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Compositional, technical and safety specifications of clays to be used as pharmaceutical and cosmetic products

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Abstract

Because of their high specific surface area, optimum rheological characteristics and/or excellent sorptive capacity, certain clay minerals such as kaolinite, talc, montmorillonite, saponite, hectorite, palygorskite and sepiolite are extensively used in the formulation of various pharmaceutical and cosmetic products. Whether as active ingredients or as ideal excipients, these minerals must comply with a number of textural and compositional requirements (concerning grain size, degree of mineral purity, water content, major and trace element contents or microbial contamination) and have specific technical properties. Their safety and stability characteristics are vitally important. This paper gives a review of the different pharmacopoeias, rules and regulations affecting the use of these natural products, whose denominations in the commercial sphere vary significantly. Particular attention is also paid to the different safety aspects associated with their processing, handling and administration.

Keywords: Clay; Pharmaceutical; Cosmetic; Excipient; Specification

1. Introduction

The technological properties of clays are directly related to their colloidal size and crystalline structure in layers, meaning a high specific surface area, optimum rheological characteristics and/or excellent sorptive ability. Clays have many different applications as reviewed in the literature (Veniale, 1990; Konta, 1995; Murray, 2000, Harben, 2002, and references therein).

The use of a clay mineral for any specific application depends on both its type of structure (1:1 or 2:1 layer-type) and on its chemical composition. The different types of cations in the octahedral sheet and isomorphic substitutions in the octahedral and tetrahedral sheets result in net charge deficits, varying according to the sheet unit, and, ultimately, in different mineral phases giving rise to very varied technical behaviour. Textural differences between structurally and chemically identical minerals also affect their adsorptive and rheological properties (Lagaly, 1989; Murray and Keller, 1993; Viseras, 1997; Yebra, 2000).

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 term 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

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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", frequently used in the same sense as indicated, sometimes also 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, sediments or as alteration products of rocks, including, apart from the phyllosilicates mentioned above, lesser quantities of other minerals and/or organic products such as quartz, feldspars, carbonates, sulphates, Fe and/or Al oxides, humus, etc.

In the field of health, certain clay minerals and clays are used in Pharmaceutical Technology and Dermopharmacy as ideal excipients and as substances with suitable biological activity in the formulation of dosage forms that are either solid (tablets, capsules and powders), liquid (suspensions, emulsions) or semisolid (ointments, creams). These are used for either topical or oral administration (Galán et al., 1985; Cornejo, 1990; Braun, 1994; Kibbe, 2000; Carretero, 2002; López-Galindo and Viseras, 2004; Viseras et al., 2007-this volume, in press).

Apart from being efficient in the pharmacological or cosmetic function for which they are chosen (as abrasives, absorbents, adsorbents, anticaking agents, glidants, coating agents, opacifying agents, viscosity-increasing agents, emulsion stabilizers, binders, suspending agents, therapeutic agents, tablets and capsule diluents or lubricants), clays should also be seen to comply with a number of chemical (1), physical (2), and toxicological requirements (3) (1: stability, purity, chemical inertia; 2: texture, water content, particle size; 3: atoxicity, safety and microbiological purity), for which there are specific technical specifications for each clay and its intended use.

Although the aims are very different, clays used for pharmaceutical (treatment) or cosmetic (care and beauty) purposes are usually taken as one. However, their intended usage should be specified, as it determines both technical aspects of their preparation as well as questions regarding code of practice and legal matters. A cosmetic product is any substance or preparation intended to be placed in contact with the outside of the human body (epidermis, hair, lips, teeth, etc.) with the main, or exclusive aim of cleansing or perfuming it, changing its appearance or smell, as well as protecting and maintaining it (European Community Directive 76/768/ECC). A medicinal product, however, is a substance or combination of substances administered to humans in order to treat or prevent illness, carry out a diagnosis or restore, correct or modify disturbed physiological functions (European Community Directive 2001/83/EC).

In addition, the European Commission (Community Directive 2001/58/EC) and the Occupational Safety and Health Administration (US Department of Labor, OSHA CFR 1910.1200) establish the safety information that must accompany different products when commercialised. In the case of clays, as for other substances, such information must include an accurate identification of the substance, its main intended or recommended uses, composition/information on ingredients, hazards identification, handling and storage, physical and chemical properties, stability and reactivity and toxicological information.

This review attempts to bring together the different data, reports and regulations on clays for pharmacological or cosmetic use that have been published or made public in the media, journals or web pages not always readily available to scientists specializing in mineral science. As pointed out by Guthrie (1992), scientists in different fields (mineralogists, geochemists, doctors, pharmacists) must collaborate to meet the pressing need to have correct mineral, textural and physical–chemical identification of the different components used in formulations and correlate them with their biological effects.

2. Some generalities on clays used for health and cosmetic purposes

Of all the phyllosilicates, only some clay minerals are used in pharmacy and cosmetics, including kaolinite, talc, smectites and fibrous clays. Their specific function in any particular formulation depends on both their physical properties (particle size and shape, specific surface area, texture, color and brightness) and chemical features (surface chemistry and charge).

The *kaolin* group is a family including kaolinite, halloysite, dickite and nacrite, of which kaolinite is the most common mineral, so kaolin and kaolinite are therefore frequently confused as synonymous terms. All these minerals have a structure in which a tetrahedral silica sheet alternates with an octahedral alumina sheet, with little or no substitution, and the charges within the structural unit are balanced, having consequently low cation-exchange capacities (<15–20 mEq/100 g). Kaolinite is white, greyish-white, or slightly coloured, and becomes darker and plastic when moistened with water. It has a characteristic earthy taste, and claylike odor when wet. It is made up of tiny, thin, pseudohexagonal sheets of crystal with a variable diameter (0.2–12 μm, average around 0.6–0.8 μm), and the chemical and physical properties may be very variable (Murray and Keller,

1993). In comparison to other clays such as smectites and fibrous clays, it has a relatively low specific surface area, but it is capable of adsorbing small molecular substances, proteins, bacteria, and viruses in the surface of the particles that can be easily removed (Schiffenbauer and Sottzky, 1982; Lipson and Stotzky, 1983). General information on the most important deposits of kaolinite and other clays, as well as the genetic models proposed, markets, technical properties, etc., can be found in Evans (1993), Velde (1995), Kendall (1996), Harben (2002) and Meunier (2005). Many recent data on global production can also be found in Virta (2004).

The crystal structure of *talc* is made up of a sheet of edge-linked $MgO_4(OH)_2$ octahedra sandwiched between two identical sheets of corner-linked SiO_4 tetrahedra, sharing the apical oxygens. Pure talc is translucent, but it is more usually white or near white. It is odorless, has a flaky habit and is easily milled, becoming a bright white, unctuous micronized powder. Both the type of talc and the preparation method cause variations in the shape and particle morphology, affecting such properties as hiding power or wettability (Laurin et al., 1986; Yekeler et al., 2004). It also has very good absorption capacity for oils and greases (it is organophilic and hydrophobic). However, the mineral composition of talc deposits varies significantly depending on geological setting and the genesis of the deposit in question. It might be said that each talc deposit is unique in morphology and chemistry (Piniazkiewicz et al., 1994), which has an enormous influence on its potential uses. The most valued characteristics of a talc are its brightness, color, particle shape, crystallinity and type and presence of non-talc minerals, particularly asbestiforms such as amphiboles and serpentine.

The term *bentonite,* which is still very frequent in the business world as well as different pharmacopoeias and cosmetic manuals, is used to designate any plastic, colloidal, swelling clay, basically consisting of a *smectite*, with no regard for its origin. The basic crystal structure of smectites (an octahedral sheet between two tetrahedral silica sheets) permits several substitutions within the lattice in terms of position and element composition. There are different minerals according to the number and nature of the octahedral cations (montmorillonite, beidellite, nontronite, saponite, hectorite, stevensite, sauconite, etc.). These substitutions cause net positive charge deficiency balanced by exchangeable cations, and bond weakness can allow water and other polar molecules to enter between layers, leading to expansion of the mineral structure. Differences in origin or chemical composition of smectites can influence their technical properties, related to their fine size, high layer charge and large specific surface area. Smectites feel greasy and soap-like to the touch, they are odorless and have a slightly earthy taste. Color varies widely, from white, yellow and pink to grey or pale green. Although commercial products generally consist of a fine-grained powder (no more than 0.5% particles larger than 75 μm), aggregates are usually 50–300 μm, although the individual particles making them up are not over 2 μm. They have an ability to form thixotrophic gels with water (75–225 cP viscosity for a 5.5 w/v aqueous suspension at 25 °C, rising with increasing concentration), to absorb large quantities of water with an accompanying increase in volume of as much as 12–15 times their dry bulk, and a high cation exchange capacity in the interlayer space (100–200 meq/100 g).

Finally the *fibrous clays* group includes two minerals: *palygorskite* (often known as attapulgite, particularly in trade circles) and *sepiolite*. Unlike other clay minerals, sepiolite and palygorskite have a fibrous morphology resulting from the 180° inversion occurring respectively every six or four silicon tetrahedra, which produces a structure of chains aligned parallel to the *a* axis, each of which has a 2:1 type structure. This particular tridimensional ordering also causes open channels containing zeolitic and crystallization water. These clay minerals occur as odorless and tasteless, fine, white-colored powders that are free from grittiness. Since they are slightly hygroscopic, the amount of water can vary a lot (5–27% in palygorskite and 17–34% in sepiolite). During manufacturing, high-heat drying to remove water may be used to enhance absorbent qualities. When the fibre bundles are micronized, the resulting particles are easily dispersed in water and other polar liquids, forming a large volume network of interlaced fibres that traps all the dissolvent, causing high viscosity suspensions.

Some studies show that the morphology of sepiolite and palygorskite differs considerably in form and fibre size from one deposit to another and, indeed, even among samples from the same deposit (Nolan et al., 1991; Torres-Ruíz et al., 1992). The most usual morphology of sepiolite is planar aggregates often with filamentous edges and fibrous bundle-like aggregates. Average fibre size ranges from 1 to 2 μm in length, with only a very small proportion (<1%) of >5 μm fibres (Bellmann et al., 1997). Palygorskite crystals form planar or ball-like aggregates, similar to those of sepiolite and fibrous aggregates, less than 5 μm long, although they can exceptionally reach up to 100 μm in length. Although samples of hydrothermal origin frequently present fibres over 20 μm long, in deposits of sedimentary origin, where almost all commercial working takes place, 95% of the particles are less than 1.5 μm long (López-Galindo and Sánchez-Navas, 1989).

3. Chemical composition and impurities

The chemical composition of the natural clays used in pharmacy and cosmetics is very variable (Table 1). It is mainly linked to the geological context of the different deposits and to the frequently associated minority minerals that are not always easily detectable and whose small size makes their separation difficult. Some such as kaolinite, talc or sepiolite have small variations from the ideal composition. Others, such as smectites, have very broad compositional ranges as a result of both the considerable isomorphic substitutions occurring in their structure and also the different types of exchangeable cations that can enter the interlayer space. Finally, enormous variations have also been found in palygorskite, particularly in the MgO, Al_2O_3 and Fe_2O_3 contents, leading Galan and Carretero (1999) to suggest that this mineral is intermediate between di- and trioctahedral phyllosilicates.

The trace element contents in these clays are likewise very variable. This is true of both those traditionally considered as toxic (As, Sb, Cd, Co, Cu, Pb, Ni, Zn, Hg, Se, Te, Tl, Ba, etc.), and other less dangerous elements (Li, Rb, Sr, Cr, Mo, V, Zr, REE). Trace elements can be located in the structure of clay minerals or their accompanying accessory phases, or adsorbed on clay particles. In this last case, mobilisation and transference to leaching solutions is considerably easier. Correct characterization of the product should therefore be accompanied by a detailed account of its trace element content, as for instance in Kogel and Lewis (2001), who provided precise data on the different elements present in the kaolinite, palygorskite, montmorillone and hectorite of the Clay Minerals Society Source Clays.

Before usage, raw materials require different concentration processes to increase the purity of the main phase and eliminate most of the accessory minerals. Kaolinite, for example, is often accompanied by phases such as quartz, feldspar, mica, ilmenite, rutile, or pyrite, which mainly concentrate in the coarse fraction of the rock and are eliminated in separation plants by screening and elutriation. Others, such as hematite, calcite or magnesite, can be removed with an electromagnet or by treatment with hydrochloric and/or sulphuric acid.

Depending on the original deposit, talc may be associated to variable amounts of other minerals, mainly tremolite, anthophyllite, serpentine, quartz, chlorite, hematite, dolomite, calcite and magnesite. Talc is sometimes concentrated by visual (hand) sorting techniques, then pulverized before being subjected to flotation to remove asbestos (tremolite), carbon, and other non-desirable minerals. Some of these impurities can remain when

Table 1
Chemical composition (in %) found in clay minerals commonly used in pharmacy and cosmetics

	Kaolinite		Talc		Montmorillonite		Saponite		Hectorite		Palygorskite		Sepiolite	
	(1)	Range	(2)	Range	(3)	Range	(4)	Range	(5)	Range	(6)	Range	(7)	Range
SiO_2	46.55	44.6–46.4	63.37	60.7–63.9	51.14	51.2–65	40.46	39.6–54.7	53.68	53.6–55.9	55.03	51–59.1	55.65	52.4–54.8
Al_2O_3	39.49	38.1–39.5		0.2–2.4	19.76	15.2–34	10.15	3.9–10.2	0.60	0.1–1.1	10.24	2.2–17.5		0.2–1
MgO		0.1–0.2	31.88	31.0–32.9	3.22	0.1–7.4	20.71	15.8–33.3	25.34	24.9–25.4	10.49	6.1–17.8	24.89	21.3–24.5
Fe_2O_3		0.1–0.2		0.6–1.9	0.83	0–13.6	3.56	0.2–12		0–0.05	3.53	0–4.2		0.1–3
FeO				0–0.9		0–1.61	4.89	0–7.8		0–0.7		0–3.8		0–0.9
CaO		0.1–0.2		0.1–3.9	1.62	0–4.2	1.94	0–2.9	0.52	0–0.5		0–2.3		0–0.8
Na_2O		0–0.1		0–0.02	0.11	0–3.7	0.25	0–0.7	3.00	0.9–3		0–0.7		0–0.3
K_2O		0–0.2		0–0.4	0.04	0–1.8	0.32	0–0.3	0.07	0.05–0.4	0.47	0–0.8		0–0.03
TiO_2		0–1.4		0–0.13		0–2.9		0–0.4		0–0.4		0–1		
Mn_2O_3														0–3.1
MnO							0.24	0–0.3				0–0.6		0–3
Li_2O									1.12	0.4–1.2				
F										3.2–6				
H_2O^+	13.96	13.8–13.9	4.75	3.6–4.8	7.99	7.2–10.5	4.24	4.2–12	8.24	5.6–8.3	10.13	9–14.5	19.46	9.2–10.7
H_2O^-		0–0.7		0–0.2	14.81	6.8–17.9	13.33	7.2–17.4	7.28	7.2–9.9	9.73	6–11.5		7.9–13.8

Range composition from Weaver and Pollard (1973), Newman and Brown (1987) and Harben (2002).

(1) Ideal composition, H_2O as total: $Al_2\ Si_2\ O_5\ (OH)_4$.

(2) Ideal composition, H_2O as total: $Mg_3\ Si_4\ O_{10}\ (OH)_2$.

(3) Montmorillon, France (Anthony et al., 1995): $(Al_{1.68}\ Mg_{0.36}\ Fe^{3+}_{0.04})\ (Si_{3.90}\ Al_{0.10})\ O_{10}\ (OH)_2\ (Na_{0.02}\ Ca_{0.14})\ 1.02\ H_2O$.

(4) Saponite, Cáslav, Czech Republic (Anthony et al., 1995): $(Al_{0.10}\ Mg_{2.37}\ Fe^{2+}_{0.32}\ Fe^{3+}_{0.21})\ (Si_{3.16}\ Al_{0.84})\ O_{10}\ (OH)_2\ (Na_{0.04}\ Mg_{0.05}\ K_{0.03}\ Ca_{0.16})$. $0.98\ H_2O$.

(5) Hector, California, USA (Anthony et al., 1995): $(Mg_{2.78}\ Li_{0.36})\ (Si_{3.89}\ Al_{0.01})\ O_{10}\ (OH)_2\ (Na_{0.42}\ Ca_{0.01}\ K_{0.02})$. $0.35\ H_2O$.

(6) Attapulgus, Georgia, USA (Anthony et al., 1995): $(Mg_{1.98}\ Al_{1.36}\ Fe^{3+}_{0.36})\ (Ca_{0.32}\ Ti_{0.08})\ (Si_{7.84}\ Al_{0.16})\ O_{20}\ (OH)_2\ (OH_2)_4\ (H_2O)_4$.

(7) Ideal composition, H_2O as total: $Mg_8\ Si_{12}\ O_{30}\ (OH)_4\ (OH_2)_4\ (H_2O)_8$.

used as excipient, but talc containing asbestos is not suitable for pharmaceutical or cosmetic use and the manufacturer is responsible for demonstrating that the product is free from asbestos. Precise information about the presence of these impurities can be found, among others, in Rohl et al. (1976), Blount and Vassiliou (1983), Blount (1991) and Soriano et al. (1996).

Although very pure bentonite deposits are quite common (>95% smectite), the clay often has to be processed to remove grit and non-swelling phases, such as illite, kaolinite, and non-argillaceous minerals, such as quartz, feldspars or pyroxenes. Cristobalite is often also present. After processing, the different fractions and sizes are dried to form a small flake and then microatomized to form various powder grades.

Finally, fibrous clays are normally associated with carbonates (calcite and/or dolomite), quartz, mica and smectites. Accessory quantities of amorphous silica, feldspars, kaolinite, gypsum, zeolites, apatite and halite are also frequently found. Sepiolite deposits can be up to 95% pure, whereas it is rare to find levels with more than 75% palygorskite.

4. Pharmaceutical and cosmetic denominations

There is a considerable variety in the terminology of European, American, British and Japanese pharmacopoeias and cosmetics manuals, and some ambiguities between mineralogical, chemical and pharmaceutical names can be observed. There are even different CAS Registry Numbers (assigned by the Chemical Abstracts Service of the American Chemical Society) for apparently equivalent substances. Table 2 summarises the clays included in well-known pharmacopoeias: European Pharmacopoeia (EP 4th, 2002), the United States Pharmacopoeia (USP 29-NF 24, 2006), and British Pharmacopoeia (BP, 2004) with their CAS and EINECS numbers (European Inventory of Existing Chemical Substances), chemical names and some of most usual synonyms and commercial correspondences.

Some of the official monographs and definitions found in these pharmacopoeias and also in Rowe et al. (2003) and Sweetman (2006) are clear and specific. Thus, "Kaolin" is a purified, natural, hydrated aluminum silicate of variable composition, "Talc" is a purified, powdered, selected, natural, hydrated magnesium silicate, "Bentonite" is a natural clay containing a high proportion of montmorillonite, a native hydrated aluminium silicate in which some aluminium and silicon atoms may be replaced by other atoms such as magnesium and iron, "Purified bentonite" is a colloidal montmorillonite that has been processed to remove grit and non-swellable ore components, and "Bentonite magma" is a mixture of 50 g of bentonite and 1000 g of purified water.

However, there is some confusion regarding the term "Magnesium aluminum silicate" (called "Aluminium magnesium silicate" by the EP), used to refer to a mixture of colloidal montmorillonite and saponite processed to remove grit and non-swellable ore components. However, the USP also says that "Activated attapulgite" is a highly heat-treated, processed, native magnesium aluminum silicate, and "Colloidal activated attapulgite" is a purified native magnesium aluminum silicate. In some revisions and manuals (see Elmore, 2003; Rowe et al., 2003) the term is used in the first sense, in identification with the commercial product called Veegum®. This product has even been designated by the Food and Drug Administration (FDA) as a raw material (FD CRMCS n° R0010045) and CAS Registry number 12199-37-0, which is generic for the smectite group. On the other hand, the BP correctly defines "Attapulgite" as a purified native hydrated magnesium aluminium silicate, basically consisting in the clay mineral palygorskite, and "Activated attapulgite" is the same product, carefully heated to increase its adsorptive capacity.

More confusion surrounds the use of the term "Magnesium Trisilicate", which is applied to a blend of Si and Mg oxides prepared to meet the pharmacopoeia requirements. USP requires not less than 20% w/w MgO and not less than 45% w/w SiO_2, whereas EP indicates not less than 29% w/w MgO and not less than 65% w/w SiO_2. Although the product can be prepared artificially, it is stated (Anonymous, 1998; Rowe et al., 2003) that it "occurs in nature as the mineral sepiolite", and several data bases consulted on the web used "magnesium trisilicate" and "sepiolite" as synonyms (for instance, the Comparative Toxicogenomics Database or the Canadian Centre for Occupational Health and Safety). USP also carries one monograph on "Magnesium Trisilicate Tablets", specifying no less than 90% and not more that 110% of the labeled amount of $Mg_2Si_3O_8$, and two other monographic articles, "Alumina and Magnesium Trisilicate Tablets" and "Oral suspensions", stipulating no less than 90% and not more that 110% of the labeled amount of magnesium trisilicate ($Mg_2Si_3O_8$) and aluminum hydroxide [$Al(OH)_3$].

In addition, information on the use of ingredients in cosmetic formulations is available from different manuals and organisms. The current FDA database (2001) indicates that "talc" is included in about 2000 formulations of some 45 different cosmetic product categories, "magnesium aluminum silicate" appears in more than 600 commercial products, "kaolin" in more than 50, "bentonite" in almost 100, "hectorite" in around 20 and "attapulgite" in

Table 2
Pharmaceutical, mineral, chemical and commercial correspondences among clays used in Pharmacy and Cosmetics

Mineral name				Pharmacopoeial name	General chemical denomination, and CAS and EINECS numbers	Other CAS registry number(s)			Other usual and common brand names
1:1		Kaolinite		Kaolin, Heavy (EP 4th)	Hydrated Aluminum silicate	1318-74-7			Kaolin, Altowhites, Bentone, Bolus alba
				Kaolin (USP 29)	1332-58-7				China clay, Electros, Emathlite, Fitrol, Glomax
					310-127-6				Hydrated Aluminum Silicate, Hydrite, Kao-Gel
2:1		Talc		Talc (EP 4th and USP 29)	Hydrated magnesium silicate	11119-41-8	12420-12-1	37232-12-5	Agalite, Emtal, Finntalc, French chalk, Micron
					14807-96-6	99638-63-8	110540-41-5		white, Mistron, Snowgoose, Soapstone, Steatite
					238-877-9				Steawhite, Talcum
	Smectites	Dioctahedral	Montmorillonite	Bentonite (EP 4th and USP 29)	Hydrated sodium calcium aluminum silicate	1318-93-0	11004-12-9	70892-59-0	Amargosite, Bentonite, Albagel, Colloidal clay
				Purified bentonite (USP 29)		68333-91-5, bentonite, lime-activated			Magbond, Otaylite, Stolpenite, Tixoton, Volclay
					1302-78-9	70131-50-9, bentonite, acid-leached			Wilkinite, Mineral soap, Soap clay, Taylorite
					215-288-5	98561-46-7, bentonite, acid-activated			Polargel, Veegum HS
						85049-30-5, bentonite, sodian			
		Trioctahedral	Saponite	Aluminium magnesium silicate (EP 4th)	Hydrated aluminum–magnesium	66732-77-2			Afrodit, Auxit, Cathkinit, Lucianite, Magnabrite
				Magnesium aluminium silicate (USP 29)	silicate 1319-41-1				Piotine, Soaptone (in part), Veegum
			Hectorite		Hydrated sodium magnesium lithium silicate 12173-47-6; 235-340-0				Ghassoulite
2:1, Inverted ribbons	Fibrous clays		Palygorskite	Attapulgite (BP 2004)	Hydrated magnesium aluminum silicate	12174-28-6	1337-76-4	37189-50-7	Attapulgite, Activated Attapulgite, Attaclay
				Activated or colloidal attapulgite (USP 29)		61180-55-0	64418-16-2	71396-54-8	Attacote, Attagel, Attapulgus clay, Attasorb
					12174-11-7 302-243-0	137546-91-9			Diluex, Permagel, Pharmasorb-colloidal, Zeogel
			Sepiolite	Magnesium trisilicate (EP 4th and USP 29)	Hydrated magnesium silicate	1319-21-7	12639-43-9	14987-04-3	Magnosil, Meerschaum, Parasepiolite, Petimin
					18307-23-8	15501-74-3	39365-87-2	53664-61-2	Silicic acid, Hydrated magnesium salt, Sea foam
						61045-54-3	61180-58-3	63800-37-3	Milcon, Hexal, Pangel, Pansil, Quincite
						64418-10-6	69423-69-4	83271-15-2	

10. The term "Fuller's earth" is also present in 3 formulations of the same database, although it is not clear whether it refers to calcium montmorillonite, as is normally understood, or to fibrous clays, as US usage has it. Finally, the use of some quaternary ammonium compounds is mentioned, such as "Quaternium-18 bentonite", used in 221 products, and "Quaternium-18 hectorite", in 176 products. However, neither "montmorillonite" nor "magnesium trisilicate" are mentioned as such, although they are in the treatise on cosmetic ingredients published by Wenninger et al. (2000). *Japanese Comprehensive Licensing Standards by Category* (CLS) (Rempe and Santucci, 1998) includes "aluminum magnesium silicate", "bentonite", and "kaolin" in all product categories. Other clays such as "montmorillonite" and "hectorite" are listed in all categories, except eyeliner preparations (the former) and eyeliner, lip and oral preparations (the latter), and "pyrophyllite", not cited until now, is listed in all groups except eyeliner, lip, oral, and bath preparations. All the names cited above, except "Fuller's Earth", can also be found in the inventory of ingredients used in cosmetic products approved by the European Commission (Decision 96/335/EC).

The Cosmetic, Toiletry, and Fragrance Association (CTFA) provides information from the industry directly to the Cosmetic Ingredient Review (CIR) on the current concentration of use, which can range from 0.5% to 84% of clay, depending on the purpose (see Elmore, 2003).

5. Pharmaceutical and cosmetic specifications

For the clays and monographs mentioned above, the cited pharmacopoeias include different tests to be carried out before use. The most significant are those concerning the correct identification of the product, acidity or alkalinity, microbial limit, water content, quantity of acid-soluble substances, presence of impurities, some chemical limitations and technical properties (Table 3). The table shows occasional small differences in the maximum limits permitted for some of the variables. Also, some data are not always comparable, given that the experimental conditions indicated can be different, as in the case of loss on ignition (determined at 550–600 °C in kaolinite, 900 °C in sepiolite (only in EP) and 1000–1100 °C in talc, bentonite and palygorskite. For this last mineral an additional content of "volatile matter" is included, to be determined at 600 °C. These specifications can sometimes be completed with others used for cosmetic products (Nikitakis and McEwan, 1990; Wenninger et al., 2000), although the figures are usually of the same order.

Generally speaking, we must refer to the degrees of mineral and microbiological purity, as use of good quality raw material is one necessary requirement. Regarding the first of these, and due to its extraordinary abundance in the earth's crust, particular attention is paid to crystalline silica (mainly quartz and to a lesser extent cristobalite), as it is usually present in all clay deposits. Crystalline silica should therefore 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, 1997a). Unless processing is able to reduce the crystalline silica content to less than 0.1%, the products require labeling and other forms of warning in the safety information. 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). Control of contamination by microorganisms is also extremely important, given that they can be the origin of diseases or may cause spoilage of the medicaments (Russell, 1988; De la Rosa et al., 1995). Since clays can be contaminated during processing and storing by *Bacillus anthracis*, *Clostridium tetani*, and *Clostridium welchii*, they may be sterilized by heating at over 160 °C for not less than 1 h, or by exposure to gamma radiation (Bubik, 1992).

Once processed, the clays are stable indefinitely when stored under dry conditions, and over a wide pH range. Due to the capacity of some to absorb water or other organic substances, they should be stored in a well-closed container, in a cool, dry place.

5.1. Some particularities

Special attention has been paid to the regulation of the use of *talc,* as it is a very common pharmaceutical and cosmetic ingredient used in manufactured drug products (Gilbertson, 1995). Specific tests should be carried out (USP and EP mention X-ray diffraction and infrared spectrophotometry) to control the presence of asbestiform minerals (amphiboles and serpentines). Apart from the specific requisites included in Table 3, cosmetic grade talc must have very high purity fineness (0.1% max. retention on 150 micra IS sieves) and color should not change when heated to 200 °C. The degree of milling required varies from 200 mesh (74 μm) for body powders, to 325 mesh (44 μm) for general cosmetic and pharmaceutical formulations, and 400 mesh (37 μm) for specialized cosmetics applications such as pressed powders (Zazenski et al., 1995).

Some important properties for particular applications of *smectites*, such as their use as suspension agent, are the sedimentation volume and swelling power. In fact, in

Table 3
Pharmacopoeial specifications for clays as indicated in EP 4th and USP 29 (and also BP 2004 for attapulgite)

					Smectites				Palygorskite			Magnesium trisilicate	
	Kaolinite		Talc		Bentonite		Mg Al silicate		USP 29		BP 2004	(Sepiolite)	
	EP 4th	USP 29	EP 4th	USP 29	EP 4th	USP 29	EP 4th	USP 29	Coloidal act.	Activated		EP 4th	USP 29
Granulometry													
Fineness of powder						Yes			Yes	Yes	Yes		
Coarse particles					≤ 0.5%								
Impurities													
Acid-soluble substances	≤ 1%	≤ 2%							≤ 15%	≤ 25%	≤ 12.5%		
Water-soluble substance			≤ 0.2%	≤ 0.1%							≤ 0.5%	≤ 1.5%	≤ 1.5%
Absence of asbestos			Yes	Yes									
Carbonate		Yes							Yes	Yes			
Organic volatile impurities	Yes	Yes				(2)			(2)	(2)			
Residual solvents		Yes		(2)		(2)		Yes	(2)	(2)			(2)
Water content													
Loss on ignition		≤ 15%	≤ 7%	≤ 7%					17–27%	4–12%	15–27%	17–34%	17–34%
Loss on drying (105–110 °C)					≤ 15%	5–8%	≤ 8%	≤ 8%	5–17%	≤ 4%	≤ 17%		
Volatile matter (600 °C)									7.5–12.5%	3–7.5%			
Chemical limitations													
Al			≤ 2%	≤ 2%			95–105 % (1)	Yes					
Ca	≤ 250 ppm		≤ 0.9%	≤ 0.9%									
Fe		Yes	≤ 0.25%	≤ 0.25%									
Mg			17–19.5%	17–19.5%			95–105% (1)	Yes				Yes	Yes
SiO_2												Yes	Yes
SiO_2/MgO													2.1–2.37
As						≤ 5 ppm	≤ 3 ppm	≤ 3 ppm	≤ 2 ppm	(2)	≤ 8 ppm	≤ 4 ppm	≤ 8 ppm
Pb		≤ 10 ppm	≤ 10 ppm	≤ 10 ppm		≤ 40 ppm	≤ 15 ppm	≤ 15 ppm	≤ 10 ppm	(2)			
Heavy metals	≤ 50 ppm				≤ 50 ppm						≤ 20 ppm	≤ 40 ppm	≤ 30 ppm
Chloride	≤ 250 ppm											≤ 500 ppm	≤ 550 ppm
Sulfate	≤ 0.1%											≤ 0.5%	≤ 0.5%
Microbial contamination (cfu/g)	≤ 1000	(2)			≤ 1000	(2)	≤ 1000	≤ 1000	(2)	(2)			
Aerobic bacteria (topical adm.)			≤ 100	≤ 100									
Aerobic bacteria (oral adm.)			≤ 1000	≤ 1000									
Fungi (topical adm.)			≤ 100/g	≤ 50									
Fungi (oral adm.)				≤ 100									
Technical properties													
pH	Yes		7–9	Yes	Yes	9.5–10.5	9–10	9–10	7–9.5	(2)	7–9.5	Yes	
Swelling power	Yes				≥22 mL	≥24 mL							
Adsorption power	Yes								Yes	(2)	5–14%		
Plasticity													
Sedimentation volume					≤ 2 mL								
Viscosity								Yes					
Acid-absorbing capacity												≥100 mL/g	140–160 mL/g

YES: There is a specific test to be done or a mention to this characteristic.
(1) Percentage of the labeled amount.
(2) It meets the requirements.

the Magnesium aluminum silicate monograph, the USP differentiates 4 types of this clay depending on its viscosity and the aluminum/magnesium ratio.

It is known that some clays used in pharmacy can interact with other components of a formulation, affecting the bioavailability of the drug, i.e., the amount and speed with which the active agent appears in the blood after oral or topical administration, and which should therefore be taken into account (see Elmore, 2003; Rowe et al., 2003, 2006 and references therein). For example, it has been reported that the concomitant administration of drugs with *kaolinite*, such as amoxicillin, ampicillin, atropine, cimetidine, clindamycin, digoxin, phenytoin, quinidine, and tetracycline could reduce drug absorption and should be avoided. Equally, it has been shown that *smectites* can adsorb amphetamine sulfate, tetracycline, tolbutamide, warfarin sodium, and diazepam. 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 (Cerezo, 2003; Aguzzi et al., 2007-this volume). Fibrous clays can also interact with some drugs. For instance, palygorskite may decrease the biovailability of loperamide and riboflavin, and "magnesium trisilicate" (sepiolite) that of mebeverine hydrochloride, proguanil, norfloxacin, sucralfate or tetracycline, or the dissolution rate of folic acid or paracetamol may be retarded.

By way of example, several pharmacological tests carried out on certain clays can be found in Gamiz et al. (1992), Soriano et al. (1998), Viseras and López-Galindo (1999) and Viseras et al. (2007-this volume, in press).

6. Other health and safety specifications

Exposure of the general population to low clay concentrations is constant, although these products are generally regarded as non-toxic and non-irritant. Like most other dusty materials, clays can cause mechanical irritation to the eyes, with redness, watering and pain after contact, and mucous membrane and respiratory irritation after inhalation. Talc may also cause severe respiratory distress in infants. Moreover, when in contact with the skin clays may cause drying in some individuals, and swallowing large amounts may cause gastrointestinal irritation. So they must be handled in well-ventilated areas using methods that minimise dust generation.

However, long-term exposure to talc or kaolinite, as in the case of workers involved in the mining and processing of clays, may lead to specific pneumoconiosis, known as talcosis and kaolinosis. The numerous studies on the possible toxicity associated with occupational exposure to mineral dusts (see, for instance, Wagner et al., 1996; Love et al., 1999, and references therein) show that risk seems to exist only when respirable dust levels are significantly higher than normal consumer exposures. Inhaled smectite is likely to be less dangerous to humans than kaolin.

Material safety data sheets accompanying the different commercialized clays include relevant information. Permissible Exposure Limit values for clays range from 1 to 5 mg/m^3 respirable, and 5 to 10 mg/m^3 inhalable by a time weighted average of 8 h (Health and Safety Executive EH40 /2002). These amounts are around 350 times higher than the worst-case consumer use of cosmetic-grade talc and a similar consideration can be made for the other clays (see revisions made by Zazenski et al., 1995; Adamis and Williams, 2005).

On the other hand, and given the enormous textural and compositional variability of clays, general studies aimed at their health-hazard evaluation should analyze samples from different types of deposit (Nolan et al., 1991; Lin and Peck, 1994; Bellmann et al., 1997). The crystalline silica content will often be the decisive factor in clay-induced adverse health effects. In the specific case of fibrous clays, and although this is not a specific requirement of any pharmacopoeia, particle size must be carefully controlled because of its possible biological effect. Results of studies in experimental animals (Stanton et al., 1981; Be'gin et al., 1987; Jaurand et al., 1987; Pott et al., 1987; Wagner et al., 1987) suggest that carcinogenicity is dependent on the proportion of long fibres (>5 μm) in the samples. The International Agency for Research on Cancer classifies long palygorskite fibres (>5 μm) as Group 2B (possibly carcinogenic to humans) and short palygorskite fibres (<5 μm) as Group 3 (they cannot be classified as to their carcinogenicity to humans) (IARC, 1997b). Studies carried out on humans exposed to sepiolite seem to bear out the fact that exposure to this mineral involves no risk (Baris et al., 1980; McConnochie et al., 1993; Governa et al., 1995), and this mineral is also classified as Group 3 (IARC, 1997c).

Regarding potentially toxic trace elements such as As, Cd, Hg, Pb, Te, Tl, Sb and Se, Tateo et al. (2001) simulated digestive processes with 14 different herbalist's clays found on the Italian market and suggested for human internal use, and Mascolo et al. (1999, 2004) carried out *in vivo* experiments on their mobility. The former observed that these trace elements are present in low concentrations after digestion, but pointed out that ingesting clays without knowledge of their composition may be dangerous. The latter analyzed the concentration of these trace elements in rats' urine, kidney, liver, heart and brain, and similarly suggested that the use of clay products in health must be legally bound due to their side effects.

The Cosmetic Ingredient Review Expert Panel evaluated the report prepared on the safety assessment of most used clays, except talc (Anonymous, 2003; Elmore, 2003), where a complete review is made of the biological effects caused by their usage. The report summarized the numerous studies made on processes of adsorption, absorption, distribution, metabolism and excretion of clays and the *in vitro* assays carried out with them. It also comments on some of the experiments done to test acute, short-term and subchronic oral and parenteral toxicity in animals, toxicity caused by inhalation, different types of irritation to the skin, eyes and mucous membrane and the genotoxicity and carcinogenicity of such products. Although it was shown that inhalation toxicity exists in animals – granulometry, particle shape, concentration and mineral composition having the greatest effect – it was concluded that the data available were sufficient to assess the safety of the clays used in cosmetic products, since most of the formulations were not respirable and in those that were the concentration of the product in question was very low. So, the Panel considered that any spray containing these solids should be formulated to minimize their inhalation.

More recently, Adamis and Williams (2005) carried out an in-depth report on bentonites, kaolinite and other selected clays for the International Programme on Chemical Safety (IPCS), a joint venture of the United Nations Environment Programme, the International Labour Organization and the World Health Organization. Their report provides abundant data on the various physical and chemical properties of such clays, as well as the sources of human and environmental exposure, levels of exposure, and effects on laboratory mammals and humans, concluding with an evaluation of human health risks and effects on the environment. The report recommends that when clays are used for medical and cosmetic purposes, not only the total content but also the mobility and bioavailability of potentially toxic substances in the products must be established.

Monographic meetings have been and are still held on the particular case of talc, such as those held at Bethesda (Maryland, USA) in 1994 (Carr, 1995) or Lyon (France), under the auspices of the IARC during 2006. This institution classified talc not containing asbestiform fibres as Group 3, and that containing asbestiform fibres as Group 1 (IARC, 1987), but a re-evaluation is scheduled (IARC, 2006) since in recent years talc has been extensively investigated for its carcinogenic potential, and it has been suggested that there is an increased risk of ovarian cancer in women using talc (Harlow et al., 1992; Harlow and Hartge, 1995; Cramer et al., 1999). The FDA has even been requested to require that cosmetic talc products be labeled with a warning that frequent application to the genital area significantly increases risks of ovarian cancer, and the National Toxicology Program (NTP, USA) proposed that talc (asbestiform) and talc (non-asbestiform) be listed in the 10th Report on Carcinogens as "reasonably anticipated to be a human carcinogen". However, the FDA declined to act on this petition because the evidence is inconclusive, and the Cosmetic, Toiletry and Perfumery Association (London), on the basis of the body of scientific evidence, considered the NTP's petition should be rejected. After evaluating all the available work done on animals and humans, Wehner (2002) concluded that there was insufficient experimental and epidemiological evidence for a causal association of cosmetic talc and cancer.

7. Concluding remarks

At present the legislation concerning the compositional, technical and health specifications to be complied with by the various phyllosilicates used in the pharmaceutical and cosmetics industries is sufficiently wide-ranging. As these substances vary widely in composition, texture and crystallinity, with significant effects on their properties, some of the tests included in the main pharmacopoeias may be obsolete or imprecise since they are usually qualitative or semi-quantitative. Moreover, other properties, such as specific surface area or ion exchange capacity, determine the suitability of phyllosilicates, but are rarely taken into account. Finally, there continues to be some confusion regarding the terminology used, particularly in the case of smectites and fibrous clays.

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