Applied Clay Science 48 (2010) 191–194

Contents lists available at ScienceDirect

Applied Clay Science

journal homepage: www.elsevier.com/locate/clay

Paramagnetic pillared bentonites — The new digestive tract MRI contrast agents

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ARTICLE INFO

Article history:
Received 10 July 2009
Received in revised form 23 November 2009
Accepted 23 November 2009
Available online 29 November 2009

Keywords:
Bentonites
Pillaring
MRI contrast
Digestive tract

ABSTRACT

The availability of sophisticated diagnostic methods such as MRI has contributed to the increased use of imaging technologies in therapy and diagnostic studies. However, gastrointestinal tract MRI generally shows poor results because of the lack of suitable contrast agents. The iron oxide is traditionally popular material for MRI gastrointestinal studies because of its well-known superparamagnetic properties. On the other hand, it has many disadvantages which include black bowel, side effects of diarrhea and, from an important analytical standpoint, the presence of artifacts arising from clumping. When paramagnetic iron concentrates, it may become ferromagnetic, drastically altering its imaging properties. Other paramagnetic species, represented by gadolinium, also seem to be potentially suitable agents for these studies. Nevertheless, this metal itself cannot be used in humans because of its toxic properties.

Therefore, there is clearly a need for orally effective, well tolerated agents that can be used in humans for digestive imaging studies. This MRI contrast should be useful for visualizing the anatomy of the digestive tract and particularly to differentiate between normal and pathological states, such as tumors. The solution has been proposed as zeolites or smectites (hectorite and montmorillonite) enclosing of paramagnetic metal ions obtained by ion-exchange methods. However, such materials could have problems of leakage of paramagnetic ions causing the appearance of the number side-effects.

We propose the usage of the pillaring method for paramagnetic metal encapsulation in bentonites. By that way, paramagnetic cations like Fe^{+3}, Mn^{+2} and Gd^{+3} are introduced between clay mineral layers as polyoxo cations. After calcination, these polyoxo cations grow to be pillars (oxides of these metals) which are incorporated into the clay mineral matrix which prevents ion-leaching and dangerous side-effects. In this study we show that paramagnetic-pillared bentonites could be successfully used as MRI digestive tract non-leaching contrast agents, altering the longitudinal relaxation times of fluids in contact with the clay minerals.

1. Introduction

The MRI (Magnetic Resonance Imaging) technique enables the direct electronic visualization of internal organs in living beings and is therefore powerful help and guide in prognosis, medical treatment and surgery. This technique can often advantageously supplement or replace X-ray tomography as well as the use of radioactive tracer compounds which may have obvious undesirable side effects. The useful parameters pertaining thereto, i.e. the relaxation time factors T1 and T2 of the water protons in the direct environment of the organs under investigation are usually not sufficiently differentiated to provide sharp images when the measurements are carried out in the absence of contrast agents. However, the differences of the relaxation time constants between protons in various parts of the organs can be enhanced in the presence, in the environment of the hydrated molecules under excitation, of a variety of magnetic species, e.g. paramagnetic (which mainly affect T1) and ferromagnetic or superparamagnetic (which mainly affect the T2 response). The paramagnetic substances include some metals in the ionic or organo-metallic state (e.g. Fe^{+3}, Mn^{+2}, Gd^{+3} and the like, particularly in the form of chelates to decrease the intrinsic toxicity of the free metal ions). Ferromagnetic and superparamagnetic contrast substances preferably include magnetic particles of micronic or submicronic size, i.e. from a few microns down to a few nanometers, for instance particles of magnetite (Fe_3O_4), ferrites and other magnetic mineral compounds of transition elements. Application of contrast-enhancing agents in clinical MRI is indispensable in contemporary medical diagnosis. Roughly, about 20% of MRIs are ordered with contrast.

MRI contrast agents designed for imaging the digestive tract mostly include solid magnetic materials generally in particular form. This is so because to be effective, the contrast agents should more or less line the walls of the digestive tract, thus requiring bulk. Obviously paramagnetic species in water-soluble molecular form would not fit the foregoing requirements and, if used, they should be associated with bulk carriers. A number of agents have been tried in humans for the purpose of distinguishing bowel from adjacent tissues (Bryant and Listinsky, 1990;

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doi:10.1016/j.clay.2009.11.041

Balkus et al., 1991; Balkus et al., 1992; Sur et al., 1993; Balkus and Bresinska, 1993; Balkus, 1994; Bresinska and Balkus, 1994; Balkus and Bresinska, 1994; Young et al., 1995; Balkus et al., 1995; Balkus and Shi, 1996). The problem of paramagnetic contrast agents is that they are generally toxic and must be rendered less toxic by one of several chemical manipulations in order to be acceptable for trial in humans. In addition, these agents usually produce high signal images which may cause bowel to be confused with surrounding tissues, particularly tissues that contain fat. Superparamagnetic particles have desirable contrast properties for purposes of bowel imaging but their long-term effects are unknown and their safety in human use remains to be established (e.g. they tend to clump in the gastrointestinal tract causing a conversion from paramagnetic to ferromagnetic properties). Additionally, superparamagnetic iron oxide administered in the quantities necessary for satisfactory imaging causes unpleasant side effects in human beings, including diarrhea and meteorism (Balkus, 1994).

At present, there is a need for a bowel contrast agent which is nontoxic and inexpensive, providing high contrast between bowel and the surrounding tissues and which comprises administration to the patient either by oral or rectal route. The requirements for such diagnostic drugs include stability under physiological conditions, low toxicity, and good image contrast at low dosages. Additionally, the contrast agent should evenly coat the bowel walls and not become diluted or absorbed as it passes through the intestines. Clay minerals can be effective water proton spin relaxation agents based on the surface effects in modifying the water molecule dynamics which govern both longitudinal and transverse spin relaxation rates (Grandjean, 2004). Furthermore, this effect should be intensified within clay minerals enclosing of paramagnetic metal ions. The process of paramagnetic metal encapsulation in clay minerals is usually performed by ion-exchange methods (Balkus and Shi, 1996). Microporous metal oxides such as zeolites (Balkus et al., 1991, 1992; Balkus and Bresinska, 1993; Sur et al., 1993; Bresinska and Balkus, 1994; Balkus and Bresinska, 1994; Young et al., 1995; Balkus et al., 1995) and clay minerals (Balkus, 1994) modified with paramagnetic metal ions or complexes have proven effective as positive contrast or brightening agents. However, within such materials there is a problem of potential leakage of toxic paramagnetic ions especially at low pH values. Accordingly, to be acceptable as MRI contrasts clay minerals should either be depleted of heavy metal contamination or to encapsulate paramagnetic by a method which confidently prevents ion-leaching.

The characteristic of modified clay minerals depend on number of parameters such as type of cations and size of clay mineral particles (Breen, 1999). One of the methods for intercalation of paramagnetic material into the clay mineral is the pillaring process (Kawano et al., 2003). Physical and chemical stability of pillared clay minerals containing transition metal ions is found to depend on the loadings of transition metal. Furthermore, the thermal stability, pore size, surface area, type and strength of acid sites of paramagnetic pillared bentonites depend on the method of pillaring and the pillaring species used (Narayanan and Deshpande, 2000). Pillared clay minerals with higher concentration of transition metal are less stable to acid attack (Carrado et al., 1986).

In this paper we propose the usage of pillaring method for paramagnetic metal encapsulation in bentonites for making efficient MRI contrast agents. By that way, paramagnetic cations like Fe^{+3}, Mn^{+2} and Gd^{+3} are introduced between clay mineral layers as metallic polyoxo cations. After calcination, these polyoxo cations grow to be pillars (oxides of these metals) which are incorporated into the clay mineral matrix which prevents ion-leaching.

2. Experimental

2.1. Sampling

Starting material was characterized domestic clay mineral from Bogovina, Serbia (Vuković et al., 2006). After milling, sieving and hydroseparation, the fraction of continuing particles up to 2 μm in diameter was used for further modification and denoted as raw clay mineral. The raw clay mineral's cation exchange capacity (estimated by ammonium acetate method) was 765 mmol kg^{-1}. The raw clay mineral was submitted to the Na-exchange procedure by repeated stirring with 1 M NaCl followed by filtering. Thus obtained filtration cake was rinsed with distilled water in order to have the excess of Na^+, Cl^- and other exchangeable cations removed from the sample. Rinsing was repeated until the filtrate was Cl^- free (confirmed by $AgNO_3$ precipitation test). The Na-exchanged clay mineral was dried at 110 °C and denoted Na–B.

2.2. Pillaring process

The process of pillaring was carried out according to a common procedure (Kaloidas et al., 1995). The initial steps of the procedure were swelling and the exchange of Na^+ ions with pillaring species (in this case Al^{3+}, Fe^{3+}, Mn^{2+}, and Gd^{2+} polyoxo cations). Pillaring solutions were adjusted to have the atomic ratio $M^{n+}/(Al^{3+}+M^{n+})$ of 10% (where $M^{n+}=Mn^{2+}$, Gd^{2+}or Fe^{3+}), $OH^-/(Al^{3+}+M^{n+})=2.0$ and metal cation/clay mineral ratio of 20 mmol M^{n+}/g. Another sample was synthesized using only Al^{3+} as pillaring specie denoted as Al-PILC and later used as a reference. The procedure included continuous stirring for 3 h at 60 °C and overnight at room temperature. In the next step the appropriate amount of the pillaring solutions, was slowly added into Na-exchanged bentonite dispersion in distilled water. After being rigorously stirred at 80 °C for 3 h the final suspension was stirred at room temperature overnight. The suspension was filtered through a Buchner funnel while hot. The obtained cake was rinsed with hot distilled water until the filtrate was NO_3^- free (tested by UV–Vis spectrophotometry), and finally air-dried overnight at 110 °C. The samples were subsequently calcined at 300 °C for 2 h and referred to as Al,Mn-PILC, Al,Gd-PILC and Al,Fe-PILC for the materials obtained using Mn^{2+}, Gd^{2+} and Fe^{3+} containing solutions, respectively. The chemicals used for Na exchange and pillaring were NaCl, NaOH and nitrate salts of Al(III), Fe(III), Mn (II) and Gd (II).

2.3. Characterzation

X-ray diffraction (XRD) patterns for powders of Na–B and pillared clay minerals were obtained using a Philips PW 1710 X-ray powder diffractometer with a Cu anode ($\lambda=0.154178$ nm).

Nitrogen adsorption–desorption isotherms were determined using a Sorptomatic 1990 Thermo Finningen at −196 °C. The samples were outgassed at 160 °C, during 20 h. Appropriate software (WinADP) was used to analyze the obtained isotherms.

Specific surface area of the samples, S_{BET}, was calculated according to Brunauer, Emmett, and Teller method (Gregg and Sing, 1967; Rouquerol et al., 1999). Total pore volume was calculated according to Gurvitch method for $p/p_0=0.98$ (Gregg and Sing, 1967). Micropores were analyzed using Dubinin–Radushkevich method (Dubinin, 1975).

The chemical characterization of clay mineral samples was performed using a Spectro Spectroflame M — inductively coupled plasma optical emission spectrometer, together with atomic absorption spectrometer.

For the purpose of MRI recording, water dispersions of grinded and homogenized clay mineral samples (4 mg/ml) were incorporated in ballistic gelatin-matrix (Sigma). Imaging process and relaxation time measurements were performed using clinical MRI device SIEMENS Impact 1.0 T (SIEMENS, Erlangen, Germany) with standard head-coil.

3. Results and discussion

3.1. Structural characterization

According to the X-ray diffraction patterns (Fig. 1) the following phases were identified in the investigated samples: smectite, quartz, feldspar and a small amount of amorphous phase (McClune, 1990).