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Cerium-doped diosmectite for topical application studies of the cerium–clay interaction

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Abstract

Cerium is used for its antiseptic and immunomodulatory properties in burn injury. We have developed a cerium-doped clay to replace existing ointments. Adsorption and release of cerium (Ce^{3+}) by diosmectite were studied at 22 ± 2°C, in the presence of various other cationic species. Simple spectrofluorimetric determination of cerium was used (λexc = 240 nm/λem = 360 nm). Cerium binding reached a plateau within 2 min and was a function of the electrolyte content of the solution in contact with the clay. Langmuir isotherm treatment led to a maximal binding capacity of 66 mg of Ce^{3+} per gram of clay. Partial release occurred within 2 min (19% in the presence of isotonic NaCl solution). The ionic strength of the solution, and the ionic radius and charge of the electrolytes present in the bathing solution significantly influenced cerium release, in contrast to pH and temperature changes. These results strongly point to a cationic exchange mechanism between diosmectite and cerium solution. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Cerium; Clay; Diosmectite; Cerium sorption; Release studies

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1. Introduction

Diosmectite (a smectite-group clay) has been widely studied for its remarkable absorption properties for various chemical species, and the large coverage that can be obtained owing to its very fine powder form; both features make it potentially suitable as a vehicle for topically applied pharmaceuticals. Each platelet (of micrometer and sub-micrometer size) is made up of lamellar aluminosilicate microcrystals. The layers

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consist of two-dimensional sheets of tetrahedral SiO_4 units (T) linked by an octahedral sheet of $Al(O,OH)_6$ units (O), forming T.O.T. sequences separated by an interlayer space of varying thickness. Isomorphous substitutions of less strongly charged cations create a negative diffuse surface charge over the basal plane of oxygen atoms of the layers, they may occur on octahedral sites (Fe^{2+}, Mg^{2+} in place of Al^{3+}) and more rarely on tetrahedral sites (Al^{3+} in place of Si^{4+}) (Fig. 1). Naturally occurring hydrated cations (K^+, Na^+, Ca^{2+}, etc.) present in the interlayer spaces neutralize this negative charge. The weak bonding between the layers and the hydrated cations enable exchanges with other inorganic or organic cations to occur. The therapeutic uses of this clay are based on these adsorption properties and the large external surface: 30–50 m^2/g for the external

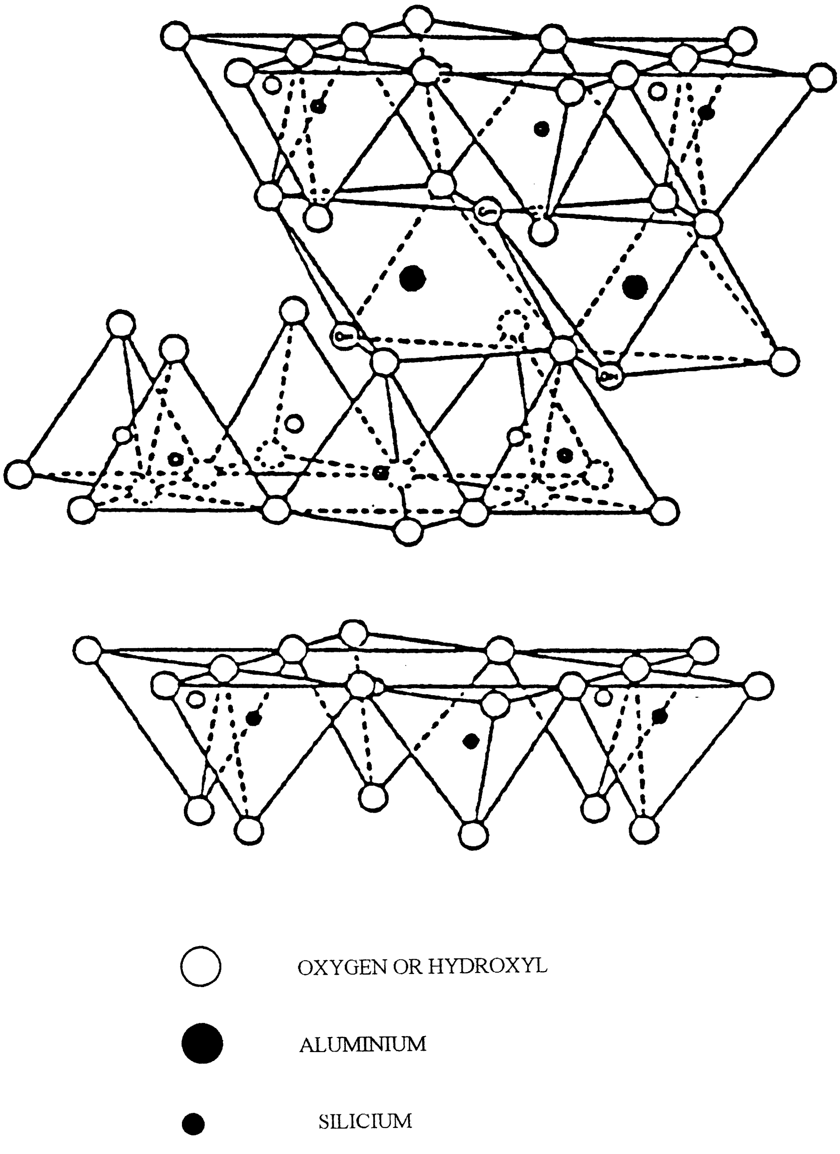

Fig. 1. Atomic structure of a layer of diosmectite, made of a sheet of $Al(O,OH)_6$ octahedra between two sheets of SiO_4 tetrahedra.

surface of the platelets, but about 700 m^2/g if the available surfaces in the expansible interlayer space are taken into account (McEwan and Wilson, 1980; Caillère et al., 1982).

In gastroenterology, the clay is used orally as a protective agent in gastritis and diarrhea. The adsorptive capacity is a serious drawback for the gastrointestinal absorption of many orally administered drugs (e.g. digoxin, quinidine, amphetamine, ciprofloxacin and tetracycline) (McGinity and Lach, 1976; Porubcan et al., 1978; Thoma and Lieb, 1983; Moustafa et al., 1987; Tuncel and Bergisadi, 1992). However, clays have been widely used in traditional dermatological remedies. In Mexico, for example, clays naturally enriched in silver are used in the treatment of burns (Triat, 1988).

The high exchange capacity of diosmectite (about 100 mEq/100 g of clay) makes it a potential drug delivery system for cationic species. Cerium has antimicrobial properties in vitro (Talbert and Johnson, 1967; Bahadur and Tripathi, 1979) and acts as an immunoregulator (Kremer et al., 1981; Hansbrough et al., 1984; Peterson et al., 1985; Zapata-Sirvent et al., 1986), a property exploited in the treatment of burns (Monafo et al., 1976). Highly promising clinical results have been obtained with topical cerium-containing ointments for burns (silver sulfadiazine plus cerium nitrate) (Fox et al., 1977; Monafo and Ayvazian, 1978; Helvig et al., 1979; Munster et al., 1980; Saffer et al., 1980; Bowser et al., 1981; Monafo, 1983; Hermans, 1984; Wassermann et al., 1989). The sensitivity of bacteria isolated from burn wounds to cerium nitrate and silver sulfadiazine has also been proved (Heggers et al., 1979; Rosenkranz, 1979; Saffer et al., 1980; Holder, 1982). Since 1993, an ointment (Flammacerium®) containing the silver salt of sulfadiazine and cerium nitrate has been marketed in some European countries.

Efforts are being made to develop new formulations of cerium salts for the topical treatment of burns. The great potential advantage of a cerium-doped clay is that it is easy to remove with water, without damaging underlying tissues.

This study deals with the spectrofluorimetric characterization of the exchanges between cerium solution and clay.

2. Materials and methods

2.1. Chemicals

Cerium nitrate and other salts (silver nitrate, lithium nitrate, sodium chloride, potassium chloride, cesium chloride, magnesium sulfate, calcium chloride, aluminium nitrate, iron (III) nitrate and silver nitrate) were provided by Aldrich Laboratories and were of analytical grade.

Diosmectite (batch: M08448/B008 005 953) was kindly supplied by Ipsen-Beaufour Laboratories (France). It has the following formula: $(Si_{3,83}\ Al_{0,17})\ (Al_{1,33}\ Fe_{0,31}\ Mg_{0,33})\ O_{10}(OH)_2\ K_{0,15}\ Na_{0,02}\ Ca_{0,14}$. The water used in this study was of MilliQ® quality (Millipore).

2.2. Apparatus

All the spectrofluorimetric measurements were performed on a LS 5B luminometer (Perkin-Elmer Instruments) in a quartz cuvette (10 mm optical path) at 22 ± 2°C. Excitation and emission slits were fixed at 10 and 5 mm, respectively. Excitation and emission wavelengths were 240 and 360 nm, respectively (Moulin et al., 1991).

2.3. Solutions

The aqueous stock solution of cerium nitrate (10^{-4} mol l^{-1}) was kept for no more than 1 week at +4°C.

Working standard solutions [5×10^{-7}–10^{-5} mol l^{-1}] were prepared by appropriate aqueous dilution of the previous stock solution.

Intraseries quality control are daily prepared from a standard 10^{-3} mol l^{-1} aqueous solution.

Aqueous stock solutions (10^{-2} mol l^{-1}) of the other electrolytes were prepared as required.

All solutions were prepared and stored in plastic volumetric flasks (Ce^{3+} adsorbs to glass).

2.4. Methods

2.4.1. Adsorption studies

In a 500-ml plastic beaker, 1 g of clay was suspended in 250 ml of aqueous cerium solution and shaken mechanically for 1 h at room temperature (22 ± 2°C). Cerium was determined fluorimetrically in the supernatant at various times (200 μl of centrifuged and diluted suspension). The remaining suspension was filtered on Büchner, and the residual cerium concentration was determined in the filtrate by means of spectrofluorimetry after appropriate aqueous dilution. The total amount of bound cerium was calculated as the difference between the initial concentration and the remaining concentration in the filtrate after 1 h of shaking.

The doped clay was then dried and stored at room temperature in a glass vial for release studies.

2.4.2. Release studies

To simulate potential conditions of therapeutic use, 0.1 g of cerium-doped diosmectite was suspended in 10 ml of release solution containing each electrolyte. After mechanical agitation for 1 h at room temperature, released cerium was determined, after centrifugation, in the supernatant (200 μl) at various times. The washed clay was then dried and stored at room temperature.

Plastic vessels were used for adsorption and release studies.

3. Results and discussion

3.1. Cerium assay method

The cerium ion belongs to the lanthanide group. Lanthanide elements are characterized by a progressive filling of the 4f atomic shell before the 5d shell (the cerium electronic configuration is schematically represented as [Xe] $4f_1$ $5d_1$ $6s_2$, where [Xe] is the electron configuration of the rare gas xenon). As a result, 4f electrons are shielded from the environment of the ion by the $6s_2$ atomic shell. Such electrons can be involved in energy transfer mechanisms through chelation of lanthanides by organic ligands (Soini and Lövgren, 1987). This characteristic confers on lanthanides long-lived luminescence, allowing time-resolved measurements to be made in solution. Moreover, emission from the luminescent species in solution is highly structured, with sharp bands corresponding to $4f \rightarrow 5d$ electron transitions. Like many lanthanides, cerium is luminescent in solution, but in contrast to samarium (Sm^{3+}), europium (Eu^{3+}) and terbium (Tb^{3+}) for instance, it shows broad UV emission (like many organic fluorophores).

The excited-state lifetime of cerium (in water) is about 77 μs, which is short in comparison with the other lanthanides (100 to 1000 μs or more depending on the solvatation and chelation conditions), but long in comparison with organic fluorophores. Moreover, no energy transfer reactions are recorded in the presence of ligands such as EDTA and tenoyltrifluoroacetone (Berthout et al., 1989; Moulin et al., 1991), indicating the weak tendency of cerium to chelate, in contrast to Sm^{3+}, Tb^{3+} and Eu^{3+}.

Given the topical use of cerium in burns and the need for interaction studies between clay and Ce^{3+}, we used these original spectral properties to develop a simple and rapid cerium assay for application to solutions in contact with clay. We thus used direct steady-state measurements rather than time-resolved fluorimetry (TRF); in addition, the former was more sensitive than the latter. The maximum of excitation and emission were respectively 240 and 360 nm. Moreover, emission intensity remains constant between pH 1 and pH 8, while $Ce(OH)_3$ precipitates at pH values over 8. Changing the anion in the cerium salt (chloride, nitrate, sulfate) had no effect on the fluorescence yield.

To check that the detection method was specific, an aqueous suspension of cerium-free diosmectite was shaken in the conditions described in the experimental section (i.e. with pure water and the different electrolyte solutions used in this study); after centrifugation, the supernatant was analyzed over a period of 12 h; no interfering signal was recorded.

Attempts to enhance the sensitivity of the analytical procedure were unsuccessful. Micellisation of the cerium-tenoyltrifluoroacetone mixture by using a surfactant such as Triton X100 (Moulin et al., 1991) provided no increase in the luminescence signal in either the steady-state or TRF method in comparison with direct steady-state fluorescence. This clearly confirms, in our experimental conditions, the weak propensity of Ce^{3+}

Table 1
Spectrofluorimetric determination of cerium: analytical figures of merit[a,b,c]

Concentration (mol l^{-1})	Repeatability RSD[d] (%)	Reproducibility RSD[d] (%)
1×10^{-6}	9.3	10.4
2.5×10^{-6}	4.7	6.1
5×10^{-6}	3.2	5.6

[a] Linearity (mol l^{-1}): 10^{-6}–10^{-5}.
[b] Limit of detection (mol l^{-1}): 2×10^{-7}.
[c] Limit of quantification (mol l^{-1}): 10^{-6}.
[d] Relative standard deviations ($n=6$).

to be chelated and involved in an energy transfer process, in contrast to species like Tb^{3+}, Sm^{3+} and Eu^{3+}. Given the inner filter effect, linearity was assumed up to 10^{-5} mol l^{-1} and the method was thus validated within this range (Table 1). The proposed method of Ce^{3+} assay in aqueous solution is thus well suited to our purpose; being rapid and simple, it can be used in cerium–clay interaction studies.

3.2. Sorption studies

At room temperature, cerium is rapidly bound by diosmectite (< 2 min), as shown in Fig. 2. The amount fixed is a function of the cerium concentration in the solution in contact with the clay. The kinetics was concentration-dependent: at cerium concentrations of 10^{-3} mol l^{-1} or less, a plateau was reached within 2 min; in contrast, equilibrium was reached more slowly at higher concentrations ($[Ce] > 2.5\times10^{-3}$ mol l^{-1}). With these high concentrations of cerium, the kinetic profiles showed marked fluctuations during the first 20 min. This variability was verified for three kinetics. In addition it is known that it depends upon experimental conditions and particularly on the presence of CO_2 dissolved in water. In order to minimize these phenomena, it is possible to work under nitrogen. As shown in Fig. 3, the binding of cerium to diosmectite depended on the amount of cerium present in the solution and exhibits a saturable trend.

One gram of clay bound 63 ± 12 mg of cerium ($n=13$) in these conditions, and a Langmuir isotherm leads to a maximal adsorption capacity of 66 mg/g (i.e. 141 mEq/100 g), in keeping with the former calculated value. These data are in keeping with published data, viz. 80 to 150 mEq/100 g for smectites (Caillère et al., 1982). In similar experimental conditions, Bonnot-Courtois (1981) reported an adsorption capacity of 50 mg of Ce/g. From a theoretical point of view, this Langmuir modelisation can be interpreted as reflecting adsorption of cerium in monolayers (McGinity and Lach, 1976).

The amount of cerium bound was also a function of the amount of diosmectite present. Nevertheless, the increase in bound cerium was not strictly proportional to the amount of clay present: with increasing amounts of clay (250, 500, 750, and 1000 mg), the weight ratios of cerium fixed to clay were respectively 44 ± 7, 51 ± 6, 52 ± 4, and 47 ± 6 mg/g. Mean fixation was 51 ± 10 mg/g, a result similar to the mean amount of cerium bound per gram of clay (66 ± 12 mg), as determined with the Langmuir

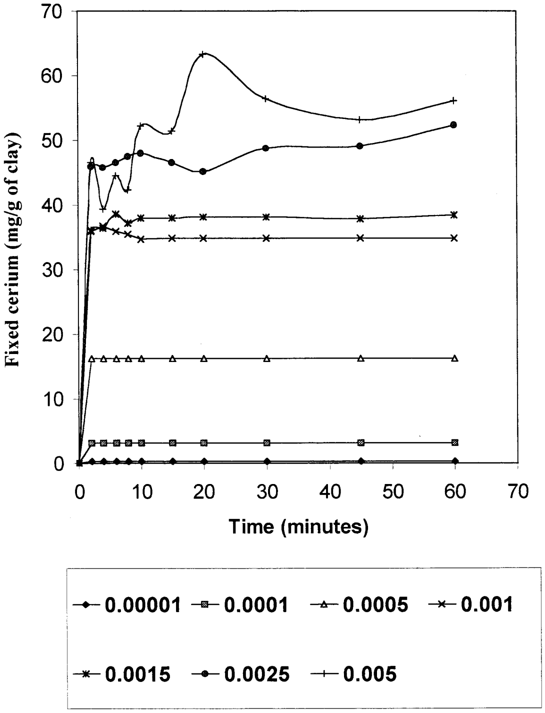

Fig. 2. Kinetics of cerium binding to diosmectite; influence of the cerium concentration.

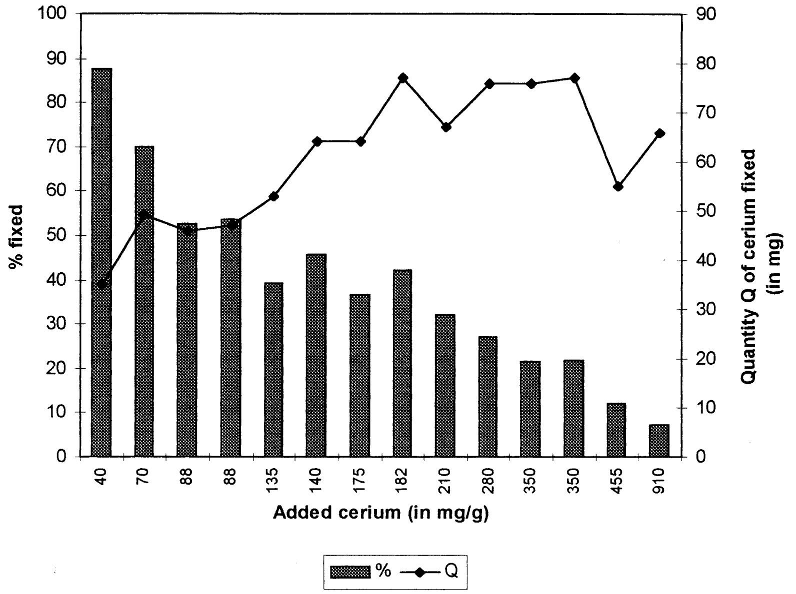

Fig. 3. Cerium binding as a percentage (left ordinate) and in absolute amounts (mg) (right ordinate) as a function of cerium in contact with clay (1 g in all experiments).

isotherm. One explanation for these results is that high clay concentrations might lead to the collapse of platelets, thereby reducing the exchange surface.

We investigated the potential influence of the solution pH (2.3 and 7.4) on the binding capacity of the clay. In keeping with published data (Frysinger and Thomas, 1960), pH had no influence. Thus, in our experimental conditions, it does not appear to be necessary to adjust the pH to a value different from that of the cerium solution (pH = 5.2). Finally, no influence of temperature on the binding kinetics was found between + 4°C and + 22°C.

3.3. Release studies

3.3.1. Influence of the electrolytes in solution

As cerium-doped clay would be in contact with physiological fluids in clinical use, release studies were performed with physiological saline.

Like its binding, the release of cerium from doped diosmectite was extremely rapid ($<$ 2 min) both at room temperature (Fig. 4) and at + 4°C. Two phases of release were observed: a rapid exchange during the first 10 min, then a plateau phase reflecting steady-state conditions.

In our experimental conditions, $19 \pm 2\%$ ($n = 5$) of the cerium was released within 1 h, whatever the initial cerium concentration (mg/g). The results were highly reproducible, whatever the doped clay sample used. No influence of pH was observed between 2.3 and 7.4.

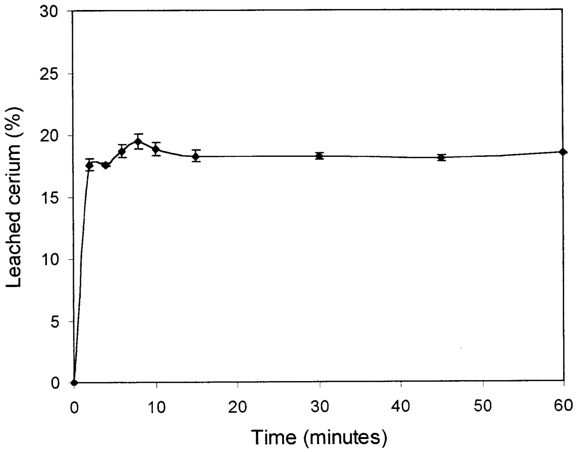

Fig. 4. Release of cerium from a doped diosmectite (76 mg of Ce^{3+}/g) (% of sorbed cerium). Releasing electrolyte solution 0.09% NaCl.

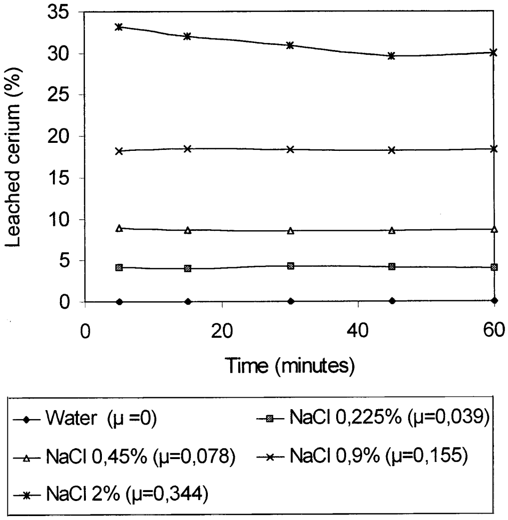

Fig. 5. Cerium release (percentage of sorbed cerium) from doped clay as a function of the ionic strength (doped diosmectite 76 mg/g).

Another important aspect of the release process is the influence of the composition of the solution (ionic strength, nature of the ions). As shown in Fig. 5, no release occurred when the doped diosmectite was in contact with pure water. This strongly suggested, as expected, that the release of cerium involves a cation-exchange mechanism between Ce^{3+} and an equivalent amount of Na^+. The same figure confirms that the higher the ionic strength, the stronger the release (ionic exchange is increased by the mass-action law effect).

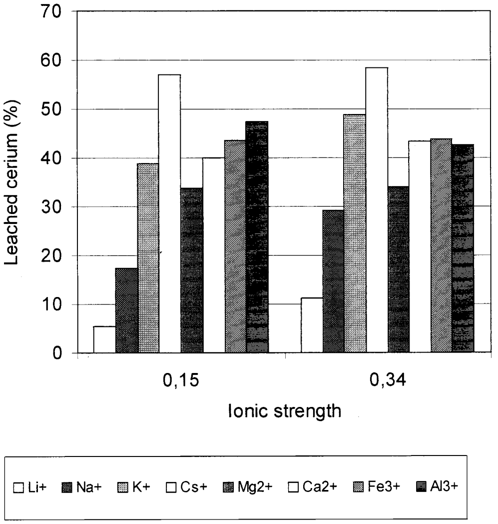

Fig. 6. Influence of the cation in solution on the releasing of cerium with two sets of ionic strength (doped diosmectite 77 mg/g).

The role of the charge and size of the ion exchanged with cerium was studied by measuring cerium release in the presence of various cations. Table 2 shows certain physical characteristics of the metal ions studied (Na^+, K^+, Li^+, Cs^+, Mg^{2+}, Ca^{2+}, Fe^{3+}, Al^{3+}) (Ball and Norbury, 1974; Dean, 1985). These characteristics appeared to account for differences in cerium exchange, as shown in Fig. 6. The cations were chosen for their biological importance (Na^+, K^+, Mg^{2+}, Ca^{2+}) or their presence in gallenic forms (Al^{3+}). Cesium

Table 2
Chemicophysical and electronic parameters of the studied cationic species

Cation	Salts-used	pH[a]	Ionic radius (Ri) (Å)	Electronegativity (according to Pauling, Ep)
Ce^{3+}	$Ce(NO_3)$	5.5	1.07	1.12
Li^+	$LiNO_3$	6.6	0.78	0.98
Na^+	NaCl	6.4	0.98	0.93
K^+	KCl	6.0	1.33	0.82
Cs^+	CsCl	6.6	1.65	0.79
Mg^{2+}	$MgSO_4$	6.0	0.78	1.31
Ca^{2+}	$CaCl_2$	5.7	1.06	1.00
Al^{3+}	$Al(NO_3)_3$	2.6	0.57	1.61
Fe^{3+}	$Fe(NO_3)_3$	1.4	0.67	1.83

[a] Of the corresponding aqueous solution [M]/0.15 mol l^{-1}.

was used in order to test the effect of an ionic radius (1.65 Å) greater than that of Ce^{3+} (1.07 Å). At constant ionic strength, the stronger the charge of the metal ion, the stronger the release, with the exception of K^+ and Cs^+. These latter two metals have far larger ionic radii than the other ions, especially cerium (see Table 2), pointing to distinct influences of the charge and size of the ions on cerium release.

Thus, for a given valency (e.g. 1), release was directly proportional to ionic radius (Fig. 7), a phenomena no doubt related to the pore diameter of the surface layers of diosmectite particles (5 Å) (Caillère et al., 1982).

Highly charged cations and those with large ionic radii seem to be preferentially exchanged with cerium. Nevertheless, the influence of K^+ and Cs^+ on cerium release is not fully explained by either charge or size. The main parameter influencing this exchange may be the hydration sphere around the cation rather than the ionic radius itself (Brown and Kevan, 1988), as the hydration sphere is a complex function of the charge of the cation and its electronegativity (Berry et al., 1980). Nevertheless, multilinear regression analysis of percentage release, ionic size, electronegativity and ionic strength failed to correlate ($r = 0.898$), underlining the complexity of the ion-exchange mechanism involved and the weakness of a model involving only these three characteristics.

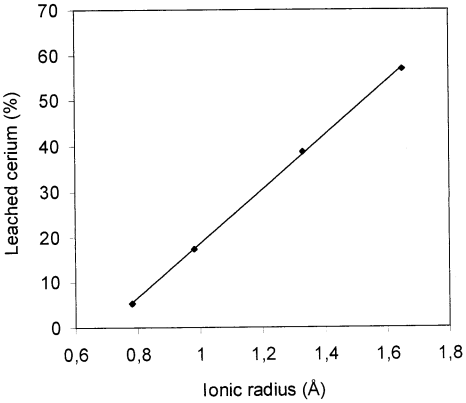

Fig. 7. Cerium release (percentage of sorbed cerium) as a function the ionic radius of the monovalent species in the releasing solution (m = 0.15 mol l^{-1}); doped diosmectite 76 mg/g.

3.3.2. *Influence of the cerium–clay ratio*

Release also appeared to depend on the amount of clay. For instance, 19 ± 2% ($n = 3$) of cerium was released from 100 mg of doped diosmectite, compared to 30 ± 1% ($n = 3$) from 8 mg of doped diosmectite. Once more, as underlined in the binding studies, this may be related to a collapsing effect of the suspended clay particles at high concentrations.

Cerium release is thus a rapid process, although it is never total. This points to at least two kinds of binding site, one of which appears to be a purely cationic exchange site.

This can be chemically depicted through the following equations:

for monovalent or trivalent species exchanged with cerium:

$$Ce^{3+} + C(M^{3/n+})_n \rightleftarrows C(Ce^{3+}) + nM_s^{3/n+}$$

for divalent cations:

$$nCe^{3+} + C(M^{2+})_m \rightleftarrows C(Ce^{3+})_n + mM_s^{2+}$$

the subscript s refers to the species in solution, while M is the cation exchanged with cerium and C refers to the clay.

The other binding site seems to correspond to a more highly bound cerium and to require more drastic conditions for bond disruption than those explored here.

More specific studies of this point are underway by means of EXAFS (extended X-ray absorption fine structure), which is suited to investigate the environment of determined photoexcited cations.

Moreover, the influence of the quantity of clay on the release was only studied for two ratios in order to detect a phenomenom limiting the release due to dispersion of the sample. Indeed, this parameter is essential since diosmectite is destined to be used in the form of a powder.

Particule aggregation could be a factor limiting the release of cerium by decreasing exchanges. Kinetic studies with increasing quantities of doped-clay will be carried out in vitro on skin samples (topical application) and no longer in solution.

4. Conclusion

This preliminary work suggests that stable cerium-doped diosmectite can be prepared for topical use in burns units. The amount of cerium bound depends on the concentration of cerium in solution and the amount of clay used, meaning that strictly standardized conditions must be used to obtain reproducible doped diosmectite. pH and temperature appear to have far less influence. Clays produced in this way can only release a fraction of the fixed cerium (19% in the presence of normal saline), by an ion-exchange mechanism.

The rapidity of the binding and release processes in the presence of various cations strongly suggests that cerium covers the surface of platelet or the layers, thereby balancing the negative surface charges of the clay layers. If so, some of the bound cerium would be readily available for rapid cationic exchange with the environment, e.g. burn wound exsiccate. The remaining fraction of fixed cerium seems to be more tightly bound, probably through interaction with constituent clay atoms (may be in intralayer zones). The cerium ion also appears to be a convenient model for studying cation–diosmectite interactions, owing to its spectroscopic properties. The physicochemical interest as well as the biological efficacy (data not shown) prompted us to register a patent (Castéla-Papin et al., 1997). In vivo studies should now be envisaged to evaluate the possible clinical use of a topical cerium/diosmectite delivery system.

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