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Pharmaceutical applications of some spanish clays (sepiolite, palygorskite, bentonite): some preformulation studies

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Abstract

In this work, a pharmaceutical preformulation study of four Spanish clays (two sepiolites, one palygorskite and one bentonite) is presented, comparing the results obtained with those of three mineral products currently used in pharmaceutical technology. The results showed that the mineralogical and chemical purity of these clays is similar and even higher than that of the three commercial products. The microorganism content is inside the range required for non-sterile pharmaceutical forms. We also determined two parameters concerning the clays' suitability for use in tablet manufacture (colour and water content) and one indicating appropriateness as an antidiarrheic product (adsorption capacity of methylene blue). The clays are yellowish white in colour, although correction does not seem necessary; water content varies according to the structure of the clay and storage conditions. Adsorption capacity of methylene blue is affected by the amount of hydration water present, dehydration temperature and the type of interchangeable cation found in the clay.

Keywords: palygorskite; sepiolite; bentonite; pharmaceutical uses; excipients

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1. Introduction

The products intended for use in the preparation of medicines, whether as excipients or as active ingredients, must fulfil a number of requirements regarding safety, stability and high chemical inertia. The fundamental property for a product to be used in pharmacy is that it should be chemically and microbiologically innocuous, while other physical attributes can also be of importance, for example, taste and colour affecting acceptance by the patient, or texture and water content affecting technical processes. Silica and some phyllosilicates such as talc, kaolinite, smectites and fibrous clays are among the most widely used minerals in the composition of medicines (Hermosín et al., 1981; Alvarez, 1984; Galán et al., 1985). These minerals can either be used as they are or after diverse chemical treatments intended to bring out one particular quality in them. The special characteristics of palygorskite and sepiolite make them ideal for use as pharmaceutical excipients, or as active ingredients.

In the preparation of a liquid pharmaceutical disperse system, it is important to maintain the phases separate before use, or to obtain a system easy to disperse before administering to the patient. To reduce this instability substances known as stabilisers are added. Some kinds of laminar and fibrous clays are particularly useful as stabilisers because of their positive thixotropic nature, which means that the viscosity of the product decreases on shaking, thus facilitating administering, and after use the product returns to its structure as a gel fast enough to avoid segregation of the components. Laminar silicate gels have the handicap of being highly unstable when electrolytes are added, whereas fibrous clay gels retain their stability in the presence of high concentrations of electrolytes and ionic and non-ionic molecules, thus making them ideal for such an application (Parkhomenko et al., 1987; Fadat et al., 1988; Eriksson et al., 1990).

The use of fibrous clays in the preparation of tablets is based on their properties as binders and disintegrants. Angulo et al. (1995) showed that the binding properties of sepiolite considerably improve the durability and quality of pellets used in animal feed.

Finally, the therapeutic utility of palygorskite as an anti-diarrhoeic and antacid product, because of its high specific surface, has been known over two centuries. In Europe there are at present four specialities commercialised in a total of seven countries that include this mineral. All of these are intended for symptomatic treatment of gastrointestinal disorders. Outside the European Community we can find six specialities in the Mexican market, and another six in USA.

The aim of this paper is to determine the suitability of our samples for use as pharmaceutical products.

2. Material and methods

Two sepiolites, from Vicálvaro, Madrid (SV), and Yunclillos, Toledo (SY), one palygorskite from Turón, Ciudad Real (PCR) and one bentonite from Cabo de Gata, Almería (BG) were studied with the aim of determining their suitability as pharmaceutical products.

For comparative purposes, two fibrous clays used as pharmaceutical products [Pharmasorb® regular (PHR) and colloidal (PHC)], and one commercial bentonite (Benthopharm®, BTP) were also included in the study.

All samples were kept in a dry controlled environment for at least 48 h before testing.

Determination of mineral composition was carried out by X-ray diffraction (XRD), using a Philips® PW1710, CuK radiation and automatic slit, and by the powder method and oriented aggregates treated with ethylene-glycol, dimethylsulphoxide and heating to 550°C. The percentages of the different mineral phases were calculated using data obtained by XRD and chemical analyses, following the method used by Torres-Ruíz et al. (1994) and López-Galindo et al. (1996).

Major elements were analyzed by X-ray fluorescence, using Philips® PW1404 equipment, Cr/Au tube and Be window. Trace and rare earth elements were measured in ICP-MS Perkin Elmer® SCIEX Elan-5000 equipment, using Rh and Re as internal standards. Accuracy is 2% and 5% for 50 ppm and 5 ppm, respectively.

Clay morphology was studied using a Zeiss® DSM 950 scanning electron microscope, and particle size distribution was analyzed both in Galai® CIS-1 System laser equipment and by computerized image analysis on SEM micrographs.

Culture studies designed for microbiological examination involve 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. Medium and incubation conditions were those described in EPC (1990) and USPC (1990a,b) to estimate the total aerobic viable microorganisms. Presence of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans* were also stabilised 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 UFC. Five replicates were made of each inoculation for three appropriate serial dilutions.

Material colour, including chromatic situation and luminance, was determined by means of a spectre-radiometer (Spectroscan® PR-704/PC, Photo Research).

Thermogravimetric analyses were carried out on 1 g samples using ATG Du Pont 2100-951 equipment operating in an air atmosphere with a heating rate of 10°C/min. TG-DTA curves were obtained in the 0°C–1000°C range.

Finally, the methylene blue adsorption capacity according to USPC (1990a,b) was examined in the original samples or after drying for 24 h at 105°C and 200°C.

3. Results and discussion

3.1. Mineralogy and chemistry

Mineralogical composition of each sample is indicated in Table 1. The sepiolite samples are quite homogeneous, with a high proportion (> 90%) of the main phase. The bentonite samples were quite different, however, as shown by the presence of opal in BTP (13%) and the higher amount of aluminium smectite (95% as against 78%) in BG. There were considerable mineralogical differences between the palygorskite samples, as well as scarcity of the dominant mineral (46–73%). There was a significantly high amount of illite and calcite in PCR, of quartz in PHC and PHR and of smectites in PHR (up to 27%).

The chemical composition of samples is shown in Table 2 (major elements) and Table 3 (trace elements). The Na/Ca ratio indicates the nature of the exchange cation in the smectites. This ratio is higher in BTP than in BG, so we can classify the former as predominantly sodium* in nature, whereas BG is predominantly calcium*. On the other hand, USPC (1990c,d,e,f) points out that the Al/Mg ratio of purified bentonite should be between 3.5 and 5.5, so that BG (4.28) would be comparable to a purified bentonite, whereas BTP (8.9) would not.

Regarding the trace elements, attention should be drawn to the amount of Pb present. The pharmacopoeiae consulted (EPC, 1990; BPC, 1988a,b,c; USPC, 1990a,b) restrict Pb to 10 ppm in palygorskites and 40 ppm in bentonites. PHC, PHR, SV, SY and BTP clearly fulfil the established limit, while both BG and PCR are outside the limit. Finally, all the samples of sepiolite and palygorskite fulfil the requirements for heavy metal contents (maximum 50 ppm). No limit is established for bentonites, although the content is over 100 ppm in both cases.

3.2. Micromorphology and fibre size

Results of particle and aggregate sizes are shown in Table 4. Sepiolite mainly appears as aggregates of imbricated fibres (Fig. 1A), as planar aggregates

Table 1
Mineralogical composition of the studied samples

	Quartz	Opal	K-feldspar	Albite	Calcite	Palygorskite	Sepiolite	Al smectite	Mg smectite	Illite	Clinoptilolite
BG	1			1	1			95		2	
BTP	3	13			2			78		2	2
PCR	7		3		9	53		3	2	23	
PHC	11				5	73		7		2	2
PHR	17				6	46		15	12	4	
SV		2	2				91		3	2	
SY			2				93	1	2	2	

Table 2
Chemical composition of the studied samples

	SiO_2	Al_2O_3	Fe_2O_3	MgO	CaO	Na_2O	K_2O	TiO_2	MnO	PPC
BG	53.78	20.09	1.45	4.69	1.79	0.69	0.52	0.41	0.05	17.40
BTP	62.00	15.30	3.40	1.72	1.53	1.85	0.36	0.14	0.08	13.90
PCR	52.89	12.62	4.17	6.68	5.23	0.14	2.16	0.34	0.02	15.72
PHC	54.90	9.72	3.49	8.27	3.28	0.16	0.76	0.48	0.07	18.60
PHR	58.40	10.30	4.11	10.20	3.62	0.15	0.60	0.50	0.07	11.20
SV	56.44	1.28	0.38	23.50	0.21	0.10	0.64	0.06	0.02	17.32
SY	55.57	1.47	0.43	23.79	0.23	0.17	0.66	0.06	0.02	17.54

frequently with filamentous borders, and as filamentous–fibrous aggregates with bundle-like aspect (Fig. 1B). Palygorskite samples, on the contrary, are normally made up of rounded aggregates, 2 to 5 μm in size, with an anarchic disposition of microfibres inside them (Fig. 1C). No notable microtexture differences were

Table 3
Trace-element contents of the samples

	Li	Rb	Cs	Be	Sr	Ba	Sc	V	Cr	Co	Ni	Cu	Zn
BG	32.7	19.8	4.0	8.0	128	98	4.6	14.5	7.5	3.5	0.0	3.4	58.5
BTP	16.7	28.5	1.4	2.4	156	277	2.7	5.8	5.5	1.1	0.0	3.5	67.0
PCR	49.1	121.3	5.9	2.1	154	656	11.2	91.2	75.9	8.3	31.6	18.6	79.2
PHC	19.9	47.0	3.0	1.7	59	143	9.3	106.5	122.6	4.5	18.0	8.5	90.5
PHR	25.4	41.9	3.2	2.1	62	125	10.1	122.3	153.2	6.8	21.5	8.4	96.2
SV	117.8	61.4	2.9	1.7	28	81	3.6	21.8	16.2	2.7	1.2	8.6	32.4
SY	92.2	23.2	2.6	1.1	15	62	3.1	58.2	21.9	4.2	0.3	8.8	27.3

	Pb	U	Th	Y	Nb	Ta	Zr	Hf	Mo	Sn	Tl	Ga	La
BG	48.0	0.2	16.0	19.8	11.0	1.0	93	3.2	0.5	5.8	0.7	23.2	39.7
BTP	28.7	7.5	22.7	17.9	18.1	1.8	112	4.4	1.9	3.4	0.1	21.6	32.1
PCR	17.1	2.0	10.6	16.3	18.0	1.2	97	2.6	0.6	6.8	0.6	20.0	32.6
PHC	9.6	2.4	6.8	21.7	8.0	0.6	66	1.9	0.6	0.0	0.4	12.4	22.9
PHR	8.2	3.0	6.5	26.3	8.2	0.6	55	1.6	0.5	0.0	0.4	13.2	23.5
SV	5.1	1.8	4.8	10.0	5.6	0.6	49	1.5	0.1	0.3	0.3	6.5	10.2
SY	8.5	1.3	2.8	5.1	3.4	0.7	20	0.6	1.0	0.0	0.2	4.6	6.8

	Ce	Pr	Nd	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
BG	77.2	8.8	30.7	5.4	1.0	4.8	0.6	3.6	0.8	2.0	0.3	2.0	0.3
BTP	70.8	7.3	25.8	4.6	0.5	4.3	0.7	3.5	0.7	1.9	0.3	1.8	0.3
PCR	77.1	7.7	29.8	5.3	1.2	4.5	0.6	3.3	0.6	1.8	0.3	1.6	0.2
PHC	41.8	5.5	21.3	3.9	0.9	3.5	0.5	3.2	0.7	1.8	0.3	1.7	0.3
PHR	43.1	5.3	21.6	4.1	0.8	4.0	0.6	3.6	0.8	2.2	0.3	2.0	0.3
SV	23.1	2.7	10.4	2.1	0.3	2.0	0.3	1.8	0.4	1.0	0.1	0.9	0.1
SY	13.6	1.7	6.4	1.3	0.2	1.2	0.2	0.9	0.2	0.5	0.1	0.4	0.1

Table 4
Distribution of particle sizes of the samples

	0–1 μm (%)	1–2 μm (%)	2–3 μm (%)	3–4 μm (%)	4–5 μm (%)	> 5 μm (%)	Particle size (μm)	Aggregate size (μm)
BG	33	21	8	15	14	9	2–3	6–8
BTP	33	28	9	14	8	8	2–3	5–6
PCR	75	17	4	2	1	1	0–2	2–3
PHC	84	12	2	1	1	0	0–2	4–5
PHR	80	13	3	2	1	1	0–2	4–5
SV	84	11	3	1	1	0	0–2	3–4
SY	83	12	3	1	1	0	0–2	3–4

observed in the three palygorskite samples. Finally, both bentonites are made up of globular aggregates of planar microparticles (Fig. 1D).

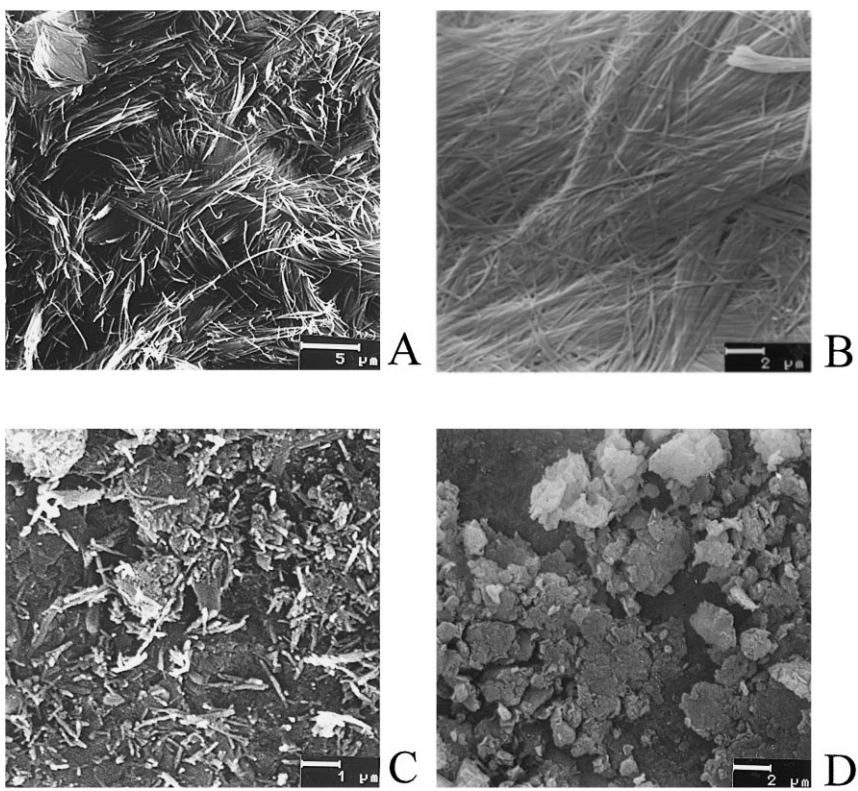

Fig. 1. SEM microphotographs showing the common textures found in the studied samples. (A) Sepiolite from Vicálvaro with an anarchic disposition of the fibres; (B) Sepiolite from Yunclillos exhibiting bundle-like aggregates; (C) Palygorskite from Turón, where little fibres and aggregates of particles can be observed; (D) Bentonite from Gádor showing how the planar particles are forming globular aggregates.

Although samples of hydrothermal origin frequently present fibres over 20 μm long (López-Galindo and Sánchez-Navas, 1989), in deposits of sedimentary origin, such as those where the samples are from, 95% of the particles are less than 1.5 μm long.

3.3. Microbiology

Microbiological studies reveal that all samples are free from pathogenic bacteria, the total amount falling within that permitted by regulations (Table 5). USPC (1990a,b) and EPC (1990) respectively establish total aerobic acceptance limits of 5000 UFC/g and 1000 UFC/g, respectively, for materials to be used in the preparation of non-sterile pharmaceutical products. Samples SY and PCR had values over these limits and should therefore be sterilized before use. None of the samples were contaminated by *E. coli*, *P. aeruginosa* or *S. aureus*. Contamination by *C. albicans* was always inside the statutory limits.

3.4. Colour

The position on the chromatic diagram (Fig. 2) and the luminance of the samples (Table 6) show that all samples have a white to yellow or cream colour, which is almost the same in the case of the sepiolites but a little whiter in the bentonites. Of all the samples PHC deviates most from perfect white.

3.5. Water content

TGA and DTG results are shown in Fig. 3. Both bentonites present similar profiles with a higher amount of initial weight loss in the case of BG, associated to hydration water. Na^+ is the interlaminar ion in BTP, whereas the main interlaminar ion in BG is Ca^{2+}. The temperature needed to eliminate hydration water from BTP is lower (144°C) than for BG (230°C). In our opinion this fact may be related to the higher link energy of divalent respect to monovalent

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

	BG	BTP	PCR	PHC	PHR	SV	SY
Total aerobic	0–200	0–100	1000	A	A	400–500	4000–5000
E. coli	A	A	A	A	A	A	A
S. aureus	A	A	A	A	A	A	A
P. aeruginosa	A	A	A	A	A	A	A
Total spores	A	A	A	A	A	A	A
C. albicans	A	200	100–300	A	A	A	200

A = absence.

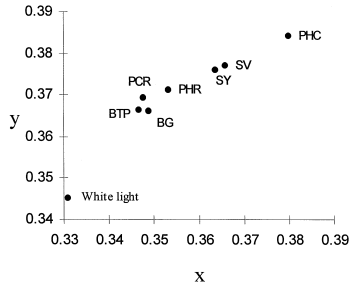

Fig. 2. Position on the chromaticity diagram of the studied samples compared to that of the achromatic point (white light).

ion–water links. Palygorskite TGA and TGD profiles showed four kinds of water: at first superficial water is eliminated, followed by zeolitic water from fibre channels, and finally, water linked to octaedric ions and water from hydroxyl groups. PCR and PHC had this typical dehydration profile, whereas PHR showed some abnormalities. Two likely reasons for these differences are possible previous treatment of the mineral and the high amount of smectite and other minerals as impurities. Finally, both sepiolite samples present very similar TGA and TGD profiles, with an initial weight loss at less than 200°C corresponding to superficial and zeolitic water, then an almost continuous weight loss (between 200°C and 350°C) associated with the elimination of water molecules linked to Mg^{2+} ions, and finally structural water loss. It must be pointed out that sepiolite does not present Al^{3+} at octaedric positions whereas palygorskite does. This explains the reduction from two stages to only one in the elimination of coordinated water.

3.6. Methylene blue adsorption

Research on methylene blue adsorption with different pretreatments leads to sample classification according to ability to adsorb the dye and, indirectly, ability to retain micro-organisms. The results shown in Table 7 correspond to the official test under pharmacopoeial regulations. We should however point out that reproducible results would only be obtained if bentonite samples were in the sodium form, and a good dispersion of the clay had been obtained. As an example, BG contains mainly calcium as exchangeable ion and it should be

Table 6
Luminous reflectance values of powder samples

	Standard	BG	BTP	PCR	PHC	PHR	SV	SY
Luminance	279	183	207	206	211	191	166	152
ρ_{n-1}	1.00	1.00	2.89	6.43	0.58	3.79	7.57	4.51

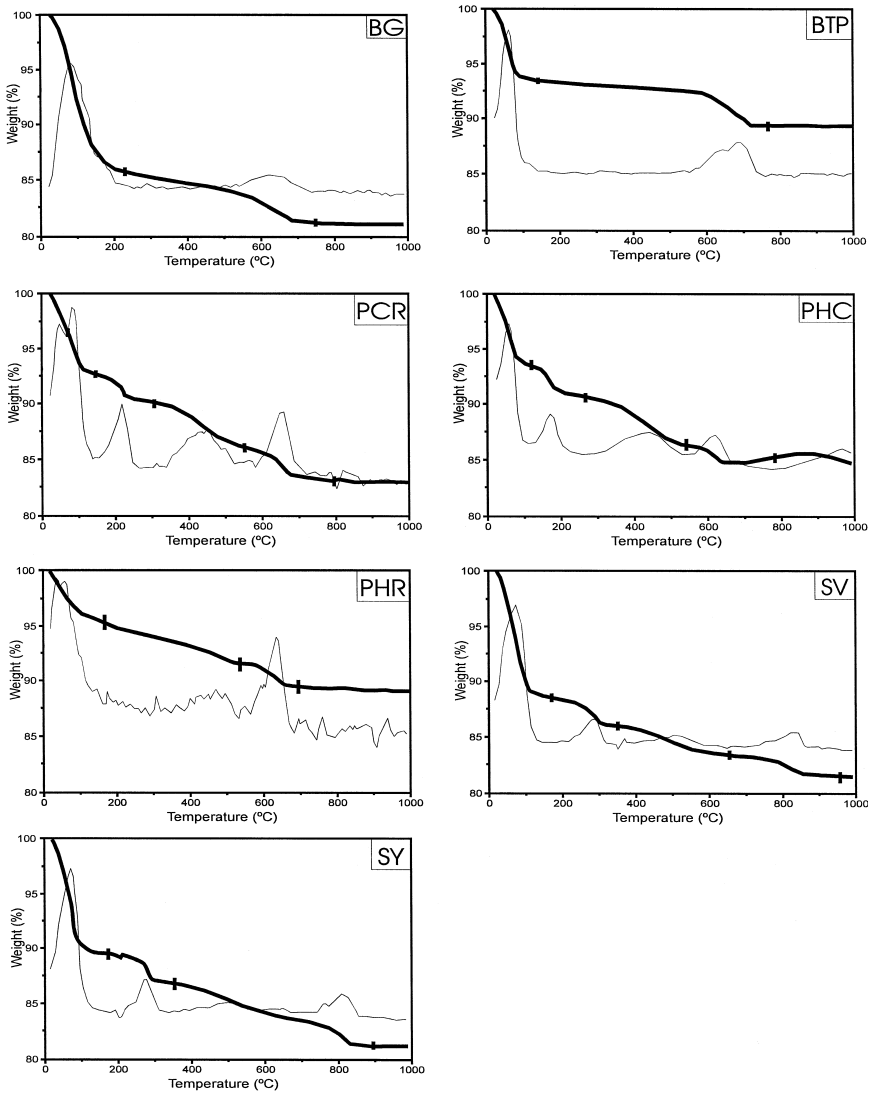

Fig. 3. TGA and TGD of the studied samples.

transformed into the sodium form before being measured. The adsorption values of sepiolite and palygorskite samples vary according to the number of surface water molecules present. When heated to 200°C these samples showed an increased adsorption capacity compared with those heated to 105°C, which in turn were more adsorbent that the original ones. This sequence was not obvious in the case of BG, where the amount of water eliminated at 105°C and 200°C is almost the same due to the Ca^{2+}–H_2O links. The first of the two water molecules linked at each Ca^{2+} is dehydrated at over 105°C, and the second at

Table 7
Methylene blue adsorption capacities of the studied samples

Samples	Relative intensity of blue
Standard solution (0.15 μg/ml)	×
BG	6×
BG (105°C/24 h)	5×
BG (200°C/24 h)	5×
BTP	6×
PCR	9×
PCR (105°C/24 h)	6×
PCR (200°C/24 h)	12×
PHC	×
PHR	4×
SV	13×
SV (105°C/24 h)	3×
SV (200°C/24 h)	2×
SY	13×
SY (105°C/24 h)	8×
SY (200°C/24 h)	5×

under 200°C. The surface area and exchange capacity of bentonite samples are highly affected by initial sample water content.

4. Discussions

Mineral products for pharmaceutical use vary according to composition, crystallinity, habit and texture, thus greatly affecting their properties. The test used by the main pharmacopoeias are either obsolete or imprecise. Sepiolite and bentonite deposits can be up to 95% pure, whereas it is rare to find levels with more than 75% palygorskite. The presence of crystalline silica 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 (Class 2A, Vainio et al., 1995).

The samples studied here have in common a fibrous and/or laminar microtexture that should be controlled, and although this is not a specific requirement of any pharmacopoeia, it is however crucial to know both the composition and the size or length of these fibres in order to determine whether they may be used in pharmacy. We must be aware of the absence of a specific regulation on the question. The control of particle size in the case of fibrous materials is highly significant because of the possible biological effects. According to our results, the samples studied have sizes clearly lower than the value generally accepted as

defining a particle as a fibre, i.e., over 5 μm in length and with a length/diameter ratio > 3:1 (Ausschuß für Gefahrrstoffe, 1988). In fact, 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).

Most pharmaceutical agents are administered as opaque solid dosage forms and, consequently, colour studies have to be made using reflectance techniques. Our interest was only in colours that can be perceived by the human eye. Regulations consulted assume colour determination on the basis of a visual interpretative measurement. This method depends on individual perception and subjective judgement. The development of an objective quantitative method for colour determination assumes the summation of selected spectral components to expressed a colour (Brittain, 1995). Accurate determination of hue, saturation and luminance (or luminous reflectance) permit objective specifications of sample colour and on this basis we can say that the colours of the samples studied can be matched. Moreover, the separation on the chromatic diagram of the x and y values from those of achromatic point (central point) is low enough to define all samples as white. The deviations are always on the yellow side of the diagram and a quantification of the distance from their respective points to that of perfect white allows us to establish an order between them.

Palygorskite is mainly used in pharmacy because of its anti-diarrhoeic properties. As regards sepiolite, it is not even mentioned as a monograph in any of the pharmacopoeiae examined by us, despite the fact that it is a very significant substitute for palygorskite in other industries (paper, drillings mud, smell adsorbents, etc.). The tests used by the consulted regulations for determination of anti-diarrhoeic properties of these minerals take methylene blue as the standard molecule to be retained. However, both the unspecified conditions of the methods proposed and the large differences between this dye and most of the biological molecules potentially involved should be revised and improved. Furthermore, use of these minerals as anti-diarrhoeic should be preceded by a better understanding of the mechanism involved in the adsorption of intestinal toxins and bacterium. Studies on the kinetics of the adsorption–desorption process of different active ingredients in fibrous clays, would doubtless lead to the development of new applications, such as controlled release forms and new transdermic release systems.

5. Conclusions

Accordingly to the presented results, it is possible to assure that the materials evaluated (BG, PCR, SV and SY) are at lest as secure as those currently used in pharmacy (BTP, PHC and PHR). Moreover, apart from their pharmacological activity, they may be included on the group of tablets excipients and consider

inoffensive when properly used (e.g., similar conditions that those of a classical pharmaceutical excipient). In the particular case of PCR some previous treatment would be required in order to reduce the amount of crystalline silica.

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