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Characterisation of halloysite for use as a microtubular drug delivery system

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Abstract

Halloysite supplied from New Zealand was shown by electron microscopy to be composed mainly of hollow microtubules having typical dimensions of 2–3 μm long and 0.3/0.1 μm outer/inner diameter. Aggregates of microtubules, double tubules and occasional split or partially unrolled tubules were observed. Energy dispersive analysis showed the mineral to be composed mainly of aluminium, oxygen and silicon, with a low content of iron. The dehydrated state of the mineral was confirmed by XRD analysis, which was partially reversible using a rehydration procedure with subsequent exchange of the intercalated water gained by glycerol, but larger molecules including the drug, diltiazem HCl, failed to exchange. The surface charge was predominantly negative over most of the physiologically relevant pH range (> 2) and the specific surface area of the material was very large (~ 57 m^2/g), indicating that the material has significant potential for extensive binding of cationic drugs. Removal of allophanc present by a hot alkali treatment had little effect on luminal porosity, which prior to treatment was estimated to be ~ 0.25 ml/g by a mercury intrusion technique and consequently should be the major site for drug loading. Halloysite also extruded and spheronised well to form smooth round pellets as an aid to further formulation development, which rapidly disintegrated in water unless prevented by sintering at 200 °C. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Halloysite; Microtubular; Physicochemical characterisation; Drug delivery

1. Introduction

Halloysite is an aluminosilicate clay mined from natural deposits in countries such as America, Brazil, China, France, Japan, South Korea and Turkey, that is chemically similar to kaolin, but differs in having a hollow microtubular rather than a stacked plate-like structure. Because of the mechanism by which halloysite is formed from amorphous allophane by long-term weathering, a small amount of this precursor may be associated with certain halloysite samples. Whereas halloysite tubules from different regions and within samples vary in dimensions, all are very small with a typical aspect ratio of less than 3.0 long × 0.3 μm outer diameter, though tubules as long as

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20 μm may be found in certain samples, indicating the need to source halloysite from one deposit where excess variability is likely to be a critical issue. Mismatch in the two-layered alignment of the tetrahedral sheet of silica bonded to the octahedral or gibbsite sheet of alumina causes the wall to curve into the cylindrical shape as explained by Bates et al. (1950). Intercalated water may occur between the repetitive two-layered sheets comprising the spiral wall, which tends to be irreversibly removed on drying. The inner and outer faces of the tubule walls carry normally a net negative charge, functioning as a polyvalent anion, whereas their edges are amphoteric with negative charge at high pH and positive charge at low pH. This unusual shape and charge distribution favours face-to-edge attachment in aqueous suspension below pH 6 and facilitates binding particularly of cations to the unreacted faces. More extensive loading should be achievable by entrapping agents within the lumen of tubules using retardant polymers, cationic coating and other approaches to moderate release rate, or possibly by swapping intercalated water if present for low molecular weight agents.

Halloysite from New Zealand is particularly prized for use in the manufacture of high quality ceramic white-ware, because it contains a low content of iron and other cations, which tend to replace aluminium ions in the gibbsite layer, causing discolouration of the native material (Noro, 1986). On crushing, halloysite yields elongated fragments that form a scaffolding in the body mix with the filler and flux agent to improve the green (unfired) strength of ceramics, enabling thinner sections to be successfully produced. Halloysite has been investigated also in the automotive industry to form the support material for catalytic converters in exhaust systems. Price and Gaber (1997) filed a patent on the use of the material for the extended delivery of a range of biocides following incorporation into marine antifouling paints, and more recently they have published greater details of this development work (Price et al., 2001), However, despite the unique potential of halloysite for drug delivery, low production cost and likely ease of regulatory approval because of its chemical similarity to kaolin, its pharmaceutical uses have yet to be evaluated. This paper describes aspects of the physicochemical characterisation of halloysite that are relevant to subsequent investigations of its use for the production of novel delivery systems for drugs and other agents. These studies should also aid an understanding of the use of the material in additional areas such as the agrichemical, veterinary, cosmetic and detergent industries, and is certain to lead to many interesting applications in these and other fields for commercial exploitation.

2. Materials and methods

2.1. Materials

A single large batch (25 kg) of halloysite, grade G, adequate for all the reported studies, was obtained from New Zealand China Clays Ltd., Auckland, New Zeland. Benalkonium chloride (Fluka), diltiazem hydrochloride (Profarmaco), glycerol (Merck), hydrochloric acid, potassium chloride (BDH), polyethylene glycol 400 (PEG), polysorbate 20 (Tween 20), potassium acetate (Sigma), polyvinyl pyrrolidone (PVP, K29/32, GAF), sodium hydroxide (Riedel de Haen) and water (glass distilled) were used.

2.2. Allophane removal procedure

To check if a sample of the bulk halloysite contained significant allophane, it was heated at 60 °C for 8 h with 0.5 M sodium hydroxide solution, which treatment selectively dissolved the allophane present. After cooling, the alkali solution was filtered off and the recovered halloysite was repeatedly resuspended and washed in water to free it of residuals, prior to drying to constant weight in a forced circulation oven (Memmert) at 50 °C for 48 h. This procedure for the removal of allophane was similar to that employed by Kirkman (1977).

2.3. Electron microscopy studies

Samples of halloysite were mounted on aluminium stubs, vacuum coated with gold film (Polaron SC 500) and examined using a scanning electron microscope (Hitachi S-4300 field emission). An energy dispersive analysis attachment (PGT energy dispersive X-ray microanalysis) was used to determine the elemental content of samples.

2.4. Particle size analysis

Particle size of halloysite samples was examined by the dry-powder technique using a laser diffraction particle analyser (Malvern 2600c).

2.5. Zeta potential measurement

Zeta potential of dilute halloysite suspensions (0.1 mg/ml) in aqueous electrolyte solution (0.001 M KCl), with pH adjustment using 0.1 M HCl or 0.1 M NaOH, was performed using a Zetasizer 3000 (Malvern Ltd., UK). Prior to each measurement, the operating conditions were checked and adjusted using a calibrated latex dispersion supplied by the instrument manufacturer (zeta potential -50 ± 5 mV).

2.6. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was performed using a Toleda TC15 TA controller (Mettler). Analysis was performed over the temperature range 30–250 °C using a heating rate of 10 K/min, The sample weights examined were between 5 and 10 mg. Nitrogen gas flowed over the open crucibles containing the sample as the analysis was performed. The percentage weight losses incurred during the heating cycle were estimated using the associated software.

2.7. Intercalation of halloysite

The procedure of Wada (1961) was employed to determine if the intercalated space of the halloysite was available for drug loading, by grinding 20 g of the clay with 16 g of potassium acetate for 20 min using a mortar and pestle. Following x-ray diffraction (XRD) analysis, the mix was repeatedly rinsed by agitation in water followed by centrifugation, and portions of the damp clay recovered were exposed to various organic liquids or aqueous solutions of organic solids in sealed sample tubes, whereupon the recovered halloysite after 3 days or 3 weeks incubation was again examined by XRD for evidence of intercalation.

2.8. XRD analysis

XRD patterns were obtained using a D500 X-ray powder diffractometer (Siemens). Powdered samples were studied by placing a thin layer in conventional cavity mounts. The samples were scanned from 5–40°2θ. A 1.00° dispersion slit and a 0.15° receiving slit were used. The Cu anode X-ray was operated at 40 kV and 20 mA in combination with a Ni filter to give monochromatic Cu Kα X-rays ($\lambda = 1.5418$ Å).

2.9. Mercury porosimetry

The porous structure of halloysite was determined by mercury porosimetry using a model 9320 Poresizer (Micromeritics) with associated software. The measurements were performed on powder samples using a 5 cm^3 ‘powder sample’ penetrometer (sample weight 250 mg). Samples were dried to constant weight using a vacuum oven set at 80 °C and removed just prior to analysis. Intrusion pressures between 0.5 and 30000 psi were used, corresponding to pore diameters between 360 and 0.006 μm. The low pressure analysis (0.5 to ~ 20 psi) was done semi-automatically and the high pressure analysis was automatically controlled, both using the equilibrium mode with a time interval of 10 s.

2.10. Surface area measurements

Surface area of halloysite was determined by a nitrogen adsorption technique using a Gemini 2370 Surface Area Analyser (Micromeritics), Moisture was removed from the samples prior to the surface area measurement by placing them in a vacuum oven for 24 h at 70 °C at a pressure of 500 mbar. Subsequently, samples were degassed using a FlowPrep 060 Degasser (Micromeritics). The FlowPrep uses a flowing gas (helium), which is passed over the heated sample (70 °C) to remove moisture and other contaminants.

2.11. Extrusion/spheronisation studies

Halloysite powder was wetted by gradual addition of the required volume of water. After being stored for ~24 h in a sealed container to ensure uniformity of hydration of the mix, the wetted mass was extruded through a 1 mm diameter screen using a gravity fed cylinder extruder (model GA 65, Alexanderwerk), The extrudate formed was spheronised on a 120 mini spheroniser (Caleva) fitted with a cross-hatch cut stainless-steel friction plate. The spheronised pellets were dried in the forced circulation oven for 48 h at 40 °C.

2.12. Sieve analysis and yield of pellets

Sieve analysis was performed using a nest of standard sieves, 1680, 1180, 850, and 300 μm, agitated for 10 min on a sieve shaker (Endecott) and the retained weight data obtained was used to construct a frequency distribution. The desired size of pellets was in the range 850–1180 μm and is referred subsequently to as 'pellets'. Those which occurred above this size range are referred to as 'large pellets', while those below are referred to as 'fines'.

3. Results and discussion

3.1. Preliminary studies

The entire batch of halloysite was thoroughly mixed in a cube mixer and six 50 g samples were taken randomly. Each sample was subjected to electron microscopy and to particle size analysis. SEM studies indicated that that the six samples were very uniform in content, containing a lot of tubular material, as well as large undesirable particle agglomerates. Despite the longest individual tubules being only 3–5 μm, the average median particle size of the six samples was determined to be 88 μm, confirming the presence of large aggregates. In an attempt to break-up and reduce the number of these aggregates, each sample was passed through a 125 μm sieve, yielding 80% approx product and indicating that the large aggregates contributed a relatively small proportion to the overall batch content. Particle size analysis of the sieved samples gave an average median particle size of 27.9 μm (S.D. 4.75 μm), confirming that break-up or removal of aggregates occurred, whereas the retained fraction had a corresponding value of 193 μm (5.35 μm). Fig. 1 shows a SEM of a typical sieved sample, illustrating the high microtubular content with the presence of occasional aggregates. The sieving step was applied to the remainder of the bulk halloysite and the sieved fraction only was used in all subsequent characterisation studies reported in this study, unless otherwise indicated.

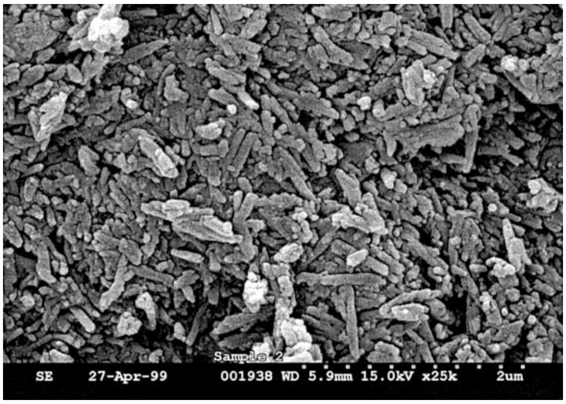

Fig. 1. SEM of halloysite after sieving through 125 μm mesh (magnification ×25000).

The detailed appearance of some typical hollow microtubules is shown in Fig. 2, whose length is quite variable, but whose outer and lumen diame-

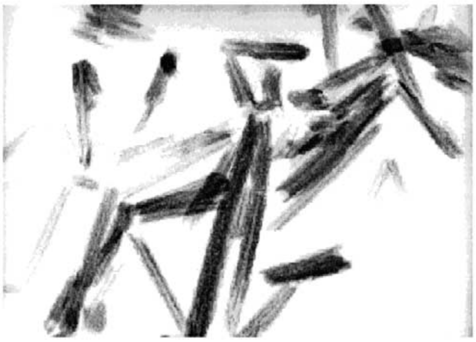

Fig. 2. TEM of typical halloysite microtubules (magnification ×100000).

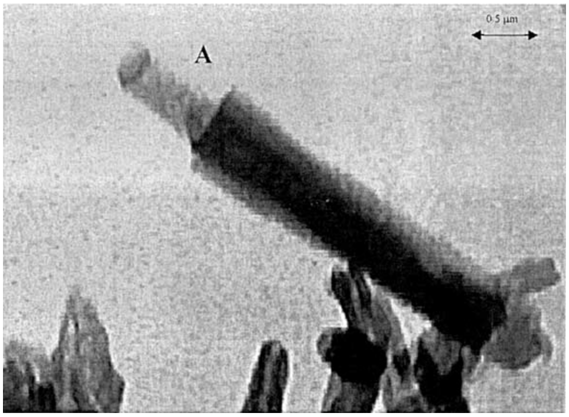

Fig. 3. TEM of double microtubule marked A (magnification × 100000).

ters are more consistent at ~0.3 and ~0.1 μm, respectively. Some splitting and unrolling of tubules was observed, indicative of low iron content and dehydration of the wall. Occasional double microtubules (tube-in-tube) were present as illustrated in Fig. 3, where the inner tube projects at both ends.

Energy dispersive analysis was performed on halloysite samples and showed well defined peaks for aluminium, silicon and oxygen as expected, as the wall is mainly composed of alternating sheets of alumina and silicon–oxygen. Two very small peaks indicative of the presence of a low level of iron (III) were detected, which has been associated with improved whiteness in halloysite samples (Noro, 1986). In addition calcium was detected, which was probably due to the presence of various calcium salts such as calcium carbonate.

3.2. Zeta potential measurements on halloysite

The zeta potential curve for halloysite was determined over a wide pH range as shown in Fig. 4. It is apparent from the plot that the surface charge of the mineral is only slightly negative at very low pH, As the pH value increases from 2 to 6 the surface charge falls sharply to reach a plateau at ~27 mV, before dropping further at pH values greater than 10. Similar results were reported by Tari et al. (1999), who examined a sample of halloysite mined in Portugal.

The reason for the generation of the negative surface charge with increasing pH is that in the curved structure, the silica is mainly positioned on the outer surfaces of the tubule, whereas the alumina is present mainly on the inner surface and edges of the tubules. Exposure of both oxides

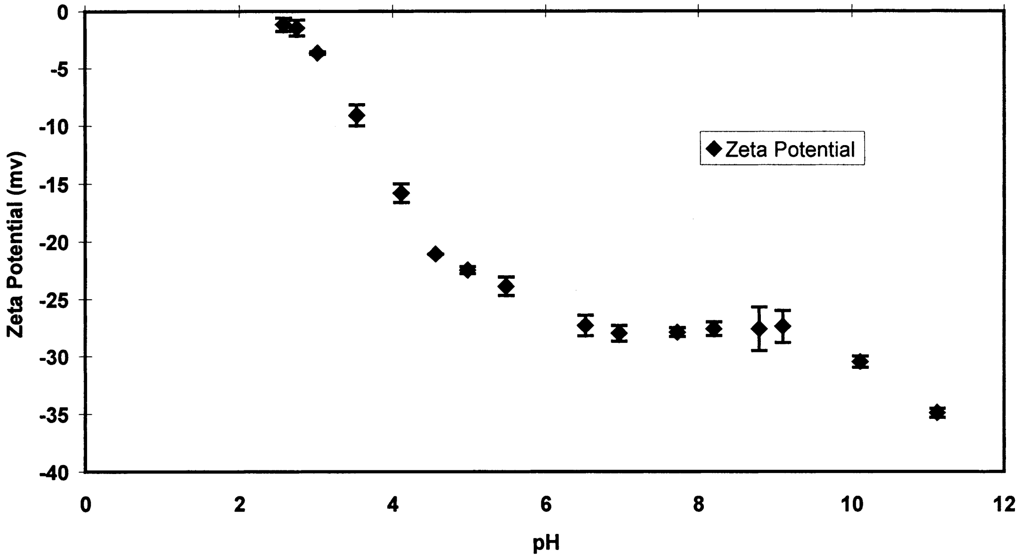

Fig. 4. Zeta-potential plot for halloysite.

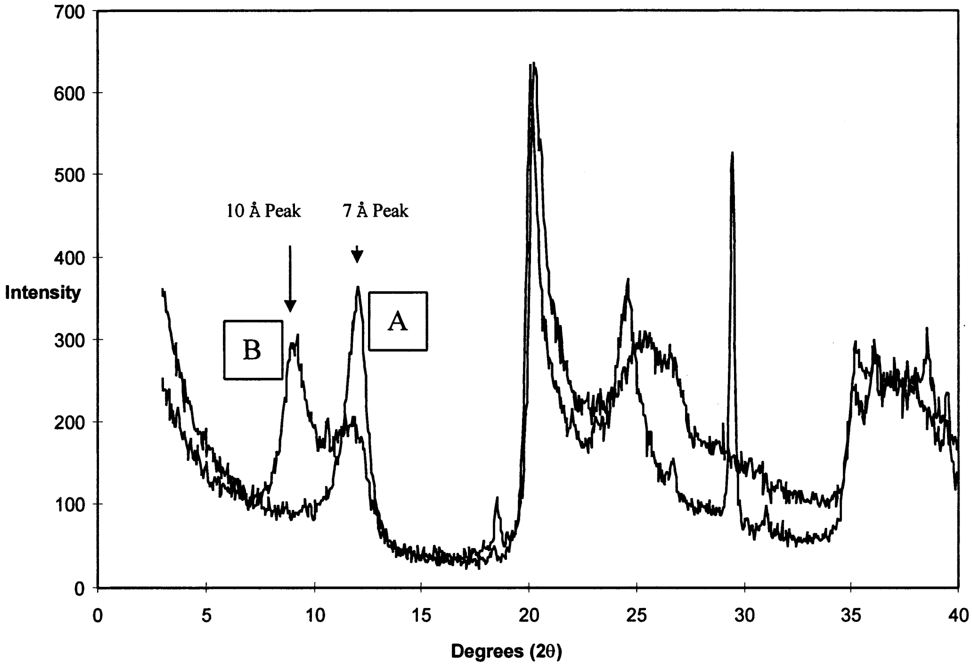

Fig. 5. XRD patterns for NZ halloysite (A) and Indiana halloysite (B).

to water causes the formation of surface hydroxyl groups (Sur-OH) that can ionise as illustrated below.

$$[\mathrm{Sur-OH_2^+} \xleftarrow{\mathrm{H^+}} \mathrm{Sur-OH} \xrightarrow{\mathrm{OH^-}} \mathrm{Sur-O^-}]$$

Silica, being an acidic oxide, causes the second reaction on the right-hand side of the equation to be predominant over a substantial range of pH values, while alumina shows a more amphoteric behaviour. Since the surface is mainly silica, the surface charge will be negative over a wide range of pH, as is evident in the zeta potential plot. As a result, halloysite tends to have a polyanionic surface, except at very low pH, and should readily bind cationic drugs or coating polymers from solution.

3.3. XRD studies

XRD techniques were used to identify halloysite and to determine whether it was present in the dehydrated, hydrated or partially hydrated form. The plot for the NZ halloysite is shown in Fig. 5. The basal spacing reflections indicate a sharp peak at 12.05°2θ, which translates to a 001 basal spacing of 7.35 Å, using Bragg's Law. There is also an absence of a peak at 8.76°2θ indicating the absence of the 10 Å-form, indicative of hydrated halloysite. Thus the NZ halloysite used this study was fully dehydrated, which is not surprising as it was supplied as a dried powder with a residual (non-intercalated) moisture content of 9.5%, as determined by drying to constant weight loss in an oven at 50 °C. Further confirmation of the dehydrated state was the presence of the 002 basal reflection at 24.55°2θ (equivalent to $d = 3.63$ Å).

Fig. 5 shows also the plot for a sample of halloysite, obtained from Indiana, USA. The main difference between it and the NZ sample is the presence of both dehydrated (7 Å-form) and hydrated (10 Å-form), which is evident as a diffuse peak between 8 and 13° (2θ), and hence can be described as a partially hydrated sample. The Indiana sample underwent minimal treatment and drying since its excavation from the ground, explaining the presence of some hydrated clay. The intensity of the 9.77 Å peak is approx twice the

7.4 Å peak. However, it is important to note that this does not correspond to the relative amounts of the hydrated and dehydrated mineral present, as the 10 Å peak tends to be considerably more intense.

3.4. Intercalation of halloysite

To check if the intercalation space in the halloysite wall could be loaded easily with small molecules such as water, glycerol or diltiazem HCl, samples of halloysite were ground with an equivalent weight of each material in a mortar and pestle for 20 min and allowed to equilibrate for 3 days at room temperature. Fig. 6 shows the XRD plots obtained for the treated samples, all having a sharp peak at 7.32 Å (12.10°2θ) and confirming that no shift in the basal spacing reflection occurred. This indicates that the dehydrated halloysite cannot be rehydrated by simple exposure to excess water. This observation is in agreement with the findings of Harrison and Greenburg (1962), who were unable to rehydrated halloysite samples even when exposed to 100% relative humidity for up to 2 months. Likewise the dehydrated halloysite does not intercalate with glycerol or diltiazem HCl.

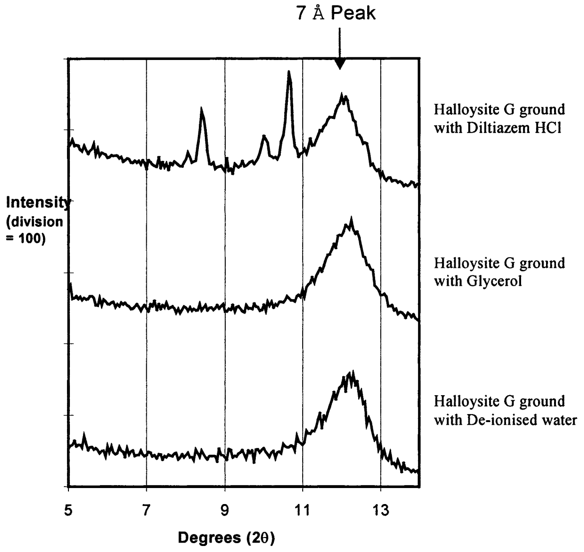

Fig. 6. XRD patterns of halloysite ground and stored for 3 days with water, glycerol or diltiazem HCl.

In order to indirectly rehydrate the halloysite with a view to subsequent exchange of the water by drug or other molecules, the procedure of Wada (1961) was adopted, whereby the halloysite was ground with potassium acetate to form an intermediary intersalation complex, followed by rinsing with water to remove the salt. XRD studies showed that rehydration of the halloysite occurred, as confirmed by a basal spacing of 9.77 Å (9.05°2θ). The intercalation experiments with glycerol, diltiazem HCl and a range of other compound of possible interest in subsequent drug loading studies were repeated on samples of this artificially rehydrated halloysite, extending the equilibration time to 3 weeks, and the XRD patterns obtained are shown in Fig. 7. Glycerol alone was shown to intercalate with the artificially rehydrated halloysite as is evident by a shift in the basal spacing from 9.77 to 10.98 Å, corresponding to a shift to lower angle. Intercalation did not occur with the other compounds examined, as all are significantly larger than the water molecule. This finding is in agreement with the observations of Carr and Chih (1971) that organic compounds tend to form a complex with halloysite by hydrogen bonding only when the molecule is very small and contains two functional groups, preferably –OH and/or –NH_2.

3.5. Mercury porosimetry of halloysite

Samples of halloysite (a) sieved, (b) sieved and milled using an ultracentrifugal mill (Retsch) and (c) treated to remove any possible allophane present were examined by mercury porosimetry. The cumulative intrusion plots obtained (Fig. 8) show that there was a gradual initial increase in intrusion volume, corresponding to the filling of the coarse pores between particles in the range 12–200 μm, followed by a more rapid increase in intrusion in the range 0.5–12 μm, corresponding to the filling of the finer inter-particulate pores. A further intrusion was evident below 0.1 μm, corresponding to filling of the tubule lumens within halloysite particles and the calculated average mercury intrusion volume within such fine pores was estimated to be 0.246, 0.130 and 0.224 ml/g for samples (a), (b) and (c), respectively. As max-

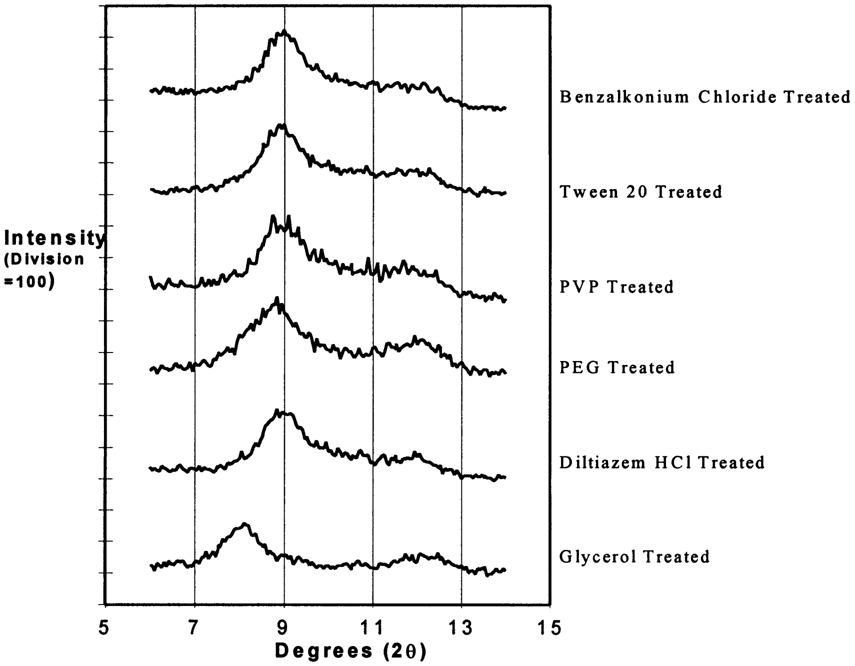

Fig. 7. XRD patterns of artifically rehydrated halloysite ground and stored for 3 weeks with various compounds.

imising inter-tubular volume is likely to be an important location for drug loading for sustained release, both the allophane removal treatment and the milling procedure, in particular, have a detrimental effect on this pore volume. This suggests that the halloysite contained very little inter-tubular allophane obscuring the lumen and that vigorous milling, as confirmed by SEM studies, not merely disrupts aggregates but smashes up some individual tubules into useless debris which has low ability to entrap drug.

3.6. Surface area of halloysite samples

The average specific surface area of the three halloysite samples (a–c) described in the previous section was determined, giving values of 57.28, 57.68 and 59.86 m^2/g, respectively. The value for the sieved halloysite (a) is close to that of 56.2 m^2/g reported by Churchman et al. (1995) for a halloysite sample mined in Australia. Whereas milling more than halved the median particle size from 27.9 to 10.8 μm (S.D. 0.24 μm), the milled sample (b) only had a slight increase in specific surface area. This suggests that the milling process disrupts predominantly the aggregates of microtubules, within which nitrogen gas can freely flow and adsorb, and has a smaller effect on breaking up individual microtubules leading to a small increase in surface area.

A bigger increase in specific surface area (2.58 m^2/g) was observed when the sieved halloysite (a) was treated to remove allophane (c). This increase can be attributed to the dissolution of the allophane associated with the mineral, to create mesopores within the tubular walls of 2–3 nm diameter as reported by Jackson et al. (1971). These mesopores were not detected by the mercury porosimetry experiments reported here, as the instrumentation used was capable only of generating pressures to intrude mercury into pores of 6 nm diameter or greater. It is possible than the film of allophane present in the sieved halloysite acts as a flux agent, aiding the formation of the observed aggregates of microtubules.

3.7. Extrusion/spheronisation studies

As halloysite is a colloidal clay used in the ceramics industry, it was examined for its ability to extrude and spheronise so as to aid the production of pelletised products. The sieved powder was moistened with 17, 19 and 21% additional water, as TGA analysis indicated that the halloysite already had a free moisture content of ~9.5%, giving an overall moisture content similar to levels used by us (Levis and Deasy, 2001) for drug mixes with lactose and novel grades of microcrystalline cellulose. Not surprisingly, the halloysite processed with ease to form smooth spherical pellets, whose yields are shown in Fig. 9. A very high percentage of pellets (~84%) was obtained using the lowest hydration level (17%), which was accompanied by the highest yield of fines. Increasing the hydration level was associated with undesirable reduction in pellet yield and increase in large pellet yield, suggestive of over-wetting of the mix. Unlike microcrystalline cellulose containing pellets that tended to remain intact due to hydrogen bonding, the dried product disintegrated rapidly when immersed in water at 37 °C, which property has interesting potential for particular applications. This premature disintegration of the pellets could be prevented by sintering them at 200 °C for 15 min, possibly causing fusion of the allophane film at contact points within the matrix.

4. Conclusions

Halloysite is not uncommon in nature being found in many subtropical and tropical soils. Within individual countries, significant differences in halloysite morphology arise, depending on the exact forces of nature involved in their formation. In New Zealand, for example, Churchman et al. (1995) examined a number of halloysite samples by TEM and showed the existence of a wide variety of morphologies including (a) thick tubular (Dunedin), (b) spheroidal (Opotiki) and (c) blocky (Te Puke). These minerals were shown also to differ significantly in terms of size, specific surface area and porosity, indicating that there are potentially many different grades of halloysite available, some of which may be more suitable for a particular pharmaceutical or other application.

The results of this study confirm that the sieved halloysite used is largely microtubular and relatively uniform with occasional aggregates, double tubules and partially unrolled or split tubules. Because of its dehydrated state, which is not readily reversible, the intercalated space is unlikely to be available for drug loading, except perhaps to very small hydrophilic molecules. However, at all pHs above 2, halloysite should readily bind cationic drugs to its outer and inner faces to delay drug release, optimum binding oc-

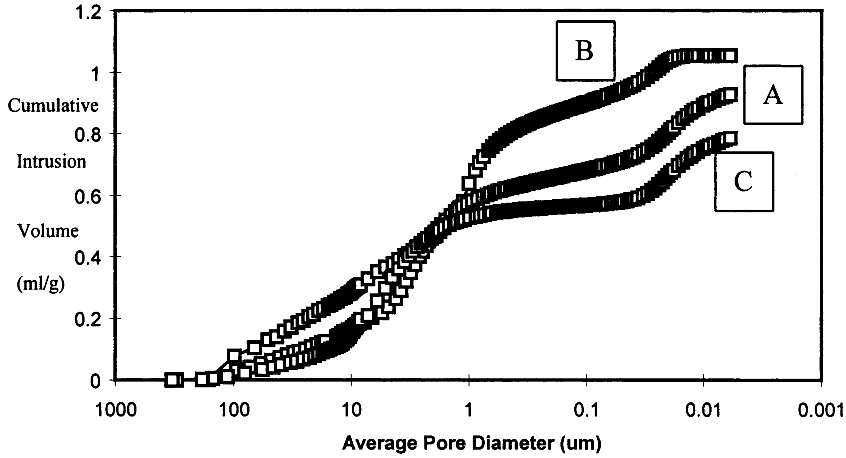

Fig. 8. Cumulative mercury intrusion curves for various samples of halloysite; (A) sieved only, (B) sieved and milled and (C) allophane removed.

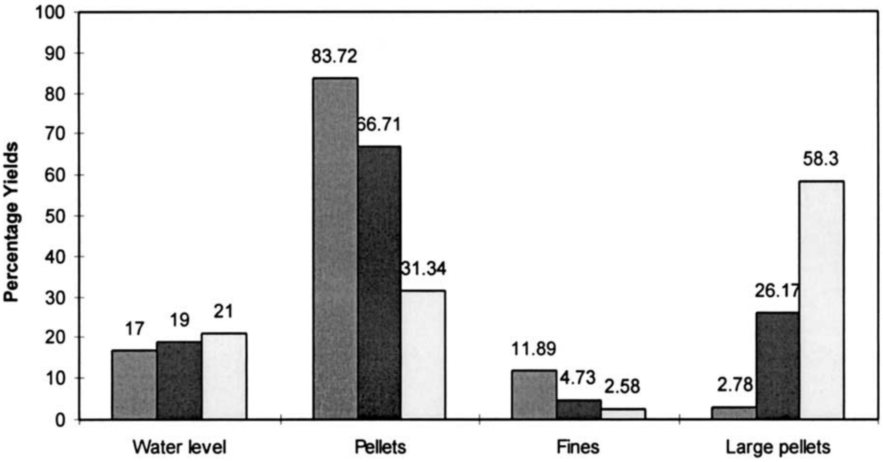

Fig. 9. Bar chart illustrating the percentage yield of pellets, fines and large pellets produced by extrusion/spheronisation of halloysite with 17, 19 or 21% added water.

curring with drug solution above pH 4, The highest drug loading should be achievable by filling the active from a concentrated solution (dry and reload solution repeatedly if possible) or better if thermostable and of low melting point as a hot melt to achieve maximum drug loading into the hollow lumen or spiral space of microtubules, which have an intrinsic volume of almost 0.25 ml/g, using retardant polymers and various coatings if necessary to further delay drug release. Release from this tubular region should tend to be zero-order, because of the constant surface area of the receding drug front at each end of the lumen. The ultrafine material obtained should be amenable also to further processing such as extrusion/spheronisation or solid lipid microparticle formation to improve handling and to further modify drug release. These possibilities will be examined in detail for a range of cation drugs suitable for development as oral sustained release products in a subsequent publication.

Acknowledgements

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