3.22	2.57	29.42	35.53	0.48	0.89
N6	94	1.39	–	6	0.13	2.94	2.57	26.82	34.77	0.45	0.84
N11	89	1.50	–	11	0.21	3.14	2.57	28.88	35.43	0.77	1.23
Min.	81	1.28	7	5	0.09	2.94	2.56	26.82	34.77	0.44	0.76
Max.	94	1.50	14	13	0.21	3.57	2.57	30.82	35.87	0.77	1.23
Aver.	89.71	1.41	10.50	7.28	0.16	3.19	2.57	28.72	35.33	0.56	0.96

an average of 89.71% and free from quartz but with noticeable amount in the sample H5. Lesser amounts of anatase and halite, and traces of hematite, magnetite, alunite and gypsum of total contents normally do not exceed 8% except the sample N11 contains 13%.

Index of compositional variability (ICV) values were calculated by the formula: $Fe_2O_3 + K_2O + Na_2O + CaO + MgO + MnO + TiO_2/Al_2O_3$ that adopted by Cox et al. (1995) to measure the abundance of alumina relative to the other major oxide constitutes in mudrocks. The studied samples exhibited insignificant variations in chemical compositions as indicated by the very low level and close ICV values ranged from 0.09 to 0.21 with an average of 0.16 (Table 1).

The studied kaolin samples exhibited significant changes in the volumes with tapping (1250 taps), leading to increase the minimum density sample from bulk density $d_0 = 0.44$ g/ml to tapped density $d_c = 0.76$ g/ml and the maximum density sample from $d_0 = 0.77$ g/ml to $d_c = 1.23$ g/ml, with an average bulk density of 0.56 g/ml and average tapped density of 0.96 g/ml (Table 1).

3.2. Cooling kinetics and specific heats of kaolin pastes

The cooling kinetics parameters of the studied paste samples are displayed in Table 1, including the experimental (Exp. C_p) and theoretical (Theor. C_p) specific heat values, the heat retention time (per minutes) taken to reach 32 °C (t_{32}), and the terminal temperature values corresponding to the minimal typical time (20 min) of mud-packs administration (T_{20}°C).

The heat retention time during cooling from 50 °C to 32 °C reached up to 30.82 min, oscillating around an average of 28.72 min. The temperature corresponding to the minimal dosage time (T_{20}) was not exceeding below 34.7 °C. Most if not all the samples yielded the same theoretical specific heat value of 2.5 J/K·g, while the experimental C_p values ranged from 2.94 to 3.57 J/K·g with an average of 3.19 J/K·g. The experimental specific heats exhibited obvious higher values than their theoretical counterparts.

3.3. Particle size, crystallite size, surface area and grading characteristics

Table 2 and Fig. 2 showing the particle size distribution, grading characteristics, geometric surface area and kaolinite average crystallite sizes of the analyzed samples. All the measured samples displayed a clear predominance of particles under 4 μm ranging from 82.47 to 94.05% with an average of 87.77%, and median size (D_{50}) ranging from 0.93 to 1.35 μm with an average of 1.19 μm. The sizes corresponding to 60% and 90% of each sample do not exceed 1.56 and 10 μm, with averages of 1.35 and 5.75 μm, respectively. The calculated uniformity C_u and curvature C_c coefficients ranged from 1.72 to 2.15 and 0.88 to 0.95 with averages of 1.97 and 0.92, respectively.

The laser measured geometric surface area of the studied samples are normally > 1 m^2/g and reached up to 3.73 m^2/g. The present kaolinite exhibits average crystallite sizes, measured across the basal plane (001), ranged between 45 and 63 nm with average of 55 nm. The measured 001 peaks exhibits very close if not all the same position and d-space values of averages 12.36 2θ and 7.15 Å, respectively (Table 2).

4. Discussion

The chemical variations of the studied kaolins are normally related to the changes in the mineralogical compositions. Hence, a good correlation ($R^2 = 0.716$) was found between the index of compositional variability ICV and the total associated mineral contents (regardless the amounts of silica and quartz, Fig. 3A). Moreover, the kaolinite order-disorder degrees of the studied kaolins are strongly influenced by variations in chemical compositions. This indicated by a strong correlation ($R^2 = 0.909$) between the "Hinckely index" HI and the calculated ICV index values (Fig. 3B).

As the thermal analysis of the studied samples showed that the heat retention time t_{32} was reached up to 30.82 min, as well as the temperature corresponding to the minimal final time of the thermal dosage administration (T_{20}) was not be dropped to below 34 °C. Consequently, these slow cooling rates are considered as appropriate to the proper heat transfer between skin and the contact mud that expected to be

Table 2
Kaolinite average crystallite size, particle size granulometry, geometric surface area and grading characteristic factors of the studied kaolin samples.

Sample code	Crystallite size (001)			Particle size distribution								Geometric surface area m^2/g	Grading factors	
	D_{001} (nm)	2θ	d-space Å	D_{10} μm	D_{30} μm	D_{50} μm	D_{60} μm	D_{90} μm	< 4 μm	4–62 μm	> 62 μm		C_u	C_c
K1	63	12.32	7.17	0.40	0.64	1.04	1.11	4.21	90.35	9.30	0.35	2.00	1.72	0.93
H5	45	12.36	7.15	0.39	0.62	0.93	1.10	3.10	94.05	5.95	–	3.73	1.80	0.88
N1	57	12.36	7.15	0.38	0.74	1.33	1.52	10.00	82.47	16.39	1.14	1.11	2.06	0.94
N3	52	12.36	7.15	0.39	0.71	1.21	1.35	6.35	86.26	13.14	0.60	1.53	1.91	0.95
N5	62	12.36	7.15	0.33	0.64	1.19	1.33	4.05	91.08	8.56	0.35	2.07	2.08	0.94
N6	51	12.36	7.15	0.37	0.71	1.30	1.47	5.62	86.56	13.44	–	2.05	2.06	0.93
N11	55	12.38	7.14	0.38	0.72	1.35	1.56	6.95	83.59	16.01	0.40	1.57	2.15	0.89
Min.	45	12.32	7.14	0.33	0.62	0.93	1.10	3.10	82.47	5.95	0.00	1.11	1.72	0.88
Max.	63	12.38	7.17	0.40	0.74	1.35	1.56	10.00	94.05	16.39	1.14	3.73	2.15	0.95
Aver.	55	12.36	7.15	0.38	0.68	1.19	1.35	5.75	87.77	11.83	0.41	2.01	1.97	0.92

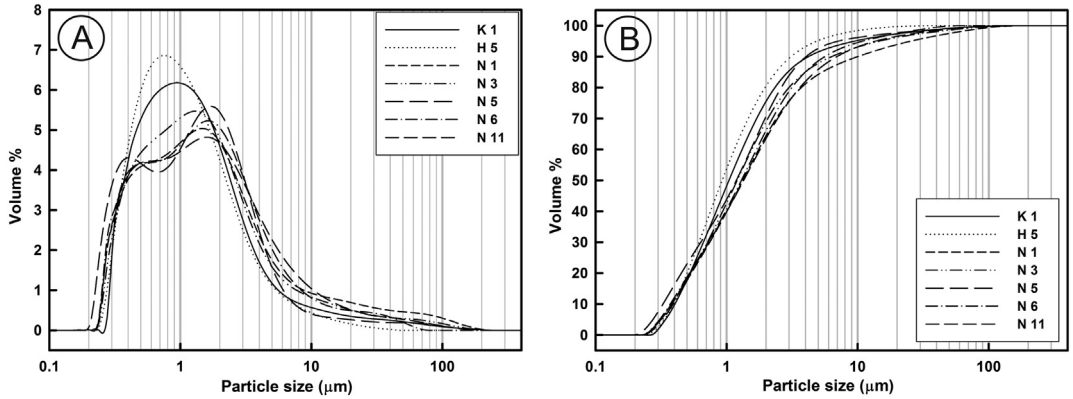

Fig. 2. Particle size distribution of the studied kaolin samples: A) frequency curves of particle volume %, (B) and cumulative curves of particle volume %.

continuous for sufficient time before reaching the normal end point. Therefore, this good cooling kinetics behaviour confirmed that the Egyptian kaolins exhibited consistent thermal dosage performance and qualified for the semisolid mud packs formulations by 50% water contents for pelotherapeutic usage.

A good positive correlation (R^2 = 0.875) was found between the heat retention time t_{32} and the experimental specific heats C_p of the studied paste samples (Fig. 4), but there are no correlations found between thermal properties against the kaolinite contents, bulk and tapped densities nor the structural order. There are obvious differences between the theoretical C_p and the corresponding experimentally determined values. However, the observed similarity in the theoretically calculated C_p values are normally attributed to the slightly differences in the compositional variability ICV of the analyzed kaolin samples (Table 1) as well as to the fixed water contents (50%) used in all the formulated pastes.

As the particle geometry is not included by the theoretical C_p calculations, however it could be considered as the reason of systematic differences between the experimental C_p values and their theoretical counterparts. In this respect, the measured powder samples exhibited low uniformity coefficient C_u (< 3) and curvature coefficient C_c (between 0.5 and 2) values (Table 2) that indicated by uniform and well-graded powder characteristics with very narrow particle size ranges (Ling et al., 2012), as well as they dominated by the fractions < 4 μm with common median sizes D_{50} < 1.4 μm. It was also noticed that, the median size (D_{50}) and the uniformity coefficient (C_u) values exhibited good positive correlations (R^2 = 0.657 and 0.852, respectively) versus the kaolinite order "Hinckley index HI" (Fig. 5), which strongly increased with the chemical compositional variability ICV index, as indicated by samples N11 and H5 (Tables 1 and 2).

The experimental C_p and the heat retention time t_{32} showed positive correlations (R^2 = 0.533 and 0.592, respectively) against the amounts

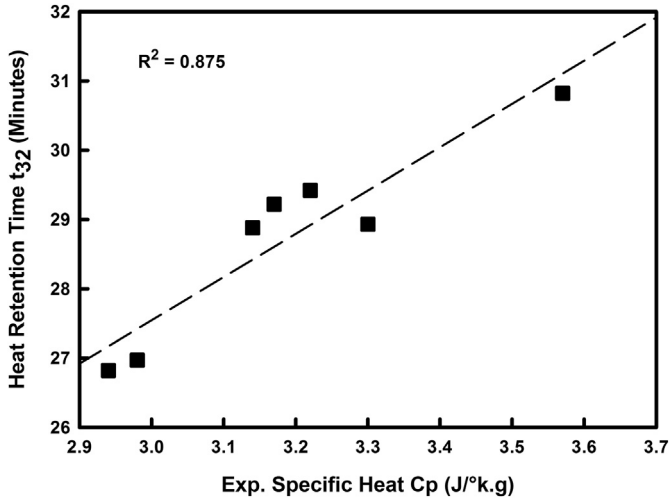

Fig. 4. Relationship between specific heats C_p (J/K·g) of the studied kaolin pastes and the retention times t_{32} (min) during heat transfer to skin till the end point of therapeutic dosage (32 °C).

of the particle size fractions < 4 μm in the measured samples (Fig. 6A and B), while these thermal parameters displayed negative correlations (R^2 = 0.636 and 0.621, respectively) versus the particle median size D_{50} (Fig. 6C and D). This indicated that the richest samples in ultrafine particles, the higher specific heats and hence provided by slower thermal releasing from 50 to 32 °C, that giving higher thermo-therapeutic performance while a time interval over the expected 20 min of administration.

Normally, as the kaolinite micro-sized particle made up of many agglomerated ultrafine nano-crystallites, so the particle size, geometric

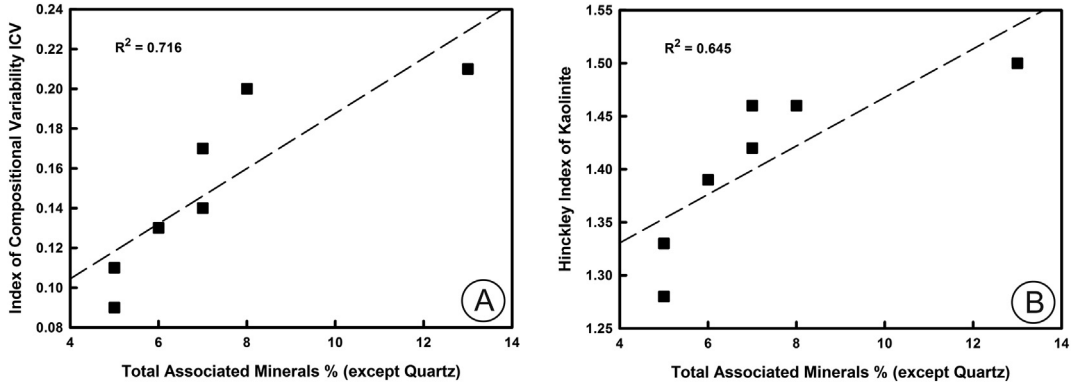

Fig. 3. Kaolin chemical compositional variability: (A) influenced by associated mineral contents; (B) effects on the kaolinite order.

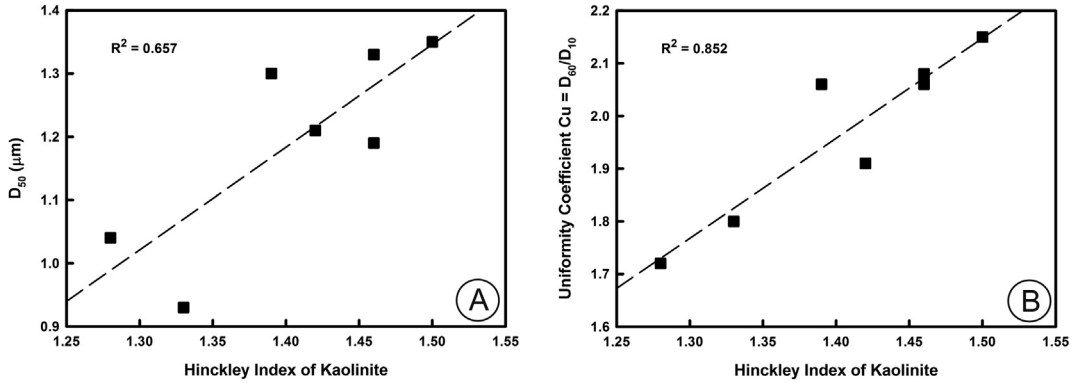

Fig. 5. The effect of kaolinite order on: (A) the yielded median particle size and; (B) uniformity coefficient of the kaolin powder samples.

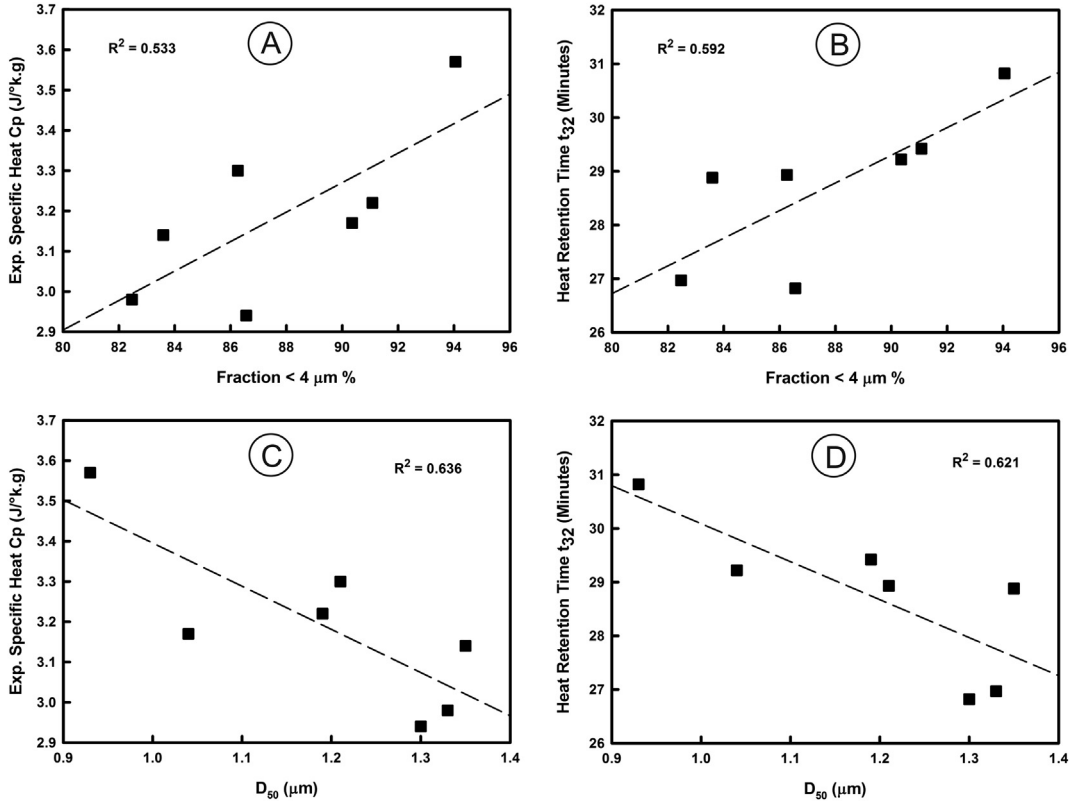

Fig. 6. The influence of kaolin powder granulometric parameters: (A) and (B) fraction % of < 4 μm particles; and (C) and (D) the median size D_{50}) on the thermal behaviour of the studied paste samples.

surface area and microporosity are different from the crystallite size, BET surface area and nano-to mesoporosity. In the studied samples, not only the particle size distribution correlated to the thermal properties but the geometric surface area exhibited positive correlations with both C_p and t_{32} (Fig. 7A and B). On the other hand, as the measured average kaolinite crystallite size exhibited the range of 45–63 nm (Table 2), in some sample variation limits, a strong correlation (R^2 = 0.977) was found between both the C_p and t_{32} determined to the kaolin pastes against the measured kaolinite crystallite size of the studied kaolin powder (Fig. 7C and D).

It is highly expected that, the thermal behaviour and performance of mud therapy could be enhanced and more developed if the particle size reduced to the nano-scale. This is because, the particle size reduction of porous crystalline materials leads to decreasing the porosity by embedding and adhering the nanoparticles to the host matrix and hence affects on the thermal conductivity giving rise to lowering the thermal release rate or even desirable design of the material heat insulation (Machrafi and Lebon, 2015). The effect of the particle geometric changes could be observed in the sample H5 as exhibited the most finer (94% of particles < 4 μm) and highest gradation character as indicated by the lowest curvature coefficient C_c value as well as displayed the most compacted sample as indicated by the largest difference between its bulk and tapped. Moreover, the kaolin mechanical, hydraulic and flow properties (i.e., liquid limit, plastic limit, hydraulic conductivity, viscosity, etc) have found to be significantly improved by the size reduction, as in the case of mixing with only 3% nanokaolin (Khalid et al., 2014). Quartz is a common associated impurity in kaolin and clay mineral deposits used as natural peloids. The purity of the samples K1 and H5 can be upgraded by removing the quartz according to the recent processing study of Bu et al. (2017).

5. Conclusion

The studied Carboniferous highly-orderd kaolinite-rich samples of

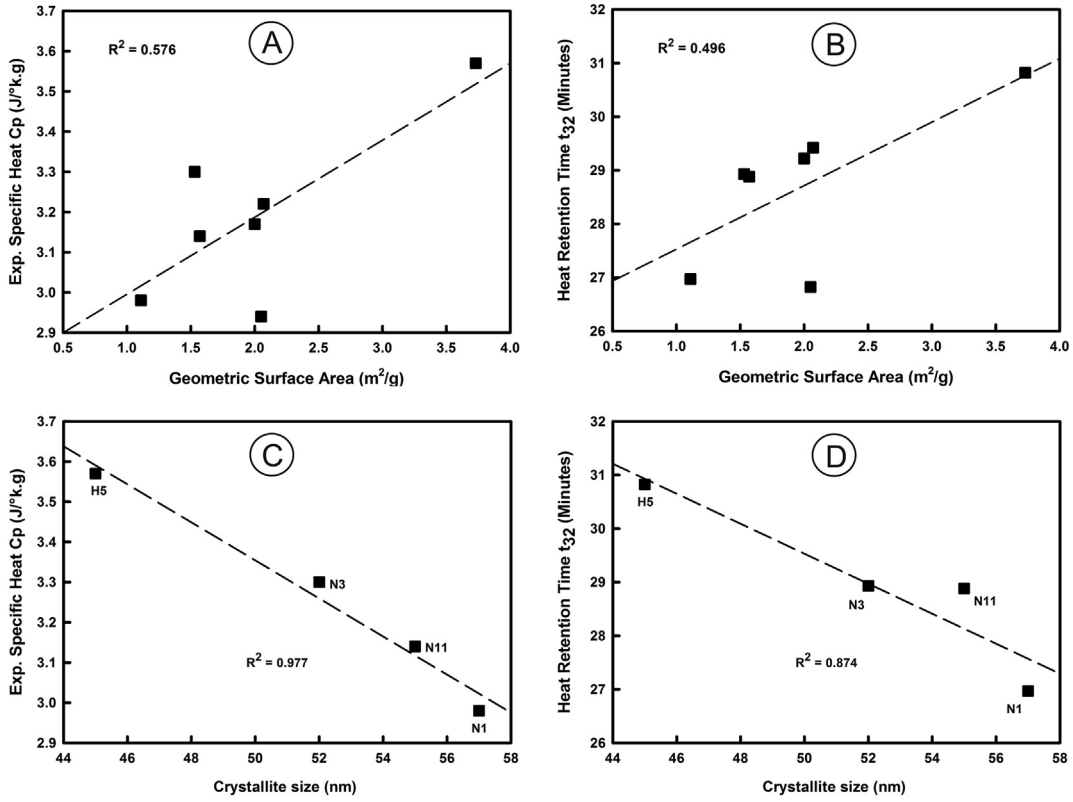

Fig. 7. The influence of geometric particle surface area (m^2/g) and kaolinite crystallite size (nm) on the thermal behaviour of the studied paste samples.

the Egyptian Abu Zenima kaolin deposits proved excellent thermal release efficiency to be used in pelotherapy. The kaolinite order-disorder was increasingly related to the kaolin chemical variability of the studied samples. The higher chemical variability and structural order (all exhibit HI > 1) raw kaolin samples yielded powders of the best median size and uniformity character with the narrower particle size range, that displayed the best thermal behaviour. The kaolin powder granulometric properties (size and surface area) were found to be the most effective factors in controlling the specific heats and the prolongation of heat retention time intervals yielded by the studied pastes, and hence can be considered as promising characteristics for development of thermal dosage release performance while mud therapy administration courses.

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6. CONCLUSIONS

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It can be summarized that, since the pharmaceutical grade of kaolins is mainly evaluated on the basis of their purity and quality, the mineralogical and chemical characterizations carried out on the Egyptian Abu Zenima kaolin (> 120 million tons in reserves) representative samples proved that 50% of the total raw samples contain > 75%, and 20% of the samples showed > 90% up to 96% of kaolinite, which represent the high grade samples.

Moreover, the purity of the lower grade samples (30% of the raw samples contain 50 – 75% kaolinite) can be upgraded by applying recently developed technologies for removing the main problematic-processing impurities (normally quartz and/or feldspars), and by traditional processing methods for the easily-removable Fe-Ti minerals impurities (mainly hematite and anatase) that normally are considered as the main host of the undesirable toxic heavy metal contents (Cd, Pb, As, Co, V, Ni, etc) which substitute for Ti in the crystal structure.

The present study also proved that, the purity level of the upgraded kaolins can be assessed geochemically and technologically by SiO_2/Al_2O_3 ratio, the contents of TiO_2 and Fe_2O_3 and the CIE-Colorimetry data as purity control parameters.

When compared to chemical and microbiological toxins limitations asserted by the international pharmacopeias as well as the ICH-Q3D guideline of the European medicines agency, the high purity samples of the studied kaolin deposits are considered as suitable raw materials for pharmaceutical industries and health-care applications, normally as excipients or active ingredients in the formulations of topical products, or also for oral uses but only after purification processes and the control of the elemental

impurities to strictly meet the permitted daily exposure (PDE) values (i.e., the maximum acceptable intake of elemental impurity in pharmaceutical products per day).

In terms of kaolin pharmaceutical functionality, the kaolin purity has to be strongly considered, besides the structural order-disorder, and the average crystallite size (i.e., coherent thickness of layers stacking) of kaolinite. The granularity and micromorphology of kaolinite particles are also regarded as very important mineralogical characteristics which influence most of the technological solid and semisolid properties that controlling the kaolin quality and development in pharmaceutical applications, either used as dosage form excipients or active therapeutical agents.

The present study discriminated all the Egyptian Abu Zenima kaolin samples into “well ordered or crystallized, exhibit Hinckley Index HI >1” and “medium to poorly ordered or crystallized, with HI <1”. The kaolinite crystallinity is normally responsible for the degree of compactness that differentiated naturally into soft and hard kaolins; the well ordered kaolins are usually soft, while the poorly ordered ones are hard. With very small differences observed in the calculated Index of Compositional Variability (ICV), as the structural order of kaolinite decreases, the average crystallite size decreases, yielding powder of finer median particle size D50 with narrower range and better uniformity character.

All the 50% w/w aqueous suspensions prepared from the representative kaolin samples showed a pseudoplastic flow character. When compared with data of the kaolin monograph published in the handbooks of pharmaceutical excipients (which are made with 70% w/v), the Carboniferous kaolin samples exhibited similar dynamic viscosity values, oscillating around 0.34 Pa.s, while the Cretaceous raw samples exhibited lower

dynamic viscosity values (around 0.14 Pa.s). The rheological characteristics of the studied kaolin pastes are influenced by the kaolinite content and its structural order, and also by the particle size distribution, microtexture of the solid fraction and pH of the suspension.

For thermal pelotherapy purposes, the semisolid 50% w/w formulation of aqueous suspensions prepared from representative Carboniferous highly-ordered kaolinite-rich samples showed the highest consistent paste with suitable rheological and thermal properties. With the small differences observed in the ICV, both the thermal dosage release (from 55ºC to 32ºC)and the specific heat values of the studied pastes are mainly influenced by the kaolin particle size distribution and the geometric surface area, as well as by the kaolinite structural order and average crystallite size.

In overall, the performed mineralogical, chemical and technological characterizations showed that a great part of the studied Abu Zenima kaolin samples exhibit suitable purity and quality for solid and semisolid pharmaceutical uses, as well as for thermal pelotherapeutic applications. The study resulted in the test of the main controlling parameters and limits that are useful for future improvements and developments for other reviewed functionalities of kaolinite.

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