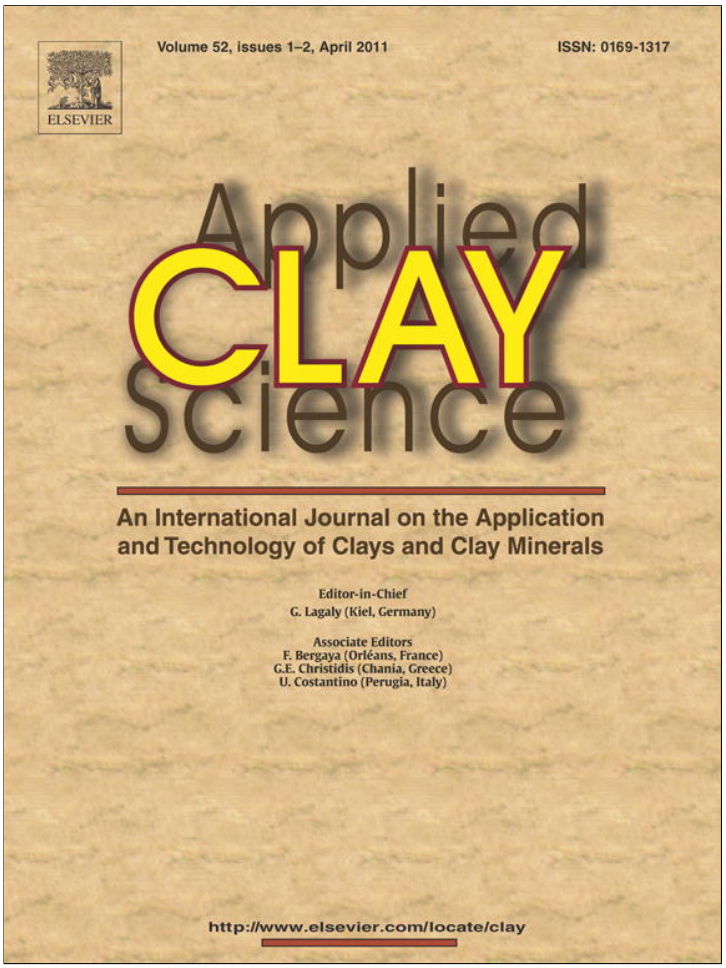

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Research Paper

Suitability of a Miocene bentonite from North Western Desert of Egypt for pharmaceutical use

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ABSTRACT

This work examines the beneficial effects for human health of bentonite, describing their use in pharmaceutical formulations. The bentonite samples must comply with some general features of pharmacopeia, including high mineral and chemical purities and absence of microbial pathogens, before considering their use in pharmacy. Specific characteristics such as sediment volume, swelling power and gel formation are also important for particular applications such as their use as suspending agents.

Mineralogical, geochemical, and microbiological analyses and pharmacopeia tests were carried out for a purified (raw and activated) Egyptian bentonite sample from North Western Desert (NWD), a Wyoming bentonite standard and a mineral currently used as a pharmaceutical product.

The X-ray diffraction data revealed that the Egyptian sample has montmorillonite as a main mineral phase. The chemical composition (ICP-MS data) and particularly the trace element content, for both raw and activated samples fulfills the pharmacopeia requirements regarding Pb and As as toxic elements. The microbial test for the studied samples revealed that they meet the specifications of the pharmacopeia microbial limit test for pharmaceutical preparations in being both free from microbial pathogens and the total number of viable aerobic microorganisms being within the allowed limit of the test.

Both raw and activated bentonites from NWD can be used after extensive purification as pharmaceutical excipients, moreover the Na-activated one can be used as an adsorbent of drugs and a drug carrier in drug release processes and in the formulation of suspension for oral products as it has a relatively high cation exchange capacity (CEC).

1. Introduction

The use of clay minerals (such as smectite, kaolinite, talc, and fibrous sepiolitic-palygorskite) for cosmetic and medical purposes has increased in the past few years, due to the increasing success of natural remedies. In particular, the medical applications of clays are well documented for internal uses (Veniale, 1997) and for the preparation of thermal mud (a poultice called peloid obtained after suitable maturation by mixing with mineral water) used in spa-centers for the therapy (pelotherapy) of rheumatism, arthritis and bone-muscle traumatic damages and for the treatment of skin diseases as acne and seborrhea (Cara et al., 2000; Sanchez et al., 2002; Veniale et al., 2007). In Egypt there is a SPA in the Safaga area, along the Red Sea Coast which uses a mix of bentonite and radioactive black sand in treatments of psoriasis and other skin diseases. Natural clay samples may vary greatly in composition and texture, so it is of crucial importance to carry out a number of specific technical and pharmaceutical tests to estimate their possible uses in pharmacy and, when possible, give them a particular profile and pharmaceutical denomination (Viseras and Lôpez-Galindo, 1999).

Bentonite has a different terminology when used by mineralogists, chemists and pharmacists. The term bentonite or bentonitic clays is used to describe mud rocks which are composed largely of smectite clays but bentonite from the pharmaceutical point of view is a naturally occurring, crystalline hydrated aluminum silicate, clay-like mineral and is available as an odorless pale buff, or cream to grayish-colored fine powder free from grit (Raymond et al., 2003). The US Pharmacopeia (2004a, 2004b) describes bentonite as a native, colloidal, hydrated aluminum silicate and uses the term purified bentonite to describe a colloidal montmorillonite that has been processed to remove grit and non-swellable compounds. On the other hand the term “magnesium aluminum silicate” is also used in the pharmaceutical market, corresponding to a blend of colloidal montmorillonite and saponite (US Pharmacopoeia, 2004c). Blends of other minerals, as in the case of some palygorskite-rich products commercialized under this nomination are permitted (Kibbe, 2000).

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Other materials such as, "magnesium aluminometasilicates" and "magnesium silicates" are defined as synthesized silicates or blends of Al, Mg and Si oxides even if their compositions are similar to natural smectite (US Pharmacopoeia, 2004d, 2004e, 2004f).

Nowadays bentonites are considered the most important type of clays involved in many types of applications due to their high specific surface area and CEC values and their ability to swell in water. The aim of this work was to study the suitability of some Egyptian bentonites to be used in new fields such as pharmaceutical and environmental applications, after physical treatment and activation of the studied sample by Na_2CO_3. The specifications of each application were carried out for both treated and untreated samples.

2. Materials and methods

2.1. Sampling area and its geological setting

The investigated area lies in the northern part of the Western Desert of Egypt. The selection of this locality was mainly based on the results of previous studies of Egyptian bentonites which indicated that the most important occurrence of bentonitic clays lies in the northwestern part of Egypt, due to the high proportion of montmorillonite content (60–90%) with the lowest amount of impurities (Egyptian General Petroleum Corporation, EGPC, 1992; Gindy and Badra, 1968; Masoud, 1983; Omara and Sanad, 1975). The bentonites in the northern part of the Western Desert occur in two main localities, south and southwest Alamein area and south of El Hammam city. These sediments are considered a part of an Oligo–Miocene sequence formed in an elongated shallow dipping basin trending E–W and extending over an area of about 115 km long and 65 km in width. (Abdel-Ghafour et al., 1997).

The samples investigated in the present work were provided by "Misr for bentonites and its derivatives company". The bentonite quarry of the company extends between latitudes (30°24′ 20″N to 30°25′ 22″N) and longitudes (29°14′ 15″E to 29°15′ 30.77″E) in the south of El Hammam city, Northern Western Desert, Egypt. The bentonitic bed inside the quarry is about 6 m thick and is confined to the Dabaa Formation (Oligocene) and the Moghra Formation (Early Miocene) and comprises mixed fluvio–marine clays (Abdel-Ghafour et al., 1997). The company is exporting such types of clays to Germany and some European countries without dressing or beneficiation. Also they buy such clays for Egyptian oil companies for use as a drilling mud.

2.2. Sample preparation and activation

The samples were collected along the bentonitic bed at an interval of one sample for each 1/2 meter thickness; the collected samples were mixed and quartered in order to form a representative sample of the whole bentonitic bed. A Wyoming bentonite (naturally sodium bentonite which contains more than 85% of montmorillonite mineral) was taken as a standard sample. A commercial product (Smecta) also was used as a pharmaceutical standard which was composed of di-octahedral smectite. This medical product is produced by Amriya for Pharmaceutical Industries, Alexandria, Egypt, under license of Beaufour IBSEN International, Paris, France. The Wyoming and Egyptian bentonite samples were prepared for investigation through hand picking, followed by wet sieving to 125 μm according to the USP/ASTM pharmacopeia and then separation of the clay fraction (using a hydrocyclone equipment) and wet magnetic separation. Both purified sample and the standard were kept in a dry controlled environment for at least 48 h and submitted for further analysis.

The representative sample was subjected to an alkali activation process to improve its properties to be suitable for some pharmaceutical applications. An activation slurry method was used. The Na_2CO_3 activator was added at various mass ratios of 2.5, 3.5, 5.5 and 10% in 100 g for bentonite in order to determine the optimum activator dose. The sample and Na_2CO_3 were added to 600 ml of boiling water; the suspension needed to be mixed well to ensure complete homogeneity. The slurry was left for about 24 h of contact time, then filtered, washed and dried at about 105 °C (Yildiz and Calimi, 2001). The changes in d-spacing and CEC were used to determine the optimum activator dose.

2.3. Mineralogy and geochemistry

The mineralogical composition was determined by X-ray powder diffraction and thermal analysis (DTA and TG). For X-ray diffraction, a Bruker D8 diffractometer, with secondary monochromatic Cu Kα as target was used. Scattering was carried out under this condition: 40 kV and 40 mA. DTA and TG were performed using a Shimadzu-simultaneous thermal analysis apparatus type DTA-50 under conditions of 0.5 g of ground sample, aluminum as inert reference and nitrogen as inert gas with a heating rate of 10–20 °C/min and water was used in the cooling system.

The chemical analyses were carried out in ACME Analytical Laboratories LTD, Canada. They were performed by a Jarrel Ash Atomcomp model 975 ICP emission spectrometer for determining the major oxides, while trace and rare earth elements were determined by a Perkin-Elmer Elan 6000 ICP emission spectrometer. The chemical analysis of the bulk sample, purified samples and standard are included in Table 1.

2.4. Microbiological analysis

The hygienic quality of bentonite samples was assured by a standard test termed as the "microbial limit test". The test includes a quantitative test involving the determination of the total number of viable aerobic microorganisms present in the samples and a qualitative test involving the demonstration of freedom of samples from designated pathogenic microbial species that are supposed to be the main cause of the relevant health problems. The tested species were *Salmonella* species and *Escherichia coli* for products intended

Table 1
Chemical composition of Egyptian and Wyoming bentonites, before and after purification.

Oxides (%)	Bulk sample	Purified sample	Bulk standard	Purified standard
SiO_2	51.08	52.16	54.15	59.77
$A1_2O_3$	16.37	17.12	17.78	19.32
Fe_2O_3	9.27	7.54	4.31	2.71
MgO	2.68	2.72	2.82	2.98
Na_2O	0.84	1.1	2.12	2.32
CaO	0.97	1.02	2.87	0.88
MnO	0.03	0.01	0.02	0.01
K_2O	1.07	0.93	0.62	0.23
TiO_2	1.26	1.05	0.16	0.13
P2O5	0.13	0.11	0.06	0.03
Cr_2O_3	0.017	0.016	0.003	0.001
TOT/C	0.09	0.12	0.94	0.22
TOT/S	0.01	0.01	0.09	0.04
LOl	15.8	16.2	14.9	11.6
Sum.	99.89	99.98	99.91	99.97
Ba(ppm)	N.A	106.4	N.A	96.4
Co	N.A	0.9	N.A	14.5
Cs	N.A	0.4	N.A	2.4
Sn	N.A	9.0	N.A	3.0
V	N.A	8.0	N.A	127
Cu	N.A	40	N.A	20.3
Pb	N.A	14.1	N.A	6.8
Zn	N.A	*95*	N.A	52.0
Ni	N.A	3.3	N.A	25.8
As	N.A	1.1	N.A	0.7
Cd	N.A	0.1	N.A	0.1
Bi	N.A	0.3	N.A	0.1
Ag	N.A	<0.1	N.A	<0.1

N.A: Not analyzed.

for internal use and *Staphylococcus aureus* and *Pseudomonas aeruginosa* for products intended for external use. The test was carried out on three bentonite samples: (A) raw (purified), (B) represented (activated) with sodium carbonate and (C) standard samples, according to the US Pharmacopeia (2004g, 2005).

2.4.1. Total aerobic microbial count

A weight of 10 g of each bentonite sample was suspended in 100 ml of phosphate buffer adjusted to pH 7.2. A 10-fold serial dilution was performed on each sample and then 1 ml from each dilution was transferred on each of two sterile Petri dishes. The soybean-casein digest agar medium (Oxoid) was melted and then added in a volume of 15 ml at 45 °C to each plate. The plates were tilted or rotated to allow good mixing of the samples with the medium. The Petri dishes were then incubated in an inverted position at 37 °C for 48 to 72 h. The number of colonies in each plate was counted and the plates comprising 30 to 300 colonies were taken into consideration while the other plates were rejected. Following incubation, the plates were examined for growth, the number of colonies was counted, and the average for the two plates was expressed in terms of the number of microorganisms per gram of specimen.

2.4.2. Test for S. aureus and P. aeruginosa

The Fluid Soybean-Casein Digest Medium (Oxoid) was added to the bentonite sample to make 100 ml, mixed, and incubated at 37 °C. The medium was examined for growth, and if growth was present, an inoculating loop was used to streak a portion of the medium on the surface of a Mannitol-Salt agar medium (Biolife) and of a Cetrimide agar medium (Biolife), each plated on Petri dishes. After incubation at 37 °C, the plates were examined for the presence of the characteristic colonies of *S. aureus* on Mannitol-Salt agar medium and *P. aeruginosa* on Cetrimide agar medium.

2.4.3. Test for E. coli and Salmonella species

A volume of a Fluid Lactose medium was added to the specimen to make 100 ml, and then incubated at 37 °C. The media were examined for growth, then 1 ml portions were transferred into vessels containing, respectively, 10 ml of Fluid Selenite-Cystine and Fluid Tetrathionate media, mixed, and incubated for 12 to 24 h at 37 °C (the remainder of the Fluid Lactose media was retained).

2.4.3.1. Test for Salmonella species. Portions from both the Selenite-Cystine and Tetrathionate media were streaked on the surface of a Bismuth Sulfite agar medium (Biolife) and a Desoxycholate Citrate agar medium (Biolife) plates. After incubation at 37 °C, the plates were examined for the presence of the characteristic colonies of *Salmonella* species.

2.4.3.2. Test for E. coli. A portion from the remaining Fluid Lactose media was streaked on the surface of MacConkey agar medium (Biolife) and Eosin Methylene Blue agar medium (Biolife) plates. After incubation at 37 °C, the plates were examined for the presence of the characteristic colonies of *E. coli*.

2.5. Cation Exchange Capacity (CEC) determination

The cation exchange capacity of both the local sample and the standard was determined using $BaCl_2$ as a saturation cation. This method involves the saturation of the exchangeable site with barium ions, equilibration, removal of excess barium with ethanol, and leaching and replacement with ammonium. Prior to conducting CEC analyses samples were washed thoroughly with deionized water to remove extraneous cations, then 1 g of dried sample was dispersed in 10 ml of 0.5 N $BaCl_2 \cdot 2H_2O$ solution, the dispersion was shaken on a reciprocating shaker for 30 min and then the clay suspension filtered under vacuum extraction using a Whatman No. 5 filter paper. The clay suspension was leached with 100 ml of 1 N $BaCl_2 \cdot 2H_2O$. The excess $BaCl_2 \cdot 2H_2O$ was rinsed from the sample by washing with 200 ml volume of ethanol. In a clean flask the sample was washed with 225 ml of 1 N ammonium acetate solution having a pH of 7 to replace the exchangeable barium. The leached solution was completed to 250 ml with deionized water using a volumetric flask. The concentration of Ba ions in the final leachate was determined using an atomic absorption spectrophotometer. The concentration of leachate Ba was 1140 and 1214 ppm and the calculated CEC was 82 and 94 meq/100 g for the local sample and the Wyoming standard respectively.

2.6. Pharmacopeial tests

The pharmacopeial tests including some physical properties needed to be carried out on samples and standards to support their usage as a pharmaceutical ingredient according to the US Pharmacopoeia (2004a, 2004b, 2004c) The raw, activated, standard samples and the pharmaceutical product sample (Smecta) were tested.

The pH according to pharmacopeial specification for bentonite, i.e., the pH value of a clay water suspension of 5 g/100 ml was measured after 2 min after continuous stirring.

2.6.1. Swelling power

Apparent volumes of swelled bentonite in a suspension of 2 g in 100 ml were quantified after 2 h.

2.6.2. Gel formation

The supernatants of bentonitic suspensions were prepared by mixing 6 g of each sample with 0.3 g of magnesium oxide in 200 ml of water using a high-speed mixer and were measured after 24 h.

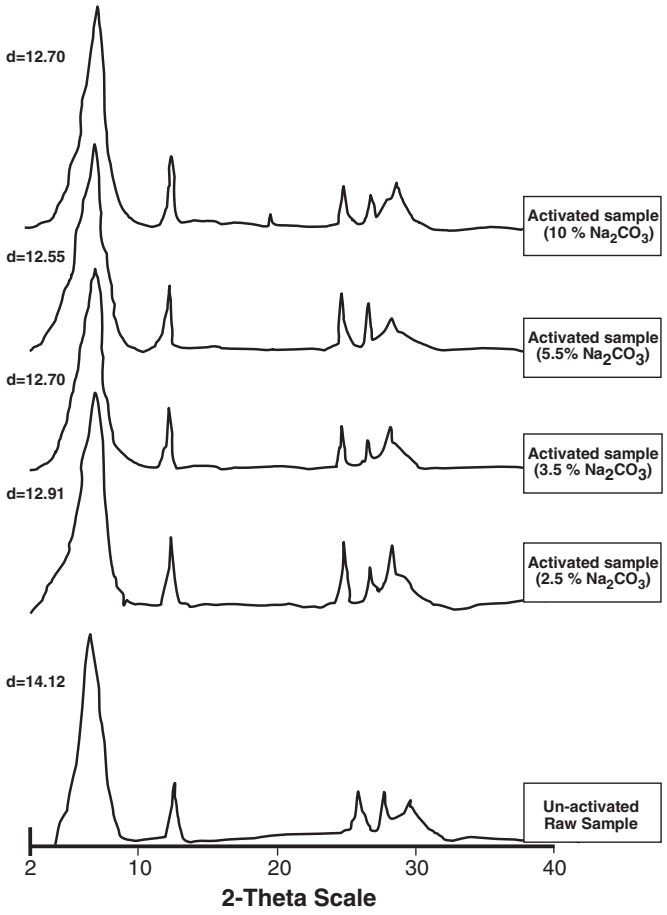


Fig. 1. XRD charts showing the changes in d-spacing with Na_2CO3 activation.

Table 2
D-spacing and CEC changes in the Egyptian Bentonite due to activation by different concentrations of Na_2CO_3.

Sample no.	Activator dose%	D-spacing (Å)	CEC
Raw bentonite	–	14.12	82
1	2.5	12.909	84
2	3.5	12.967	86
3	5.5	12.54	90
4	10	12.707	76

3. Results and discussion

3.1. Activation effect

Montmorillonite with sodium as the interlayer cation has one water molecule in the intermediate spaces and the dimension of the space in the direction of the c-axis is about 12.5 Å, Grim (1968). Fig. 1 shows the X-ray diffraction pattern indicating the variation in basal spacing by changing the activator dose. As the basal spacing decreased with an increase of Na_2CO_3, this reflected that the Na^+ ions replaced Ca^{+2} ions in the montmorillonite interlayers and have been changed into Na-form (Yildiz, et al., 1999). The activated samples with the nearest basal spacing (12.45 Å) to the Wyoming sample correspond to a 5.5% activator dose, and this indication was confirmed by the elevation in the CEC value (Table 2, Fig. 1).

3.2. Composition

The local sample is composed mainly of Ca–Na montmorillonite, kaolinite and illite as clay minerals, and quartz and albite as non-clay minerals. The Wyoming standard is mainly composed of Na montmorillonite and illite as clay minerals; quartz, calcite, albite and microcline are the non-clay components. The clay fraction of the Egyptian sample is composed mainly of montmorillonite (~85%), illite, and kaolinite, and quartz is the main non-clay mineral (<2% in total). The Wyoming clay fraction is composed mainly of pure montmorillonite. Fig. 2 shows the X-ray diffraction pattern of the pharmaceutical product Smecta and indicates that pure montmorillonite is its main constituent. The thermal analyses data represented in Fig. 3A and B indicates the same mineralogical composition for both Egyptian samples and the Wyoming standard. The grain size analysis of the studied raw bentonite was done by using a Laser Diffractometer (Fig. 4).

Chemical analyses for both sample and standard (Table 1) confirm that the purification steps affected the concentration of some elements (expressed as oxides). The main element affected was iron (due to the removal of free iron oxides and oxyhydroxides in magnetic separation steps). Decrease in the calcium oxide percent confirms the removal of carbonate from the standard sample. The increase of SiO_2, Al_2O_3 and

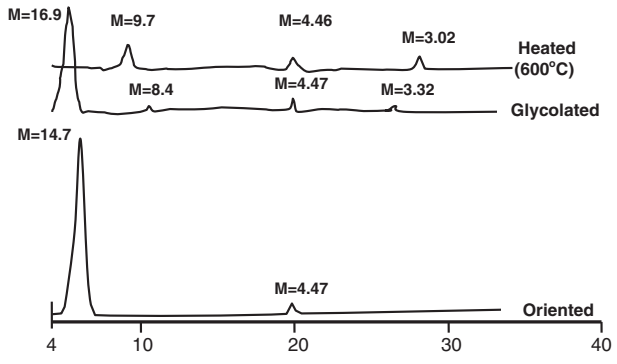


Fig. 2. XRD chart of the pharmaceutical product (Smecta) showing pure montmorillonite composition.

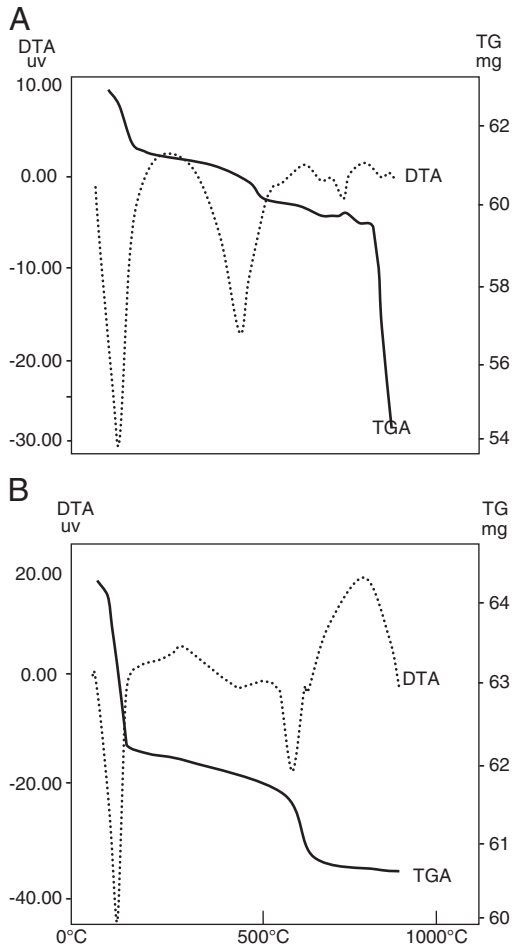
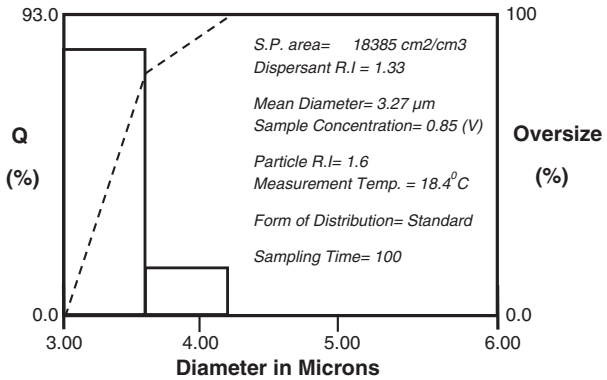


Fig. 3. A. DTA and TG chart of the Egyptian bentonite sample. B. DTA and TG charts of the standard bentonite sample (Wyoming).

Na_2O confirms the increased content of montmorillonite. The most abundant element in the octahedral layer of the purified sample is iron (as the ferric ion) followed by magnesium because the MgO/Fe_2O_3 ratio equals 0.36, while in the purified standard both magnesium and ferric ions are equal in the octahedral layer as the MgO/Fe_2O_3 ratio is equal to one (Todor, 1976). Attention must be drawn to the amounts of Pb and As in the pharmacopeia limits for "Bentonite" and "Purified Bentonite".



No.	Diameter in microns	Quantity %	Oversize%
1	3.41	83.719	83.79
2	3.91	16.281	100.00
3	4.47	0.00	100.00
4	5.122	0.00	100.00
5	6.00	0.00	100.00

Fig. 4. Grain size analysis of the studied raw Bentonite using Laser Diffractometer.

Table 3
Pharmacopeial values and specifications of different bentonitic samples and the pharmaceutical product (Smecta).

Sample	A	B	C	(Smecta)	Pharmacopeia specification
pH value (5 g/100 ml)	8.5	10.5	9.8	–	9–10
Gel formation (6 g/200 ml)	75	5	1	90	Supernatant not more than 2 ml
Swelling power(2 g/100 ml)	8.0	11	35	4.0	Supernatant not less than 22 ml

Sample (A) purified Egyptian raw sample.
Sample (B) activated sample with (5.5% Na_2Co_3).
Sample (C) Wyoming bentonite.
Smecta traditional pharmaceutical product.

The limits are 40 and 15 ppm for Pb and 5 and 3 ppm for As (US Pharmacopeia, 2004a, 2004b). The studied Egyptian sample and standard clearly fulfill the established As and Pb limits for "Purified Bentonite" (Table 2).

3.3. Microbiology

Microbiological studies revealed that all samples were free from pathogenic bacteria; the total amount was within the permitted amounts. US Pharmacopoeia 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 was contaminated by *E. coli*, *P. aeruginosa* or *S. aureus*; contamination by *C. albicans* was always inside the satisfactory limits (US Pharmacopoeia, 2004g).

3.4. Exchangeable cations

The exchange capacities (meq/100 g) of the raw and activated samples with different activator doses are given in Table 2. Relatively high CEC values were measured for the samples compared to the standard. The high CEC values recorded in the sample with the activator dose of 5.5% make it suitable for pharmaceutical uses.

3.5. Pharmacopeia requirements

The pH values of 5% aqueous dispersions (Table 3) meet the pharmacopeial requirements, with values between 8.5 and 10.5. The supernatant volume prepared for sediment volume measurement or gel formation reveals that activated Egyptian bentonite samples exhibit few differences in comparison with Wyoming samples and pharmacopeial requirements. This is attributed to the fact that Egyptian samples are not pure sodic types even after activation and also suggests the Egyptian bentonite can be used after extensive purification with or without activation as pharmaceutical excipients. The activated bentonite sample may be used as an adsorbent for drugs and as a drug carrier in drug release processes as it has a relatively high CEC value.

4. Conclusions

The chemical composition of the studied bentonite and particularly the trace element content, for both raw and activated samples fulfill the pharmacopeia requirements regarding Pb and As toxic elements. Raw and activated samples fulfill the microbial content limits of USP requirements. Both chemical composition and microbial content of both raw and activated samples would allow their uses for pharmaceutical purposes, but the activated sample would be used particularly in the formulation of suspensions for oral products which appears as a promising field of applications on the basis of the obtained results. Finally the Egyptian bentonite may be used after extensive purification with or without activation for pharmaceutical uses, and the activated bentonite may be used as an adsorbent of drugs and drug carriers in drug release processes.

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