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Characterisation of northern Patagonian bentonites for pharmaceutical uses

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Abstract

This paper evaluates the suitability of some smectite-rich samples from northern Patagonia (Argentina) for pharmaceutical use. The clays must comply with some general features before considering their use in pharmacy, including high mineral and chemical purity and the absence of microbial pathogens. Specific characteristics such as sediment volume, swelling power and gel formation are also important for particular applications such as their use as suspending agent. The mineralogical and chemical compositions of the samples are typical of bentonites, mainly consisting of montmorillonite. Considering the requisites of major pharmacopoeias for the use of silicates in pharmacy and taking into account the microbiological results, we could designate a pharmaceutically acceptable denomination for all samples, although some of them might need removal of quartz. The chemical, textural and porosimetric properties showed some differences between the samples that would affect their particular technical properties as pharmaceutical excipients. The samples could be used in pharmacy for topical applications as suspending agent. Regarding their use as adsorbents, specific sorption studies could help to discriminate their usefulness, as suggested by their high CEC values.
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Keywords: Montmorillonite; Bentonite; Aluminium magnesium silicate; Excipients; Pharmaceutical use; Patagonia (Argentina)

1. Introduction

Clays are used in the manufacture of medicines, both as excipients and actives (Browne et al., 1980; Galán et al., 1985; Cornejo, 1990; Braun, 1994; Veniale, 1997; Parfitt, 1999; Reinbacher, 1999; Kibbe, 2000; Murray, 2000; Carretero, 2002; López-Galindo and Viseras, 2004). Before considering their use and because natural clay samples may vary greatly in composition and texture, it is of crucial importance to carry out a number of specific technical and pharmaceutical tests to estimate possible uses in pharmacy and, when possible, give them a particular profile and a pharmaceutical denomination (Viseras and López-Galindo, 1999).

Despite their usefulness in pharmacy and market presence, there are certain ambiguities in the exact meaning of the terms clay and clay mineral in the field

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Fig. 1. Deposit location of the studied samples (black points).

of pharmacy. Sometimes, they are even considered synonyms or used without specification of some crucial characteristics. A reason for these ambiguities is the different terminology used by mineralogists, chemists and pharmacists. Mineral classification does not coincide with the pharmaceutically accepted denomination of the materials or with chemical terminology. The term bentonite corresponds to a rock mainly consisting of minerals of the smectite group, but from a pharmacist's point of view and on the basis of its specific pharmacopoeia monograph, a "Bentonite" is a native, colloidal, hydrated aluminium

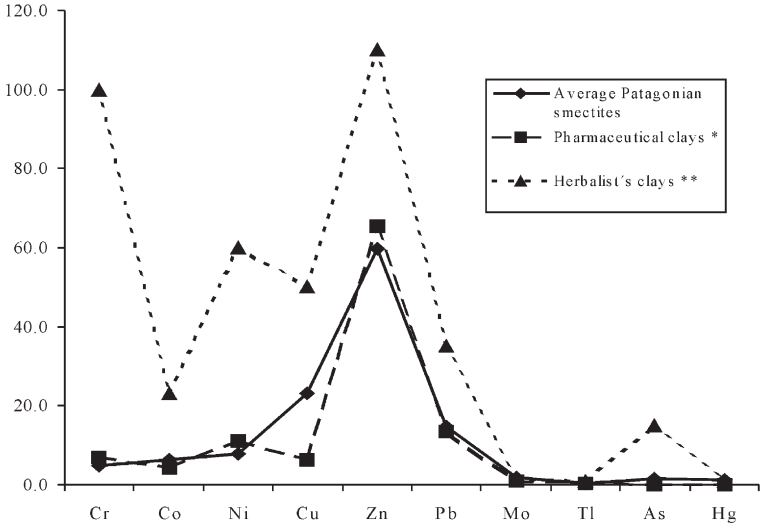

Fig. 2. Average trace elements content of the studied samples compared with those of pharmaceutical clays and Spanish herbalist's clays.

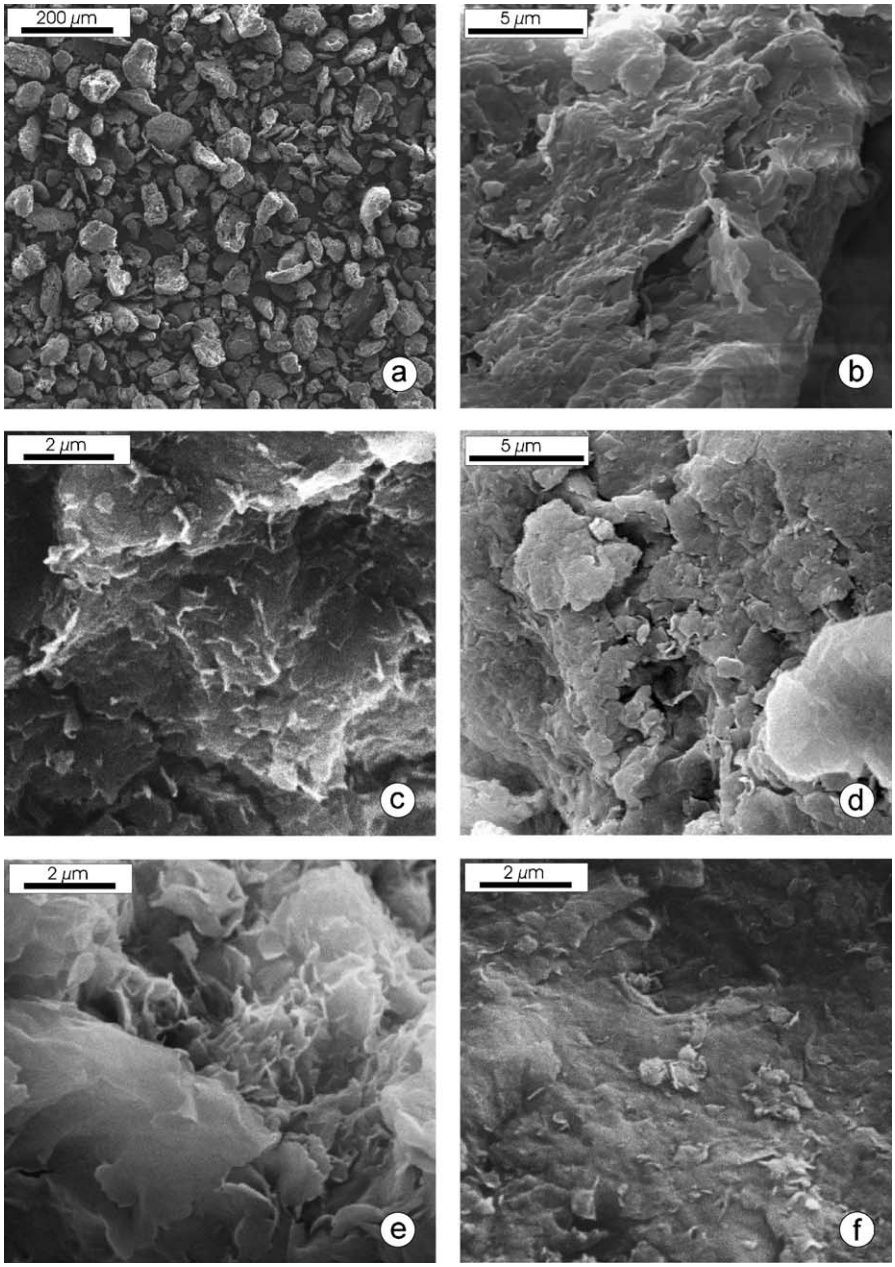

Fig. 3. SEM microphotographs of the studied samples. (a) General view of globular aggregates in sample A7; (b) detailed image of larger particle aggregates in sample A3; (c) particles with laminar habit and curled edges in sample A6; (d) particle aggregates with different shapes in sample A1; (e) spongy fabric in sample A9; (f) particle aggregates with different sizes in sample 11.

silicate (US Pharmacopoeia, 2004a), whereas "Purified Bentonite" corresponds to a colloidal montmorillonite processed by removing grit and nonswellable components (US Pharmacopoeia, 2004b), excluding other minerals of the group.

On the other hand, the term "magnesium aluminum silicate" (US Pharmacopoeia, 2004c) is also used in the pharmaceutical market, corresponding to a blend of colloidal montmorillonite and saponite, that permits the inclusion of other minerals, as is the case of some palygorskite-rich products commercialised under this denomination (Kibbe, 2000). Other similar materials such as "magnesium aluminosilicate", "magnesium aluminometasilicate" and "magnesium silicate" are defined as synthesised silicates or blends of Al, Mg and Si oxides, even if their

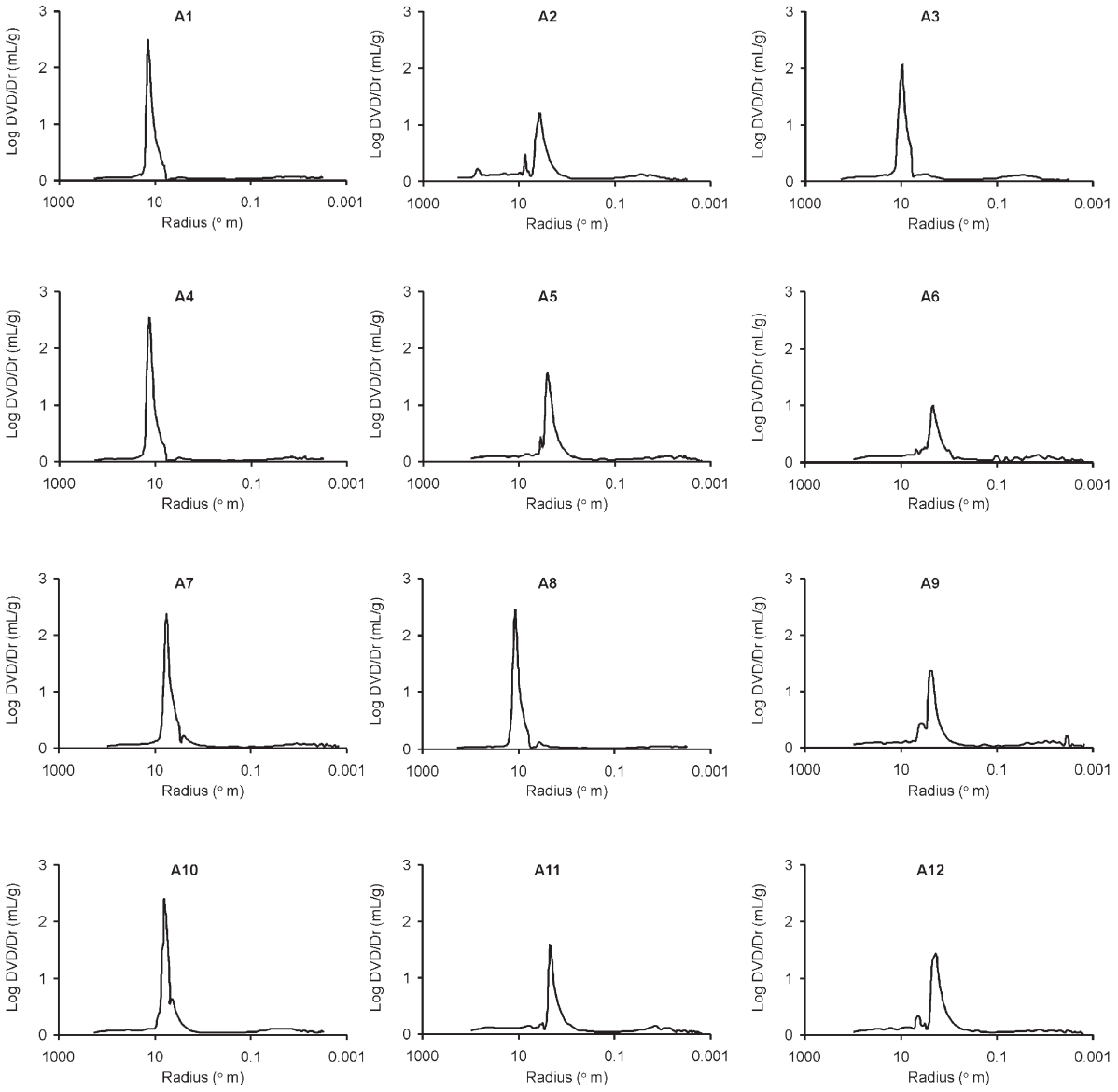

Fig. 4. Porosimetric profiles of unimodal samples.

compositions are similar to natural smectites (US Pharmacopoeia, 2004d,e,f). In Table 1, the correlations between the different mineralogical, chemical and pharmaceutical terminologies of special phyllosilicates are summarised.

Lombardi et al. (2003a) recently studied the mineralogical and chemical characteristics of a number of natural bentonite samples from deposits located in northern Patagonia and also (Lombardi et al., 2003b) their use as support agents of a proposed fungicide. These natural materials can also be used in other applications, in particular in pharmacy and, with this aim, we carried out preformulative specific analyses to determine the suitability of the studied samples for use as pharmaceutical products.

2. Materials and methods

Twelve bentonite samples from northern Patagonia, Argentina were studied. The Upper Cretaceous bentonite deposits are located in the sedimentary basin of Neuquén (Fig. 1), one of the richest areas in the country for this type of clays. They mainly belong to the so-called Allen Formation (Malargüe group), as part of its transitional littoral marine sedimentary sequences (Vallés et al., 1989; Impiccini, 1995). The most significant development of the deposits is found near Pellegrini Lake.

All samples were dried at 60 °C, sieved to 125 μm (a normal working range; below this size particle aggregates commonly form) and kept in a dry controlled environment for at least 48 h before testing.

2.1. Mineralogy and geochemistry

The mineral composition was determined by X-ray powder diffraction (XRPD), using a Philips® PW1710 with an automatic slit, Cu$K\alpha$ radiation, 3° to 60° 2θ range, with 0.05° 2θ s^{-1} steps in goniometer speed. Diffraction data were recorded by a completely computerised system using the XPOWDER® program (Martín-Ramos, in press). The percentages of the different mineral phases were calculated using data obtained by XRD and chemical analysis, following the method used by Torres-Ruiz et al. (1994) and López-Galindo et al. (1996).

Bulk chemical analyses were performed by X-ray fluorescence (XRF), using a Philips® PW1480. 1 g of each sample was thoroughly ground in an agate mortar before being pressed into an Al holder for disk preparation. ZAF (atomic number, absorption and fluorescence) correction was performed systematically (Scott and Love, 1983). The estimated detection limit for major elements was 0.01 wt.%. Because of their important biological effects, trace elements were also measured using an ICP-MS Perkin Elmer® SCIEX Elan-5000 equipment, with Rh as internal standard (5% accuracy for 5 ppm).

2.2. Microbiological analysis

Culture studies designed for microbiological examination involved transfer of colony forming units (CFU) to a nutrient medium. In all cases, clay suspensions were made up with a known amount of clay and the aggregates broken up with a Waring blender using $Na_4P_2O_7$ as dispersing agent. Serial dilutions were then made and replicate 1 ml portions were transferred to each culture medium for incubation. The presence of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans* were also determined by adjustments to media and conditions (selective media and enrichment techniques). When possible, single plate colonies were counted. The number of single colonies was equated to the number of single CFU in the suspension. If plate count was not appropriate, dilution counts were made and the highest dilution that could still provide growth was equated with the more probable number (MPN) of CFU. Five replicates were made of each inoculation for three appropriate serial dilutions.

2.3. Morphology, particle size and pore distribution

A Zeiss® DSM 950 scanning electron microscope (SEM) was used to study the morphology of the clay particles. The grain size of particles was determined by a computerised laser-beam particles analyzer (Galai® CIS-1), which measures particles up to 150 μm in diameter dispersed in a liquid (resolution 0.3% of full scale, minimum 0.2 μm). Given the planar morphology of the clay mineral particles, we chose the area distribution option of the equipment as the most appropriate.

The pore access size and surface area were then determined by mercury injection porosimetry (MIP) using a Micromeritics Autopore III model 9410 porosimeter with 414 MPa

Table 1
Mineral, chemical and pharmaceutical denomination of some smectites

Clay mineral	Pharmacopoeial name	Pharmacopoeial requirements	Chemical name and CAS registry number	Empirical formula approx.	Usual names
Montmorillonite	Bentonite (EP 4th and USP 25)	Alkalinity (acid demand), pH, heavy metals (arsenic, lead), coarse particles (fineness of powder), gel formation (sedimentation volume, swelling power, loss on drying, microbial contamination or limits), viscosity assay (Purified Bentonite)	Aluminium magnesium silicate (1302-78-9)	$(Na,K,Mg)_{0.33}(Al,Mg)_2Si_4O_{10}(OH)_2 \cdot nH_2O$	Mineral soap, clay soap, taylorite, wilkinite, Veegum HS, Albagel, mineral colloid
Group: smectites	Purified Bentonite (USP 25)		Aluminium magnesium silicate (12511-31-8)		
Subgroup: dioctahedrical					
Saponite	Aluminium magnesium silicate (EP 4th)	pH (9.0 to 10.0), arsenic, lead, loss on drying, microbial contamination. Also aluminium and magnesium assays. Viscosity and Al/Mg ratio used to distinguish subtypes.	Aluminium magnesium silicate (12511-31-8)	$(Ca,Na,K)_{0.33}(Mg,Fe)_3(Si,Al)_4O_{10}(OH)_2 \cdot nH_2O$	Veegum R-K-HV-T-F, Carrisorb, Gelsorb, Magnabites Colloidal, Colloidal complex
Group: smectites	Magnesium aluminium silicate (USP 25)		Magnesium aluminium silicate (1327-43-1)		
Subgroup: trioctahedrical					

Table 2
Mineralogical composition of the studied samples

Sample	Smectite	Quartz	Gypsum	Feldspar	Calcite	Zeolites
A1	96	2	1	1	–	–
A2	96	2	2	–	–	–
A3	94	1	1	3	1	–
A4	98	1	1	–	–	–
A5	97	2	–	1	–	–
A6	97	2	–	1	–	–
A7	96	2	2	–	–	–
A8	98	2	–	–	–	–
A9	98	1	–	–	–	1
A10	99	1	–	–	–	–
A11	95	1	1	–	1	2
A12	87	8	–	5	–	–

maximum pressure, capable of measuring pores between 0.003 and 360 μm in diameter.

2.4. Cation-exchange capacity (CEC) and individual exchangeable cations determination

Prior to conducting CEC studies, samples were washed thoroughly with deionised water to remove extraneous cations. Then, clay powders (1 g) were dispersed in 25 ml 1 M aqueous solution of tetramethylammonium bromide to displace the constituent cations. The dispersions were shaken overnight at 50 rpm in a water bath at 25.0±1.0 °C and then filtered. The cations in solution were determined by atomic absorption (Na^+, Ca^{2+}, Mg^{2+}) or atomic emission (K^+) spectroscopy (Perkin Elmer spectrophotometer 5100 mod.) and the CEC was calculated as the sum of exchangeable cations, expressed in meq/100 g dry clay.

2.5. Pharmacopoeial tests

- pH measurement: according to pharmacopoeial specifications for bentonite (US Pharmacopoeia, 2004a), the pH values of clay water suspensions (2 g/50 ml) were measured after 2 min continuous stirring.
- Sediment volumes (European Pharmacopoeia, 2002) or gel formation (US Pharmacopoeia, 2004a): supernatant volume of suspensions were prepared with 6 g of each bentonite in 200 ml of water using a high-speed mixer at 10,000 rpm and measured after 24 h repose.
- Swelling power: apparent sediment volumes in suspensions of 2 g bentonite in 100 ml were quantified after 2 h.

3. Results and discussion

3.1. Composition

The mineralogical composition of the samples is shown in Table 2. All samples are quite rich in smectite (>85%), some being almost pure (>98%).

Even though impurities are generally minimal (only sample A12 has less than 90% of the main mineral phase), it is important to consider the particular type of impurities present in each sample. In general, all samples contain quartz and most of them also other phases such as gypsum or feldspar. Low quantities of calcite and zeolites are also present in some of the samples. Crystalline silica (both quartz and cristobalite) should be controlled and avoided as far as possible in minerals intended for use as pharmaceutical materials (International Agency for Research on Cancer, IARC) because these silicas show sufficient evidence of carcinogenicity in laboratory animals and limited evidence in humans (group 1, IARC Monographs, 1997). Impurity above 2% quartz should be avoided. Consequently, sample A12 would require some treatment to reduce the amount of crystalline silica, otherwise must be excluded.

As the mineralogical compositions are rather similar, there are very few differences between the

Table 3
Chemical composition of the studied samples (in %)

Sample	SiO_2	Al_2O_3	Fe_2O_3	MnO	MgO	CaO	Na_2O	K_2O	TiO_2	P_2O_5	H_2O
A1	59.43	19.20	4.67	0.05	3.79	0.51	2.85	0.34	0.75	0.09	7.91
A2	58.63	18.99	4.42	0.03	3.07	1.28	2.65	0.25	0.45	0.12	9.59
A3	60.27	20.83	5.53	0.01	2.31	1.54	3.12	0.14	0.66	0.33	5.64
A4	59.50	18.75	4.88	0.04	3.77	0.54	2.78	0.34	0.74	0.09	6.89
A5	60.66	19.73	3.82	1.07	3.55	0.61	2.63	0.24	0.46	0.05	7.28
A6	60.19	21.11	5.56	0.01	2.57	0.84	2.93	0.17	0.60	0.24	5.84
A7	59.68	18.64	5.32	0.02	3.45	0.99	2.86	0.62	0.30	0.08	7.42
A8	60.06	20.26	3.60	0.02	4.12	0.20	2.95	0.35	0.80	0.06	6.58
A9	59.90	20.59	5.76	0.14	2.86	0.28	2.80	0.12	0.79	0.08	5.95
A10	60.23	20.74	5.42	0.05	2.94	0.26	2.68	0.14	0.85	0.06	5.93
A11	62.55	20.63	4.72	0.04	3.40	0.45	2.25	0.23	0.18	0.03	5.94
A12	63.29	17.03	5.62	0.11	2.63	0.32	2.04	1.43	0.69	0.06	6.87

Table 4
Trace element content (ppm) in the studied samples

Sample	Cr	Co	Ni	Cu	Zn	As	Mo	Hg	Tl	Pb
A1	5.65	10.56	12.82	40.59	28.03	0.84	1.89	0.93	0.42	11.38
A2	5.71	3.52	4.73	16.43	38.87	0.28	1.88	0.69	0.15	14.55
A3	5.23	2.56	4.90	16.27	30.88	1.02	3.43	0.62	0.05	36.25
A4	6.22	7.18	10.29	43.90	26.84	1.51	2.01	1.22	0.27	10.25
A5	5.74	4.41	8.31	23.88	99.06	0.38	2.58	1.50	0.17	12.55
A6	5.52	2.33	3.92	16.42	32.02	0.77	2.38	0.70	0.05	18.44
A7	5.46	3.07	4.56	14.19	17.93	4.02	1.34	0.83	0.26	25.52
A8	7.03	3.12	4.06	27.23	23.75	0.89	1.62	0.62	0.42	8.70
A9	3.83	21.47	4.79	24.92	36.02	0.36	0.74	1.55	0.28	7.45
A10	3.35	5.52	4.53	24.80	24.42	0.27	0.47	1.40	0.06	3.06
A11	0.52	4.54	23.60	3.91	300.05	5.28	0.40	2.08	0.10	12.04
A12	39.05	18.51	36.62	40.13	71.22	0.91	0.64	1.24	0.72	11.75

proportions of the major elements (Table 3). Taking the average of the four purest samples (A4, A8, A9, A10), the mean structural formula of smectite is as follows: $(Si_{3.88}Al_{0.12})O_{10}(Mg_{0.29}Al_{1.40}Fe_{0.25}Ti_{0.04}Mn_{0.003})(OH)_2(Ca_{0.03}Na_{0.35}K_{0.02})$, very close to that calculated by Lombardi et al. (2002). All smectites are sodium-rich montmorillonites and their chemical composition is quite homogeneous.

Attention must be drawn to the amount of Pb and As present (Table 4), the pharmacopoeial limits for "Bentonite" and "Purified Bentonite" being 40 and 15 ppm for Pb and 5 and 3 ppm for As (USP, 2004a,b). The studied samples clearly fulfill the established As and Pb limits for "Purified Bentonite". Fig. 2 shows the average trace element content of Patagonian bentonites (except for sample A12, excluded for its unusually high contents in transition trace elements, probably linked to mineral impurities), compared to the calculated average values for pharmaceutical grade 2:1 phyllosilicates taken from Mascolo et al. (1999) and Viseras and López-Galindo (1999). Finally, average heavy metal contents of Spanish herbalist's commercial clays are also included (unpublished data). As observed, the studied samples exhibit a rather similar pattern to that of pharmaceutical clays, whereas herbalist's clays present the highest quantities of Cr, Co, Ni, Cu, Zn, Pb and As, as also has been noted by Mascolo et al. (1999).

3.2. Microbiology

Microbiological studies reveal that all samples are free from pathogenic bacteria, the total amount is within the permitted amounts (Table 5). US Pharmacopeia establishes total aerobic acceptance limits of 5000 UFC/g for materials to be used in the preparation of non-sterile pharmaceutical products (US Pharmacopoeia, 2004g). None of the samples were contaminated by *E. coli*, *P. aeruginosa* or *S. aureus*. Contamination by *C. albicans* was always inside the statutory limits (US Pharmacopoeia, 2004g).

3.3. Morphology and texture

The samples consist of globular aggregates of planar microparticles (Fig. 3). Single aggregates, composed of around 2 μm single particles, do not exceed 200 μm in diameter. Almost all samples follow this general pattern. Only two of the studied samples (A7 and A12) show different morphology. The aggregates are bigger (several hundreds of microns), but the single particle constituents are morphologically similar to the other samples (Fig. 2C).

Porosity of the samples varies from 67% in sample A7 to 57% in sample A6 (Table 6).

Table 5
Results of microbial analysis (no. UFC/g sample)

Sample	Total aerobic	*E. coli*	S. aureus	P. aeruginosa	Total spores	*C. albicans*
A1	0–200	A	A	A	A	100
A2	0–200	A	A	A	A	300
A3	0–200	A	A	A	A	A
A4	0–100	A	A	A	A	A
A5	A	A	A	A	A	A
A6	A	A	A	A	A	200
A7	0–200	A	A	A	A	1000
A8	0–100	A	A	A	A	500
A9	A	A	A	A	A	100
A10	A	A	A	A	A	A
A11	200–300	A	A	A	A	A
A12	A	A	A	A	A	A

A = absent.

Table 6
Porosity parameters of the studied samples

Sample	P	As	ρ_a	ρ_r
A1	61.60	30.13	1.00	2.59
A2	59.04	34.14	0.82	2.00
A3	63.73	27.43	0.87	2.40
A4	61.88	29.41	0.98	2.56
A5	63.24	35.44	0.94	2.57
A6	56.75	34.19	0.86	2.00
A7	66.60	35.42	0.94	2.80
A8	60.38	26.41	1.03	2.59
A9	60.75	38.19	0.89	2.28
A10	58.57	40.71	0.92	2.22
A11	62.91	36.42	0.90	2.44
A12	64.72	37.05	0.83	2.36

P = apparent porosity (%); Sw = specific surface area by weight (m^2/g); ρ_a = apparent density; ρ_r = real density.

Porometric distribution is characterised by the presence of one main type of pores with $2<r<3$ μm (Fig. 4). Nevertheless, some samples (A9 and A12) show another small peak with $r>3$ μm. It is difficult to classify these pores, as the size limits chosen by different authors are arbitrary, depending on the instrumental technique used. Accordingly to the IUPAC Gold Book (McNaught and Wilkinson, 1997) and Rouquerol et al. (1999), the pores of the bentonites studied here should be considered macropores. Interparticle voids should also be considered as they were probably included in the total porosity.

The results obtained for granulometry are given in Table 7. It was observed that, except for samples A5 and A12, almost half the total particles in all smectites were under 1 μm long. The highest frequencies of such particles were found in samples A9 and A10. It must be emphasised that all particles are below 20 μm.

Table 7
Granulometry (%) of studied samples

Sample	<1 μm	1–2 μm	2–5 μm	5–20 μm
A1	63.64	18.16	16.92	1.28
A2	27.83	16.69	26.50	28.98
A3	50.55	18.62	28.05	2.78
A4	63.20	14.81	11.47	10.52
A5	28.33	16.77	40.13	14.77
A6	56.14	17.52	23.03	3.31
A7	49.61	17.78	23.85	8.76
A8	50.43	21.16	20.42	7.99
A9	76.85	14.49	8.66	0
A10	76.95	8.95	14.10	0
A11	66.84	19.53	13.63	0
A12	19.30	15.84	32.96	31.90

Table 8
Cation-exchange capacities (CEC) and individual exchangeable cations (meq/100 g) of the studied samples

Sample	Ca^{2+}	Mg^{2+}	Na^{+}	K^{+}	CEC
A1	6.24	14.98	62.42	0.46	84.09
A2	18.41	10.94	48.54	0.43	78.34
A3	4.84	5.18	53.94	0.13	64.09
A4	8.03	16.29	63.72	0.46	88.51
A5	4.19	20.33	49.15	0.00	73.67
A6	3.14	6.58	58.42	0.28	68.43
A7	12.92	11.60	46.28	0.43	71.24
A8	2.25	20.41	62.29	0.54	85.48
A9	4.54	5.43	63.20	0.23	73.40
A10	0.75	7.49	59.11	0.36	67.71
A11	3.94	10.20	47.15	0.08	61.37
A12	0.00	7.32	37.02	0.92	45.26

3.4. Exchangeable cations

Amounts of individual exchangeable cations and cation exchange capacities (meq/100 g) of the samples are given in Table 8. Similar high CEC values were measured for the samples, with exception of A12. The high CEC values in most of the samples make them suitable, a priori, for use as pharmaceutical excipients for controlled release.

In all cases, the main exchangeable cation is Na^{+}, allowing the samples to be classified as sodium montmorillonites. Low amounts of K^{+} and variable amounts of Mg^{2+} and Ca^{2+} were also present.

3.5. Pharmacopoeial requirements

The pH values of the aqueous dispersions (Table 9) meet the pharmacopoeial requirements, with values between 8.5 and 10.5. The supernatant volume prepared for sediment volume measurement or gel formation reveals only few differences between samples. The

Table 9
Properties of the water suspensions

Sample	pH values (4 g/100 ml)	Supernatant volume (3 g/100 ml)	Swelling power (2 g/100 ml)
A1	9.1±0.1	1±0.1	26±0.5
A2	9.2±0.2	0±0.5	27±1.0
A3	10.1±0.1	2±0.2	25±0.5
A4	8.8±0.1	0±0.5	24±1.5
A5	8.9±0.4	1±0.5	26±1.0
A6	9.6±0.4	1±0.1	25±1.0
A7	9.5±0.2	0±0.5	24±0.5
A8	9.0±0.1	0±0.5	23±1.0
A9	10.0±0.1	1±0.2	25±0.5
A10	10.2±0.1	2±0.3	28±1.0
A11	8.9±0.3	1±0.4	25±1.5
A12	8.7±0.1	15±1.5	12±0.5

values obtained for swelling power of the samples fell within the expected values for sodium smectites, i.e., sediment volumes higher than 20% of total and clear supernatants, corresponding to highly coagulated systems.

4. Conclusions

The suitability of the bentonites for pharmaceutical applications is established.

The studied samples have montmorillonite as main mineral phase, although some tetrahedral substitution of Si^{4+} by Al^{3+} is present. Differences in the type of the predominant phase allow us to establish their particular usefulness and appropriate pharmaceutical denomination. Despite their particular composition, these samples may be considered as pharmaceutical "bentonites", even though some could be processed to reduce the amount and/or type of impurities. In particular, sample A12 should be treated before considering its use in pharmacy, due to its high quartz and feldspar contents.

The chemical composition, and particularly the trace element content, fulfill the pharmacopoeial requirements regarding Pb and As as toxic elements. Moreover, when compared with pharmaceutical grade clays, individual heavy metal amounts showed similar values, which are much lower that those found in commercial herbalist's clays.

Both chemical composition and microbial content would allow their safe use as pharmaceutical excipients. In particular, their application in the formulation of suspensions for topical products appears as a promising field of application on the basis of the results obtained in the pharmacopoeial suspension test.

The possibility as adsorbents, able to delay drug release or to mask undesirable tastes, depends on their particular porosities and CEC. Differences in porosimetry suggest differing behaviour as supports of active molecules, as previously indicated for similar materials (Cerezo et al., 2001).

Although the samples showed very similar CEC, the differences observed in exchangeable cations could result in changes in drug retention abilities, as recently pointed out by Aguzzi et al. (2005). In consequence, specific sorption studies with drug molecules are advisable.

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