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Clay Surfaces
Fundamentals and Applications

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PHARMACEUTICAL AND COSMETIC APPLICATIONS OF CLAYS

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Clay Surfaces: Fundamentals and Applications
F. Wypych and K.G. Satyanarayana (editors)

1 - Introduction

Clays are substances found throughout the earth's surface, as they are the main component of soils and pelitic sedimentary rocks. Because of their frequency of occurrence and their particular properties, they have been used by man since prehistoric times for therapeutic purposes, such as to cure wounds, relieve irritations or treat gastro-intestinal disorders.

In Europe, Asia, Africa and America, most ancient civilizations used some form of clays in this manner, the best known examples being those of Mesopotamia, Egypt, Greece and Rome as they were mentioned by numerous classical authors. The medicinal "earths" were normally named according to their place of origin, and were thus known as Egyptian, Nubian, Lemnian, Samian, Cimolian earths, Armenian bole, etc. Lemnian earth, from the Greek island of Lemnos, can be considered the first medicine recorded in history [1] and was in use until the beginning of the last century. Its importance is reflected in its being mentioned, among others, by Homer, Theofrastes, Pliny the Elder, and Galenus, who twice travelled to Lemnos in the Aegean Sea to study its preparation.

In the Middle Ages the Arabs added new varieties to those familiar to the Greco-Roman world, with significant contributions by Avicena and Averroes. Later, both the Spanish king Alfonso X the Wise, in the collection of his texts and previous translations known as the *Lapidario*, and Agricola, in his *De Re Metallica*, dedicated extensive chapters to the properties and applications of medicinal earths.

During the Renaissance, when the first Pharmacopoeia appeared, the use of these clays was regulated to a certain extent. In modern times, with the change of mentality brought about by scientific and technological progress, their use has become considerably more restricted, although they continue to be used as natural remedies for the prevention, relief or cure of certain pathologies of the skin, inflammations, dislocations, contusions and the treatment of wounds. Those interested can find numerous examples of such applications in historic times for both health and beauty in literature [2,3,4,5,6].

The development of some branches of sciences such as Mineralogy, Chemistry and Pharmacy in the 18^{th} and 19^{th} centuries was decisive for understanding the nature of these materials, but it was not until the beginning of the 20^{th} century, with the improvement in instrumental techniques, in particular the discovery of X-ray diffraction, when the causes of the singularly useful properties of clay began to be understood, which are related directly to their small particle size and their crystalline structure, which makes them suitable for application as absorbent, sterilising, anti-inflammatory and detergent substances.

At present, environmental awareness and interest in the use of natural products has led to an increase in the use of clayey geomaterials in medical and thermal treatment. In Europe, where the greatest number of spas and therapeutic centres using clays is found, Italy is probably the country with the longest tradition and most frequent use of these materials. For this reason courses and scientific meetings have recently been organised there on the subject [3,4] and where the protocols and norms qualifying the different materials used in fangotherapy are drawn up [7,8].

We should here point out that there is some confusion in the literature regarding the terms "clay mineral" and "clay". The former is a mineralogical terms referring to part of a family (the phyllosilicates) consisting of hydrated aluminosilicates containing considerable amounts of Mg, K, Ca, Na and Fe and, occasionally, less

common ions such as Ti, Mn, or Li. Despite their varied chemical composition, they can be classified in just a few major groups – smectites, micas, kaolin, talcum, chlorites, vermiculites, fibrous and interstratified. The word "clay", on the other hand, refers to natural materials composed of very fine-grained minerals, with some plasticity when mixed with water and which harden on drying. It is, therefore, applicable to all small-sized particles, normally < 2 μm, found in soils or sediments, including, apart from the phyllosilicates mentioned above, other minerals and/or organic products such as quartz, feldspars, carbonates, sulphates, Fe and/or Al oxides, humus, etc. The expression "healing clays" applies mainly to the second term and refers, therefore, to natural clays that, after appropriate treatment to bring out a particular property, are used for pelotheraphy in spa centres.

2 - Structure and texture

Clay minerals are among the most widely used materials in pharmaceutical formulation, because of their properties as excipients and/or their biological activities [2,6,9,10,11,12,13,14). These features depend on both their colloidal dimensions and high surface areas (basic properties), resulting in optimal rheological characteristics and/or excellent sorption capacities. For these reasons, clays have been used for many years in the formulation of solid (tablets, capsules, and powders), liquid (suspensions, emulsions) and semisolid (ointments, creams) dosage forms, either for oral or topical administration.

Only some clay minerals are used in pharmacy, including kaolin, talc, smectites (montmorillonite and saponite), and fibrous clays (palygorskite and sepiolite). The kaolin group is a family including kaolinite, halloysite, dickite and nacrite, of which kaolinite is the most common mineral, so that kaolin and kaolinite frequently become synonymous [13]. The smectite group includes, among others, montmorillonite, beidellite, nontronite and saponite, although rocks containing montmorillonite as main mineral are also referred to as bentonites [15]. Finally the palygorskite-sepiolite group includes two minerals - palygorskite (often known as attapulgite) and sepiolite.

The particular use of a clay mineral for any specific pharmaceutical application depends firstly on its structure. The structural unit of clay minerals consists of a combination of Al or Mg octahedra and Si tetrahedra, resulting in layered structures that may be organised as consecutive strata of octahedral and tetrahedral sheets (T:O or 1:1 clays), or structures with one octahedral sheet "sandwiched" between two tetrahedral ones (T:O:T or 2:1 clays), allowing for an initial classification. The main difference in the behaviour of these two classes is their performance when dispersed in polar solvents. 1:1 clays do not swell, whereas 2:1 ones do, creating highly structured systems with interesting rheological properties.

Further discrimination can be made on the basis of chemical differences. In some of these minerals, isomorphic substitution in the octahedral or tetrahedral layers creates negative charges compensated by exchangeable ions in the interlayer space. The swelling properties of clay minerals are strongly affected by the type and hydration grade of the predominant exchangeable ion [16]. Finally, textural differences between structurally and chemically identical minerals affect their adsorptive and rheological properties [17].

As a result of their structural and chemical characteristics, both kaolinite (1:1 layered silicate of Al) and talc (1:1 layered silicate of Mg) show minimal layer charges,

presenting low cation-exchange capacities (< 15-20 mEq/100g). On the other hand, smectites are 2:1 layered silicates, characterised by octahedral and tetrahedral substitutions and high ion-exchange capacities (100-200 mEq/100g). Differences in the number of cations in octahedral sites lead to the division of smectites into di- and trioctahedral groups, montmorillonite falling into the first group and saponite into the second. Finally, sepiolite and palygorskite are 2:1 phyllosilicates, but, unlike other clay minerals, they have a fibrous morphology resulting from the 180° inversion occurring every six (sepiolite) or four (palygorskite) silicon tetrahedra, causing a structure of chains aligned parallel to the "a" axis, each of which has a 2:1 structure. This three-dimensional ordering also causes open channels measuring 3.7 x 6.4 Å (palygorskite) and 3.7 x 10.6 Å (sepiolite) and containing zeolitic and crystallization water. Sepiolite has a BET surface area of approximately 300 m^2/g and palygorskite 120-180 m^2/g. These values can increase as the adsorbed and zeolitic water evaporates when the mineral is heated.

Figure 1 shows the most common morphology of these minerals when observed under scanning electron microscopy (SEM).

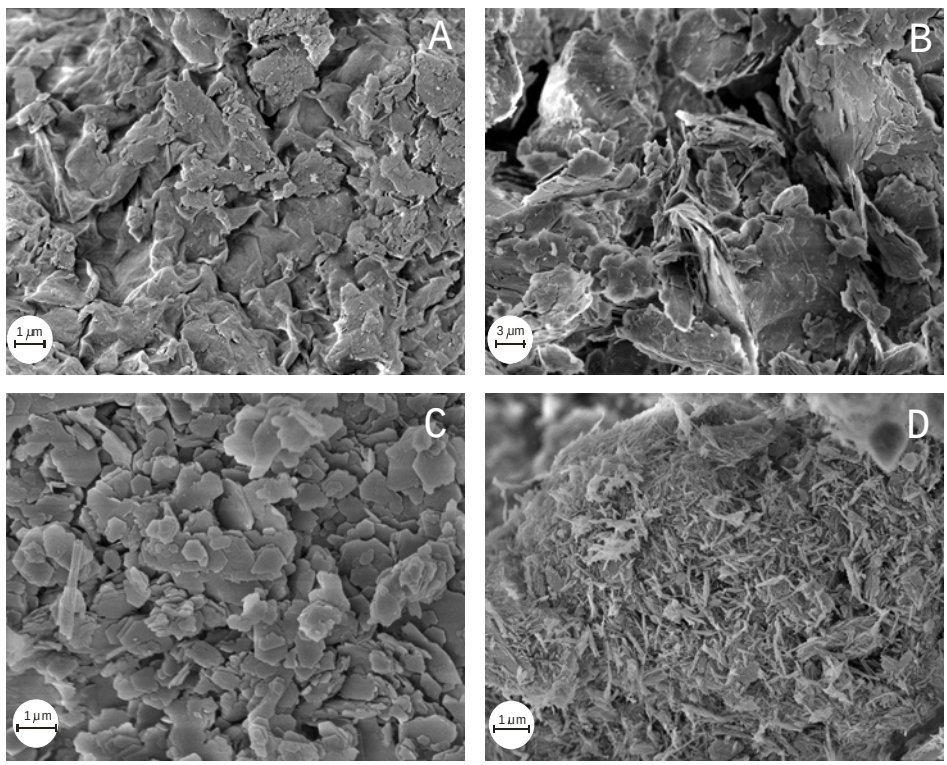

Figure 1. Usual clay morphology observed by SEM. A) Smectite; B) Talc; C) Kaolinite; D) Palygorskite.

Although all the particles are small-size (always < 5 micras) the differences between the different types of phyllosilicates are clear. Smectites (A) are usually present as scarcely differentiated planar particles with quite irregular edges and a size of

less than 2 micras, while the particles of talcum (B) are clearly individualized, with clear edges and a quite larger size. The particles of kaolinite (C) are better crystallised, with abundant pseudo hexagonal shapes, while palygorskite samples (D) are normally made up of large aggregates containing randomly arranged microfibres, although this mineral is sometimes found as small fibres covering other crystals.

As a result of these basic characteristics, clay minerals are used in numerous industrial applications involving ceramics, plastics, paper, paint, catalysis, cosmetics, etc., as reviewed in the literature [18-26].

3 - Use in pharmaceutical formulations

3.1 - Pharmaceutical denominations

Both the European Pharmacopoeia (EP) and the United States Pharmacopoeia (USP) contain monographs regarding clay mineral materials. In the EP 4th [27], official monographs of "Aluminium Magnesium Silicate", mixture of montmorillonite and saponite (a), "Bentonite" (montmorillonite, b), "Kaolin" (c), "Magnesium Trisilicate" (sepiolite, d)) and "Talc" (e) are included. Besides these monographs the USP 25 [28] adds the following: "Activated Attapulgite" (f), "Alumina and Magnesium Trisilicate Oral Suspensions" (g), "Alumina and Magnesium Trisilicate Tablets" (h), "Bentonite Magma" (i), "Colloidal Activated Attapulgite" (j), "Magnesium Trisilicate Tablets" (k) and "Purified Bentonite" (l).

Table I summarises the clay minerals included in EP 4th and USP 25, with their chemical and commercial correspondences. Some ambiguities between mineralogical, chemical and pharmaceutical names can be observed. The term "bentonite" is too generic, as it can be used both for a rock consisting mainly of smectites (mineralogy) or a material mainly containing montmorillonite (pharmacy). On the other hand, "Aluminium Magnesium silicate" (EP 4th) and "Magnesium Aluminum silicate" (USP 25) are not univocal names, creating some confusion. Both mainly refer to blends of montmorillonite and saponite, according to their specific Al/Mg ratio (between 95 and 105% w/w of that stated on the label). Moreover, palygorskite samples are frequently commercialised under these denominations, as well as attapulgite. Finally, sepiolite seems to correspond to the so-called "Magnesium Trisilicate", described as a blend of Si and Mg oxides prepared to meet the pharmacopoeia requirements. USP 25 requires not less than 20% w/w of MgO and not less than 45% w/w of SiO_2, where EP 4th indicates not less than 29% w/w of MgO and not less than 65% w/w of SiO_2.

3.2 - Pharmaceutical specifications

As intended for use in the preparation of medicines, clay mineral materials must fulfil certain requirements concerning their chemistry (stability and high chemical inertia), physical characteristics (texture, water content, dimensions) and toxicological nature (chemical safety, microbiological purity). Some of these properties, such as those regarding safety and stability, are vital.

It must be remarked that minerals intended for use as pharmaceutical materials may contain crystalline silica (both quartz and cristobalite), that should be controlled and avoided as far as possible, as it is classified by the International Agency for Research on Cancer (IARC) as a product with sufficient evidence of carcinogenicity in laboratory animals and limited evidence in humans (group 1, IARC Monographs) [29]. On the other hand, amorphous silica, found in nature as biogenic silica (e.g. diatomaceous earth) and as silica glass (volcanic genesis), is not classifiable as

carcinogenic to humans (group 3) [29].

Regarding kaolin, USP 25 specifies that it must be “powdered and freed from gritty particles by elutriation”. Impurities such as quartz, mica, hematite or pyrite are mainly contained in the coarse fraction of the rock, and should be eliminated. Concomitant administration of drugs, such as some antibiotics (amoxicillin, ampicillin, clindamycin), cimetidine, atropine, phenytoin, digoxin and quinidine could reduce drug absorption as a result of drug-kaolin interaction, and should be avoided [30-36].

Talc, presented as a white or almost white, impalpable and unctuous powder, may contain variable amounts of other minerals, such as hydrated Al silicate, magnesite, calcite and dolomite that can remain when used as excipient. Talc containing asbestos is, however, not suitable for pharmaceutical use because of its carcinogenic activity in humans. According to the IARC monograph [37,38], talc not containing asbestiform fibres is not classifiable as to its carcinogenicity to humans (group 3), while there is sufficient evidence for the carcinogenicity to humans of talc containing asbestiform fibres (group 1). In fact, the EP 2002 monograph on talc includes specific tests (infrared, x-ray diffractometry and optical microscopy analysis) to detect asbestos and to determine asbestos character in talc.

Because of their cation-exchange capacity smectites can interact with certain drugs affecting their bioavailability. Nevertheless, this interaction could be advantageous in the formulation of controlled release systems, which is one of the most attention-grabbing fields of clay applications at present, as discussed below.

Table 1. Pharmaceutical, mineral, chemical and commercial correspondences among clays used in Pharmacy

Clay Mineral	Rock	Pharmacopoeial name	Chemical name and CAS registry number	Empirical formula	Usual names
Kaolinite	Kaolin	Kaolin, Heavy (EP 4th) Kaolin (USP 25)	Hydrated aluminium silicate (1332-58-7)	$Al_2 Si_2 O_5 (OH)_4$	China Clay, bolus alba, porcelain clay, weisserton, white bole.
Talc	Talc	Talc (EP 4th and USP 25)	Talc (14807-96-6)	$Mg_3 Si_4 O_{10} (OH)_2$	Magsil osmanthus, Magsil star, powdered talc, purified french chalk, purtalc, soapstone, steatite.
Montmorillonite Group: Smectites Subgroup: diocthaedral	Bentonite	Bentonite (EP 4th and USP 25) Purified Bentonite (USP 25)	Aluminium magnesium silicate (1302-78-9) Aluminium magnesium silicate (12511-31-8)	$(Na, Ca, K)_{0.33} (Al, Mg)_2 Si_4 O_{10} (OH)_2 .nH_2O$	Mineral soap, clay soap, taylorite, wilkinite, Veegum HS, Albagel, mineral colloid
Saponite Group: Smectites Subgroup: triocthaedral	Bentonite	Aluminium magnesium silicate (EP 4th) Magnesium aluminium silicate (USP 25)	Aluminium magnesium silicate (12511-31-8) Magnesium aluminium silicate (1327-43-1)	$(Ca, Na, K)_{0.33} (Mg, Fe)_3 (Si, Al)_4 O_{10} (OH)_2 .nH_2O$	Veegum R-K-HV-T-F, Carrisorb, Gelsorb, Magnabites Colloidal, Colloidal complex
Palygorskite	Palygorskite	Attapugite (USP 25)	Aluminium magnesium silicate (12511-31-8) Magnesium aluminium silicate (1327-43-1)	$(Mg, Al, Fe)_5 (Si, Al)_8 O_{20} (OH)_2 (OH_2)_4 (H_2O)_4$	Attapulgite, Attasorb, Pharmasorb
Sepiolite	Sepiolite	Magnesium trisilicate (EP 4th) and (USP 25)	Hydrated magnesium trisilicate (39365-87-2) Magnesium aluminium silicate (1327-43-1) Anhydrous magnesium trisilicate, magnesium metasilicate, magnesium ortosilicate	$Mg_8 Si_{12} O_{30} (OH)_4 (OH_2)_4 (H_2O)_8$	Silicic acid, hydrated magnesium salt, meerschaum, parasepiolite, sea foam, talcum plasticum.

Finally, regarding fibrous clays, although this is not a specific requirement of any Pharmacopoeia, the particle size of fibrous minerals must be carefully controlled because of its possible biological effect. In a preformulation study, Viseras *et al.* [39] showed that samples corresponding to different clay minerals used in pharmacy

presented particle sizes lower than the value generally accepted for defining a particle as a fibre (> 5µm in length and a length/diameter ratio > 3:1) [40]. Moreover studies carried out on humans exposed to some sepiolite samples confirmed that exposure to these minerals involves no risks [41,42,43]. The IARC clearly distinguishes between palygorskite and sepiolite [44,45]. Palygorskite samples are classified as long (>5µm) clay fibres and short(<5µm) clay fibres. Long palygorskite samples are possibly carcinogenic to humans (group 2B), while the short ones cannot be classified as to their carcinogenicity to humans (group 3). On the other hand, there is inadequate evidence in humans for the carcinogenicity of sepiolite (group 3), whatever the length of the fibres, although there is limited evidence in laboratory animals suggesting carcinogenicity of long (>5µm) fibres.

3.3 - Use as excipients

In the preparation of pharmaceutical products particular importance attaches to the selection of suitable excipients, *i.e*., auxiliary substances contained in the formulation with the purpose of providing the product with an adequate presentation. Excipients must facilitate the administration of the active ingredients, improve their efficiency and ensure stability until the expiry date for usage by the ill. The fundamental property for a product to be used as excipient is innocuousness, while attention should also be paid to other attributes affecting the organoleptic characteristics of the end product, such as taste, smell and colour.

Clays are regarded as essentially non-toxic and non-irritant materials at the levels used in pharmaceutical excipients and are included in the *Inactive Ingredients Guide* [46] published by the Food and Drug Administration (FDA). This guide contains all inactive ingredients present in approved (or conditionally approved) drug products marketed for human use. Table 2 shows a summary of the applications of clay minerals as pharmaceutical excipients in drug products as provided by this guide.

3.3.1 - Solid dosage excipients

In Table 3, clay minerals are classified according to their functionality as excipient in solid dosage forms. Kaolinite is mainly used as a diluent because of its white to greyish-white colour. Its suitability as pharmaceutical excipient greatly depends on the geological nature (sedimentary, residual, and hydrothermal) and mineral composition of the deposits, which have an important effect on texture and particle size distribution, and consequently, on the rheological properties (flow) of the powder mass [26,47,48].

Talc is mainly used as diluent, glidant and lubricant in tablet and capsule formulations. In addition, talc is used as an additive to promote film coating of tablets and particles [13,49,50]. Several studies have shown that the chemical composition and physical properties of talc depend on the source and the method of preparation [47,48,51-55]. Smectites, such as bentonite and Mg Al silicate, are used in solid dosage forms as tablet and capsule disintegrants, tablet binders and adsorbents. The use of bentonite in the formulation of tablets has been studied in the past by several authors [56-58]. Feinstein and Bartilucci [59] investigated the disintegrant efficiency of bentonite, concluding that its effectiveness is comparable to other typical disintegrants, such as cellulose derivatives. Wai *et al*. [60] indicated that laminar clays are not good disintegrants when used as intragranular agents. In contrast, Fielden [61] proposed that a suitable technological procedure results in good disintegrant characteristics, even

when used as an intra-granular agent.

Table 2. Pharmaceutical applications of clays as excipients in drug products for human use.

Pharmacopeial name	Administration	Dosage form	Potency range (*)
Kaolin or Heavy kaolin	Oral	Immediate release (IR) and Modified release (MR) (delayed or sustained) tablets	Non specified
Talc	Oral	Film coated tablets	0.189 – 204 mg
		MR (Sustained or Repeat action) tablets	0.2 – 3 mg (sustained) and 73.93 mg (repeat)
	Sublingual	Tablet	5 mg
	Topical	Lotion	Non specified
		Ointment	
		Powder	
Bentonite or Purified Bentonite	Oral	Capsules	Non specified
		Tablets	
		Suspensions	0.45 % w/w
	Topical	Suspensions	2.1 % w/w
	Transdermal	Film	Non specified
	Vaginal	Suppository	
Mg Al or Al Mg silicate	Oral	Drops	Non specified
		Granule	
		Reconstitution granules	
		Syrup	
		Suspensions	0.15 – 2 % w/v
		Tablets	8 mg
	Rectal	Suspension	Non specified
	Vaginal	Ointment	
	Topical	Emulsion (creams)	
		Lotion	1.5 % w/w
Magnesium Trisilicate	Oral	IR Tablets	Non specified
		Coated Tablets	
		Sustained Release Tablets	

(*) POTENCY RANGE: Minimum and maximum amounts of inactive ingredient for each route/dosage form

The use of fibrous clays in the formulation of tablets is based on their properties as glidants and binders. The suitability of some laminar and fibrous phyllosilicates as additives in solid dosage forms was recently investigated [12,62]. Fibrous clays can also be used as disintegrants. Viseras *et al*. [63] showed that, in comparison to other silicates, sepiolite could be used as direct compression disintegrant even at low concentration. Regarding binding properties, Angulo *et al*. [64] showed that sepiolite considerably improved the durability and quality of pellets. Moreover, their

high surface area allows fibrous clays to be used in solid formulations as adsorbents of liquid drugs. Finally, unlike palygorskite, sepiolite may be used as a pharmaceutical excipient for drugs subject to oxidative degradation, such as hydrocortisone. Sepiolite avoids degradation because of its lower ferric iron content in comparison with palygorskite [65,66].

Table 3. Uses of clay minerals as excipients in solid dosage forms

Excipient	Dosage forms	Functional category
Kaolin and Heavy Kaolin	Tablets and capsules	Diluent and adsorbent
Talc	Tablets, capsules and powders	Coating aid, lubricant, diluent and glidant
Bentonite	Tablets, capsules and granules	Adsorbent, binder and disintegrant
Magnesium Aluminium Silicate		
Magnesium Trisilicate	Tablets and capsules	Adsorbent, glidant, binder and disintegrant

3.3.2 - Liquid and semisolid dosage excipients

Pharmaceutical dispersions are shaken several times during their “life”, leading to changes in the system structure, and when administered orally they encounter a special pH environment that may severely affect their properties. Both suspending and anticaking agents are used to prevent drastic changes in dispersion properties. Some types of laminar and fibrous clays are particularly useful as stabilisers because of their positive thixotropic nature [39,67-70]. Table 4 summarizes the main uses of clays in liquid and semisolid formulations.

Kaolinite and talc are employed in liquid formulations as suspending and anticaking agents [13]. Lagaly [71] pointed out the importance of particle morphology and surface charge in the rheological behaviour of kaolin suspensions. Yuan and Murray [72] compared the rheological characteristics of kaolin dispersions prepared with different crystal morphologies (planar kaolinite and tubular or spherical halloysite), concluding that particle morphologies strongly affected the dispersion viscosities.

Bentonite and Magnesium Aluminum Silicate are commonly used as suspending and stabilising agents in the formulation of suspensions, gels, ointments and creams for oral or topical administration. USP 25 describes four types of Magnesium Aluminum Silicate (IA, IB, IC, IIA) with different viscosity and Al/Mg ratio contents. When laminar clays are dispersed in a polar medium, face-edge and face-face interactions are the two major mechanisms implied in the formation of a rigid network [73-78]. Recently, the colloidal and rheological properties of bentonite suspensions were reviewed by Luckam and Rossi [79], who emphasise that laminar silicate gels are sensitive to the addition of electrolytes. In addition, Ma and Pierre [80] considered the influence of Fe^{3+} ions on the colloidal behaviour of montmorillonite suspensions, concluding that both Fe^{3+} and its hydrolytic products acted as counter ions to neutralise

the electric double layer around clay particles. By means of absorption on clay particles, the hydrolysis products could also modify the surface charge of the clay thus improving suspension coagulation. The effect of ion type and ionic strength on the sol-gel transition of sodium montmorillonite dispersions was studied by Abend and Lagaly [81], who obtained phase diagrams of different states (sol, repulsive gel, attractive gel, sediment) of the dispersions, showing that the borderline between gel and sediment depends on the type of counter-ion and co-ion.

Table 4: Uses of clays as excipients in liquid and semisolid dosage forms

Excipient	Dosage forms	Functional category
Kaolin and Talc	Creams and pastes	Emulsifying agent
	Suspensions	Suspending and anticaking agent
Bentonite and Magnesium Aluminium Silicate	Ointments, Creams and Gels	Emulsifying agent
	Suspensions	Suspending and anticaking agent
Magnesium Trisilicate	Suspensions	Suspending and anticaking agent

Fibrous clays dispersed in water form a three-dimensional structure composed of interconnecting fibres [82]. Fibrous clay gels retain their stability in the presence of high concentrations of electrolytes, thus making them ideal for such an application [83-85]. Some investigations have focused on the effects of hydrodynamic factors, such as size and shape of the particles, on the final product properties. Viseras *et al*. [39] assessed the effects of shear history on the rheology of laminar and fibrous clay dispersions, concluding that the degree of dispersion and the structural changes resulting from differences in particle shape significantly affect the rheological properties of the systems. A linear relation was found between mixing energy and apparent viscosity in the laminar systems, while apparent viscosity was related to mixing power for the fibrous ones. A subsequent study examined the filtration behaviour of some Spanish clay-water dispersions, the results of which were compatible with the rheological properties of the systems [70].

Some authors have evaluated the use of clay minerals in combination with other agents. Ciullo [86] showed a synergic effect of Veegum® and natural gums as stabilisers in the formulation of emulsions. Recently, Lagaly *et al*. [87,88] studied the use of smectites in combination with non-ionic surfactants as stabilisers in the formulation of oil in water emulsions. The main mechanism of stabilisation was the formation of a mechanical barrier around the oil phase droplets, preventing their coalescence. The rheological behaviour of the emulsions was also investigated and a strong influence of the clay mineral and surfactant was found.

3.4 - Use of clay minerals as active substances

Clay minerals are also used in pharmacy because of their biological activity, both in the treatment of gastro-intestinal and topical diseases. Moreover, they are used in the treatment of some much more specific illnesses. Marketed preparations containing clays as active substances are summarized in Table 5.

Table 5: Uses of clays as active principles in marketed products

Active	Therapeutic use	Brand names
Kaolinite	Antidiarrhoeal & gastrointestinal protectors	**EU**: Dystomin-E, Entrocalm, Collis Browne's, Kaoprompt-H, Kaopectate, Kaopectate-N, Enterosan, Kaodene, Kalogeais, Pectipar, Carbonaphtine Pectinée, Kao-Pront
		USA: Kao-Spen, Kapectolin, K-P Generic, Kaopectate
		Other: Bipectinol, Donnagel-MB, Kaomagma, Kaomagma with Pectin, Chloropect
	Antacid	**EU**: Neutroses Vichy , Neutroses, Kaobrol Simple, Kaomuth, Anti-H, Gastropax
		Other: De Witt's Antacid
	Anti-inflammatory	**EU**: Cicafissan, Antiphlogistine
		USA: Mexsana
	Homeopathic Product	**Other**: Alumina Silicata
Talc	Anti-rubbing	**EU**: Ictiomen, Aloplastine, Lanofene 5, Poudre T.K.C.
	Anti-haemorrhoids	**EU**: Titanoreine
	Pleurodesis	Formulated and prepared in hospitals just before their use
Palygorskite (attapulgite)	Antidiarrhoeal	**USA**: Diar-Aid, Diarrest, Diasorb, Diatrol, Donnagel, Kaopectate, Kaopectate Advanced Formula, Kaopectate Maximum Strength, Kaopek, K-Pek, Parepectolin, Rheaban and Rheaban Maximum strength, Quintess
		EU: Streptomagma, Actapulgite, Gastropulgite, Mucipulgite, Norgagil, Diasorb
		Others: Fowler's and Kaopectate
	Antacid	**USA**: Streptomagma, Kaopectate
Magnesium Trisilicate	Antacid	**EU**: Neutroses Vichy, Neutrose S. Pellegrino, Instatina, Masbosil, Silimag, De Witt's antacid, Anti-acide-GNR, Gastric Expanpharm, Gastropax, Magnesie compose Lehning, Triglysal, Contracide, Gelusil
		Other: Trisil,. De Witt's Antacid, Gasulsol Tab
Smectite	Antacid	**EU:** Smecta
	Antipruritic and local anaesthetic	**Others**: Calamine Lotion
	Antidiarrhoeal & gastrointestinal protectors	**EU:** Diosmectite

3.4.1 - Antidiarrhoeal uses

Antidiarrhoeals are usually categorized in four groups; antiperistaltics, adsorbents, antisecretory and digestive enzymes. Palygorskite and kaolinite are included in the second group of adsorbent agents [89,90].

Kaolinite, used as oral adjunct in the symptomatic treatment of diarrhoea because of its adsorbent properties, is administered orally in doses of about 2-6 g every four hours [13]. It may be formulated alone or in combination with other actives, such as pectin, loperamide, aluminium and magnesium salts, belladonna extract and morphine.

As regards palygorskite, it has been described as even more effective than kaolinite in the symptomatic treatment of diarrhoea because of its capacity to adsorb and retain water, bacterium and some toxins [91]. Cerezo *et al*. [92] evaluated the possibilities of fibrous clays as non specific anti-diarrhoeic agents, concluding that both palygorskite and sepiolite comply with the pharmacopoeial specifications and may be taken into account. The daily dose of palygorskite can be up to 9 g in the form of oral suspension, conventional and chewable tablets. For oral suspension and tablets, the usual dose is 1200 to 1500 milligrams (mg) taken after each loose bowel movement, with no more than 9000 mg being taken in twenty-four hours. For chewable tablets, the dose is slightly less, and no more than 8400 mg should be taken in twenty-four hours. However, no conclusive evidence is available to show that palygorskite use may reduce the duration of diarrhoea, stool frequency, or stool fluid losses [93].

Smectite is equally effective in the treatment of infectious diarrhoea as it reduces the duration and frequency of liquid stool by mechanisms including absorption of water and electrolytes in the intestine, decrease of mucolysis caused by bacteria and protection of the luminal surface against pathogenic bacteria [94,95]. Moreover, some authors have described the use of smectite in the treatment of acute diarrhoea, although this clay is not currently recommended for this purpose [96,97,98]. On the contrary, Carretero [6] recently illustrated the use of Na^+ smectite as osmotic laxative, although no experimental evidence supports this statement.

3.4.2 - Gastrointestinal protector

Mucus forms a 200 micra thick layer of gel on the gastro-duodenal mucous membrane [99], which acts as a physical barrier preventing direct contact between the gastric enzymes and the cells of the mucous membrane, thus avoiding digestion of the latter [100] and mechanical erosion. In patients suffering from peptic ulcer, the thickness of the mucus layer decreases, while the mucolytic activity of the gastric juices and the enzyme levels increase [101,102). Clays provide multiple gastro-intestinal protection mechanisms associated with the different etiologies of deterioration – mechanical erosion, enzyme attack, bacterial toxins, drugs, alimentary allergies, genetic factors, environmental factors such as tobacco, alcohol, etc. Several adsorbent agents (bentonite, kaolinite, active carbon) present anti-endotoxemic activity both in vivo and in vitro that reduces the alteration of the mucous membrane to the levels of healthy individuals [103,104]. The protective effect of clays on intestinal barriers is related to their influence on the rheological properties of the mucus. As discussed previously, clay particles dispersed in a water solution medium greatly increase its viscosity and, consequently, its stability.

On the other hand, the mucoadhesivity of clays, *i.e*., their positive interaction with and binding to glycoproteins present in the mucus, is probably an important

protective mechanism. Deterioration of glycoproteins by reactive agents, such as free radicals, ethanol or some drugs, is reduced when the polymer is complexed to the clay [105-108].

3.4.3 - Antacid uses

Clay minerals such as palygorskite and magnesium trisilicate (sepiolite) may be used as symptomatic antacid agents, because of their capacity to neutralise acidity in the gastric secretions. They are used in combination with aluminium hydroxide and kaolinite in suspensions and chewable tablets. Magnesium trisilicate is given in doses from 1 to 4 g, reacting with hydrochloric acid to form magnesium chloride and silicon dioxide, with an H^+ neutralising capacity of around 15 meq/g. It is indicated in the treatment of gastric and duodenal ulcers. Magnesium chloride resulting from the neutralizing action may induce diarrhoea in some cases. Kaolinite in combination with sodium bicarbonate and magnesium trisilicate is commercialized, having an H^+ neutralising capacity of around 56 meq /g.

3.4.4 - Anti-inflammatory and antiseptic purposes

Purified talc is used in dusting powders to calm irritation and prevent roughness, while kaolinite is used for sore throat symptoms, including tonsillitis, pharyngitis and stomatitis, and is responsible for the adsorption of waste products. Mixtures of kaolin, bentonite and palygorskite have been proposed for use as dressing for the treatment of skin injuries, especially burns [109]. Kaolinite is applied topically as kaolin poultice to reduce inflammation [110]. Finally, pastes of kaolin and salicylic acid are applied as percutaneous anti-inflammatory in the treatment of muscular pain and tendonitis.

Fibrous clays are also used in the treatment of aqueous inflammations, adsorbing the aqueous fraction and probably also retaining the proteic fraction of the inflammation [111-113]. They are probably able to effectively retain toxins and bacteria as happens in the gastrointestinal tract. Bentonite is included in antipruritic and local anaesthetic preparations for topical use.

3.4.5 - Topical applications

The use of clay minerals as actives in topical dosage forms (creams, milks and powders) has been proposed on the basis of their capacity to efficiently adsorb a variety of undesired substances, including greases, skin exudates and external agents such as bacterial toxins [114]. However, clay minerals in such formulations are normally employed as excipients, *i.e*., as auxiliary substances intended to maintain the dose of the active principle in the area to be treated by increasing the viscosity of the system, promoting skin-adhesivity and keeping a high concentration of drug in the proximity of the treated skin-area.

3.4.6 - Other uses

Kaolin is included in human homeopathic preparations, when it is known as alumina silicate, in the form of drops, globules and oral granules. Bentonite may be used as adsorbent in paraquat poisoning [110].

Talc is concomitantly used with carrageenates in suppositories administered as mucoprotectors and lubricants of rectal mucosa in the treatment of haemorrhoids. Finally, this mineral is also indicated as the preferred treatment for pleural effusion, a

complication in patients with malignant neoplasms caused by disturbance of the normal reabsorption of fluid in the pleural space [115]. Talc pleurodesis for the treatment of malignant pleural effusion is an effective method, preventing recurrent effusion in 80-90% of cases and being less painful than tetracycline [116]. Talc can be insufflated in a dry state or instilled as slurry. The dose should be restricted to 5 grams [117].

4 - New uses in modified drug delivery sistems

Most of the clays used in pharmacy can interact with other components of the formulation and, in the specific case of drug-clay interaction, this can affect the bioavailability of the drug itself [118-120 among others]. The best known cases are those of montmorillonite and saponite, which are fairly common, well studied smectites [121,122]. Later studies have evaluated the effect of factors such as ionic strength, the dielectric constant of the medium and the addition of polymers, confirming that ionic exchange is the main mechanism involved in absorption [123-127]. More recently, Tolls [128] examined the influence of the molecule's lipophilia in the absorption by clays of various veterinary drugs. On the other hand, the oral administration of fibrous clays could also affect the bioavailability of some drugs, such as mebeverine, folic acid, contraceptive steroids, promazine, atropine, glycosides (digoxin, digitoxin), erythromycin, paracetamol, chloroquine, quinidine, propranolol and tetracycline. Moreover antimicrobial preservatives, such as parabens, could be inactivated [129-133].

In recent years, there has been discussion on how to take advantage of these interactions for aims that are biopharmaceutical (modification of drug release or solubility), pharmacological (prevention or reduction of side-effects) and chemical (increased stability) [134].

Ideally, a pharmaceutical form should be designed to fulfil the therapeutic requirements, while avoiding or minimising the side effects. Conventional pharmaceutical forms are designed to release the dose immediately and achieve rapid, complete absorption of the drug. However, immediate release forms require repeated administration to maintain efficient concentrations of the drug. To avoid this, modified release pharmaceutical forms attempt to fulfil the therapeutic requirements by optimising the time, rate and location of drug release [28] and are known as "sustained release" (reducing frequency of administration to at least half that of a conventional form), "delayed release" (releasing the drug over a predetermined period) and "site-specific release" (releasing the drug at or near the place of physiological activity). These release objectives can be achieved by using products of drug-clay interaction.

Delgado *et al.* [135] examined the use of kaolinite samples with different degrees of crystallinity as vehicles for the controlled release of drugs and found a linear relation between the crystallinity of the mineral and the release of amilobarbitone. Halloysite, a tubular polymorph of kaolinite, has recently been proposed for pharmaceutical use and, specifically, the tubules of this mineral could act as natural vehicles for microencapsulation and controlled release of both hydrophilic and lipophilic agents [136-138]. Moreover, the alternative absorption of macromolecules of opposite charge, including proteins, clays and poly-ions, has been proposed for the preparation of immobilisation vehicles, characterised by their capacity to guarantee the biological activity of the enzyme [139]. The halloysite microtubes filled with NAD coenzyme were assembled with ADH (alcohol-dehydrogenase) coenzyme and used as sustained release vehicle of the cofactor of the immobilised enzyme [140].

Regarding the use of swelling clays, Cameroni *et al.* [141] studied the effect of different factors on drug release from compounds of papaverine and Veegum® (a commercial smectite) and found that the amount released depended on the pH, the ionic strength of the dissolution fluid and the elimination rate of the drug from the medium. Moreover, optimisation of the formulation, obtained by surface deposit of the papaverine on the compound, gave *in vitro* absorption profiles with zero kinetics, together with rapid achievement of constant drug concentrations in the gastro-intestinal tract [142]. Finally, Forni *et al.* [143] showed that montmorillonite affects release in matrices of polyvinyl alcohol by interaction with the drug. More recently, Oya *et al.* [144] proposed the use of Ag / montmorillonite compounds instead of a conventional organic agent, as a thermostable inorganic agent with high antimicrobial and antifungic activity for the treatment of muco-cutaneous conditions. Similar results were found using chelates of Ag and Tiabendazol in montmorillonite [145]. Fouche [146] examined the use of antibiotic-clay compounds in the treatment of gastric ulcer determined by *Helicobacter pylori*, with the conclusion that the clay aided penetration of the drug through the gastro-intestinal barrier. Absorption of 5-fluorouracil by montmorillonite has been considered for the development of new therapeutic systems for oral administration in the treatment of colo-rectal cancer [147]. In recent years, five Spanish clays, including smectites and fibrous minerals, have been evaluated with regard to enzyme immobilisation, with the conclusion that at least the fibrous minerals could be used as vehicles for biotransformations [148]. These same clays can be used to obtain compounds with different types of drugs (timolol, tetracyclines, imidazolic antifungics) in which the release profiles have suitable kinetics for use as modified release systems [134,149-151).

Preparation of the compounds is carried out by interaction of the solid (clay) with solutions of the drug in different media. However, Rives-Arnau *et al.* [152] proposed a new dry process for the preparation of drug-clay compounds, as an alternative to the more common wet process, consisting in complexing by grinding the clay and the drug together. A third formation mechanism of these compounds would involve contact between the drug and the clay at the melting temperature of the active agent (Viseras *et al.*, unpublished).

5 - Use in cosmetics

The pharmaceutical (treatment) and cosmetic (care and beauty) uses of clay minerals are normally mentioned together, even though their aims are very different. It is therefore advisable to specify the intended use of a clay, as this will determine not only the technical aspects of its treatment, but also legal questions or matters of code of practice.

A “cosmetic product” is any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning, perfuming, changing their appearance and/or correcting body odours and/or protecting or keeping in good condition (Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products). On the other hand, Council Directive 2001/83/EC on the Community Code relating to medicinal products for human use defines “a medicinal product” as any substance or combination of substances administered to human beings for treating or preventing disease, making a medical

diagnosis or restoring, correcting or modifying physiological functions.

A detailed study of all the possibilities of clays in the field of cosmetics falls outside the scope of this review, and so we shall concentrate on some examples that show the close relationship between their cosmetic applications and the properties resulting from their high specific surface and small size, which have been extensively discussed above.

In most cases, cosmetic preparations make use of clays' rheological properties with the aim of the physical stabilising of the end product, just as they are used as excipìents in medicinal preparations. Similarly, the use of clay minerals as active in cosmetics is closely related to their adsorbent capacity. They are used in deodorant powders and creams as they eliminate the gases responsible for the bad smell [153], in bath powders and baby powders, where they absorb sweat and humidity, keeping the folds of skin lubricated and thus avoiding friction; in facial powders to reduce the shine of talcum and increase the adherence of the preparation; and, finally, in face packs to clean the skin of grease.

Other cosmetic uses are related to their emulgent capacity, whose mechanism has already been discussed, examples being the use of palygorskite and smectite in dry shampoos, which are widely used in North African countries.

They can also be used as protection against external agents, in particular solar radiation, as proposed by Del Hoyo *et al.* [154], who determined the capacity of phenyl-salicylate complexes in sepiolite to prevent sunburn. In cosmetic preparations the clays act as a physical barrier against UV radiation, considerably increasing the protection factor of the compound. This is a question of much interest at present, given the appreciable increase in skin pathologies caused by radiation.

6 - Topical use: clays in spas

Applications of clays to the human body for therapeutic purposes (geotherapy, fangotherapy and pelotheraphy) are very ancient techniques which have become increasingly popular in recent times. The beneficial effects for particular rheumatic-arthritic pathologies and sporting injuries, as well as in dermatological and cosmetic applications, are based on the rheological properties, the high capacity for cation exchange and absorption, and the slow cooling rate of clays when properly prepared using different types of water. The term "peloid" refers to the product resulting from the mixture of a liquid phase (salt, saline or mineral-medicinal water), a solid inorganic phase (clay minerals and other minerals such as quartz, calcite, feldspars, etc.) and a third organic phase (bacteria, algae, diatomeas, protozoa, arthropods, etc.), which is applied topically as a therapeutic agent in the form of poultices or baths [6].

The preparation of thermal muds and peloids (medical and not mineralogical or geological terms) from clayey materials rich in smectites and other clays requires a process known as "maturation" affecting the clays when they are brought into contact with thermal and/or mineral water [155-160]. Traditionally, sulphurous water is used when the aim is to produce dermatological masks and bromo-iodic water for thermal treatment of bone and muscular injuries [161]. The maturing process lasts from 3 to 20 months and causes important changes technical properties of the clays, whose plasticity, absorption capacity, cooling index and grain-size alter as a result of the profound interaction between the different phases involved and the biological activity of the organisms themselves and their metabolic products. The nature of both the mineral and organic components involved is decisive for the final properties of the

therapeutic mud [7,162-166], which varies from spa to spa according to the type of clayey material used and the composition of the thermal-medicinal water.

The peloid obtained after maturation is applied to the whole body or on selected parts of the patients for 10 to 15 days at a temperature of 40-45ºC in 1 to 2 cm layers for 20-30 minute sessions. The application produces relaxing, anti-inflammatory and analgesic effects in the treated area due to vasodilation, perspiration and stimulation of the cardio-circulatory and respiratory systems. It is particularly beneficial in the treatment of degenerative arthropathies and the associated painful syndromes, bone and joint injuries, rheumatism and arthritis in different parts of the body, spondylosis, myalgia, neuralgia, chronic phlebopathy, certain skin ailments, etc. [167-169].

Although there is no specific protocol for qualification of any one "peloid" thermal mud, in recent years considerable progress has been made in this direction, particularly due to the various proposals of the Italian Group of the AIPEA [3,4]. In many spas, after the local reserves of clays are exhausted, artificial mixtures of clayey materials are used whose nature is not always clearly determined. The choice of a suitable material should be made with clear ideas as to factors such as mineral composition, chemistry, pH, grain-size, specific surface, cation exchange capacity (total and for the main cations Na^+, K^+, Ca^{2+}, Mg^{2+}), consistency parameters (liquid and plastic limits, plastic index), rheology (activity, adhesivity, viscosity, water retention), thermal behaviour (heat capacity and conductivity, cooling kinetics), and organic matter and micro-organisms content. The most suitable materials are those with a high content in swelling clay minerals, fine granulometry and a low amount of "abrasive" materials (quartz, feldspar) for a pleasant application of the "peloid" mud, good thermal, rheological and adhesive properties and a low content in hazardous trace elements and minerals (such as free silica and asbestiform minerals). In this sense, we should point out the importance of control of the contents in certain, potentially toxic trace elements and their mobility during the maturing process (such as As, Sc, Tl, Pb, Cd, Cu, Zn, Hg, Se and Sb) in order to avoid possible intoxication during treatment [164,170,171].

7 - Concluding remarks

The development of certain instrumental techniques during the second half of the 20th century led to the discovery of the enormous compositional and textural variability of clays, thus improving understanding of the different mechanisms involved in their physical-chemical properties, in particular, those related to their surface characteristics (adsorbent capacity and rheological properties). These theoretical advances, which helped understanding of the processes behind the traditional uses of clays since antiquity as natural products with therapeutic and cosmetic aims, also resulted in the development of new applications. Of all the applied sciences using these "new" materials, those concerning health seem to be where most future investigation will take place on clays, to determine their possibilities in the treatment of illnesses and in the care and protection of the human body. What is at present known, as briefly described in this survey, informs of the variety and number of applications in use and allows us to foresee important advances in the coming years, particularly in the development of new drug delivery systems. The global increase in standard of living also suggests that body care in specialized centres will become increasingly popular, involving a reconsideration of the geomaterials used in such centres, which will inevitably require a correct qualification of the materials used and the exchange mechanisms involved.

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