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Microporous material from kanemite for drug inclusion and release☆

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Abstract

A microporous material obtained from kanemite, a layered polysilicate, was studied in order to investigate its feasibility of including drugs and then releasing them. Diphenydramine hydrochloride was chosen as a model drug. The preparation of the microporous material and its loading with the drug are described. As kanemite is able to intercalate anions between its layers, the intercalation compound of diphenydramine and kanemite was also prepared. Both the drug-loaded microporous material and the intercalation compound were submitted to dissolution tests at pH 7.5. The drug release profiles from these two different materials and from a physical mixture were compared. © 2001 Éditions scientifiques et médicales Elsevier SAS

Keywords: Kanemite; Microporous material; Intercalation compound; In vitro release

1. Introduction

Kanemite [1] ($NaHSi_2O_5 \cdot 3H_2O$) is a layered polysilicate, whose layers are composed of single-layered sheets of SiO_4 tetrahedra. It is able to exchange the sodium ions intercalated between the layers with other ions, with a consequent increase of the interlayer distance.

Kanemite has also been used for the preparation of micro- and meso-porous materials [2] that could find application as catalysts, molecular sieves and hosts for the inclusion of a large variety of compounds. The preparation of micro- and meso-porous materials is possible thanks to the capacity of the layer to generate a specific tridimensional reticulate during the intercalation of an appropriate organic compound.

In this paper the microporous material obtained from kanemite was studied in order to investigate its feasibility of including drugs and then releasing them. Diphenydramine hydrochloride was chosen as a model drug. Moreover, as kanemite is able to intercalate ions, we realized the intercalation of diphenydramine hydrochloride in kanemite and compared the release profile of the drug from the intercalation compound with that from the drug-loaded microporous material.

2. Experimental

2.1. Materials and methods

All chemicals and solvents were of reagent grade and were used without further purification. Diphenydramine hydrochloride was purchased from Sigma Chemical Co., St Louis, MO.

X-ray powder diffraction patterns (XRDP) were taken with a PW 1710 Philips diffractometer (Lelyweg, The Netherlands), using Ni-filtered Cu Kα radiation. Elemental analyses (C, N, H) were performed with a Carlo Erba Elemental Analyzer mod. 1106 and the results were within $\pm 0.4\%$ of the theoretical values. The N_2 adsorption–desorption isotherms were determined by nitrogen adsorption at -196°C using a Micromeritics ASAP 2010 apparatus. The preparation of samples was made by degassing the materials at

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350°C, overnight. The specific surface area was determined by the BET method, while the porosity was evaluated by BJH and *t*-plot analysis [3]. Drug determinations in samples were performed by UV spectrophotometry using a JASCO V-520 (Tokyo, Japan) at $\lambda_{max} = 259.6$ nm. The Na^+ content was determined by atomic emission spectroscopy using a Perkin–Elmer 3100.

2.2. Preparation of kanemite/DOD complex

Kanemite, prepared according to Beneke and Lagaly [4], 1 g (0.0047 mol), was added to 100 ml of an aqueous 0.1 M solution of dodecyltrimethylammonium (DOD) hydrochloride and stirred for a week at 65°C, keeping the pH between 8 and 9. The solid was collected by filtration and the same procedure was repeated. Finally the product was filtered, washed with acetone and dried. The kanemite/DOD complex was characterized by XRDP, and its formula was determined by elemental analysis. The Na^+ content was determined by atomic emission spectroscopy, after equilibration for 1 day of a known amount of kanemite/DOD complex with 0.1 M HCl solution.

2.3. Preparation of microporous material

The kanemite/DOD complex was calcined at 700°C for 6 h until pyrolysis of the organic moiety was complete. The calcined product was characterized by XRDP, and superficial area and porosity determinations.

2.4. Preparation of inclusion compound of diphenydramine hydrochloride and microporous material

Microporous material (200 mg) was equilibrated with 20 ml of a 2 M aqueous solution of diphenydramine hydrochloride for 1 day. The solid was collected by filtration.

2.5. Determination of drug content of the inclusion material

A known amount of the inclusion material was treated with 50% HF until decomposition of the inorganic fraction took place. Drug content was determined by UV spectroscopy.

2.6. Preparation of the physical mixture of kanemite and diphenydramine hydrochloride

A physical mixture was prepared by lightly triturating an appropriate quantity of diphenydramine hydrochloride and of kanemite, using a small mortar and pestle.

2.7. Preparation of the intercalation compound

Kanemite, (1 g, 0.0047 mol), was added to 80 ml of an aqueous diphenydramine hydrochloride 0.6 M solution. The suspension was stirred at room temperature for 2 weeks. The solid was collected by filtration, washed with acetone and dried.

This compound was characterized by X-ray powder diffraction and elemental analysis. The determination of the drug content was realized as described above for the inclusion material.

2.8. In vitro dissolution studies

The drug release was performed in the dissolution apparatus, USP paddle type (Steroglass, Perugia, Italy). The paddle rotation speed was 100 rpm and the flasks were kept in a thermostatically controlled circulation water bath at 37 ± 0.5°C. The dissolution media were simulated intestinal fluid at pH 7.5 ± 0.1 without pancreatine according to USP. The dissolution studies were done under sink conditions. Samples of 4 ml were withdrawn at pre-determined intervals, followed by replenishment after each withdrawal with the same volume of fresh medium equilibrated at 37 ± 0.5°C. Samples were appropriately filtered (13 mm Filter Unit 0.45 μm NY PP, Lyda, WI), diluted when necessary and analyzed by UV spectrophotometry ($\lambda_{max} = 259.6$ nm). The drug release from the microporous material and from the intercalation compound was compared with that obtained from the physical mixture (kanemite/diphenydramine hydrochloride). The tests were made in triplicate and the results were registered as an average.

3. Results and discussion

The pillaring method is the most frequently used way of preparing micro- and meso-porous materials [5], but in the case of kanemite a different strategy can be used [6]. It consists of interlayer cross-linking of a layered silicate during the ion exchange reaction with appropriate organic cations. In these conditions the silicate layers of a single-layered polysilicate-like kanemite are condensed to form three-dimensional silicate networks. Then, by calcination, the silicate–organic complexes are converted to micro and mesoporous materials with uniform pore size distributions.

Thus the preparation of the drug inclusion compounds consisted of two steps, first the preparation of the microporous material and then the loading with the drug.

Kanemite was suspended in a solution of dodecyltrimethylammonium chloride in order to obtain ionic exchange of the interlayer Na^+ with the organic

ions. The XRDP of kanemite (Fig. 1) and the product obtained by reaction with dodecyltrimethylammonium (DOD) chloride (Fig. 2) show the disappearance of the peak at 1.03 nm characteristic of kanemite [1] and the appearance of a peak at 3.73 nm consequent upon the increase of the interlayer distance and as proof of the DOD intercalation [6]. From elemental analysis and atomic emission spectroscopy the formula of this compound was $HNa_{0.43}Si_2O_5 \cdot 0.57DOD \cdot 0.1H_2O$. This result

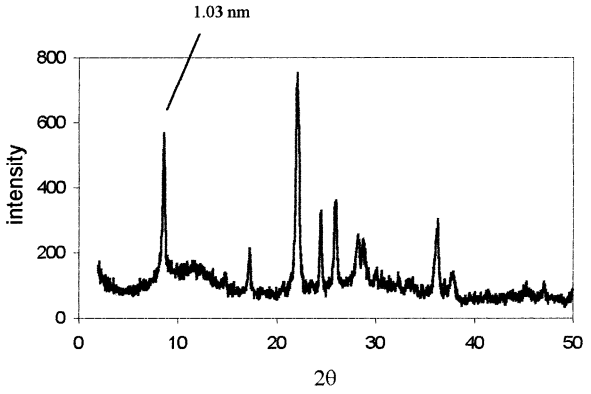

Fig. 1. XRDP of kanemite.

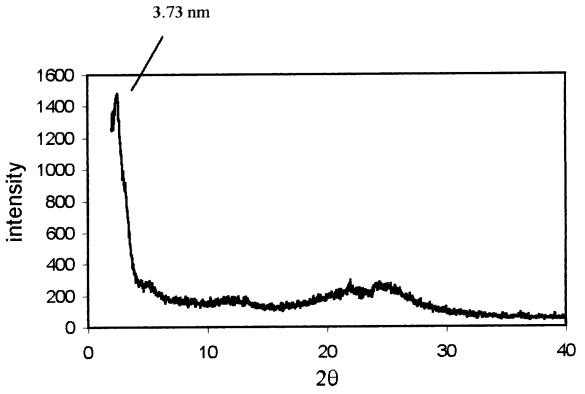

Fig. 2. XRDP of kanemite/DOD complex.

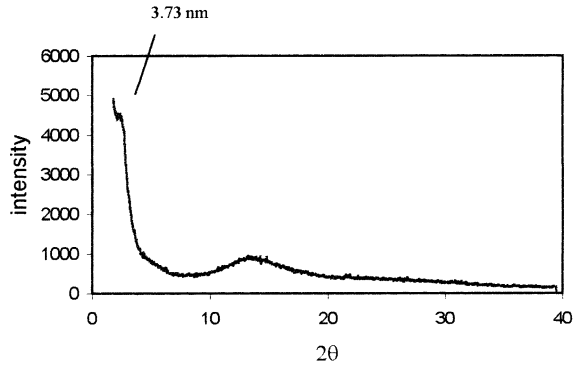

Fig. 3. XRDP of microporous material.

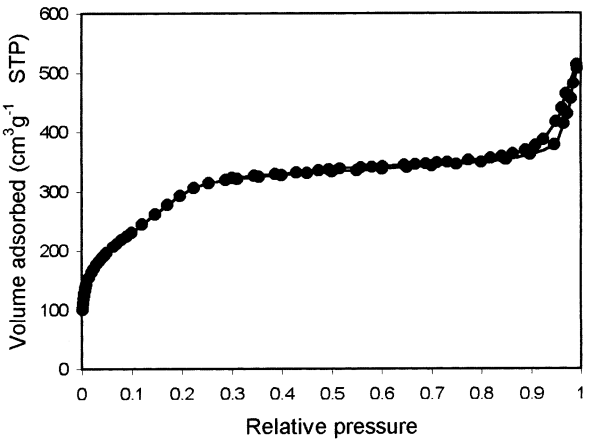

Fig. 4. Nitrogen adsorption–desorption isotherm at −196°C of kanemite calcined material.

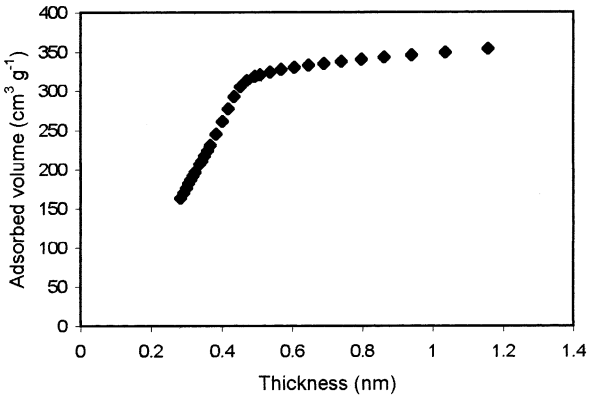

Fig. 5. *t*-Plot analysis of kanemite calcined material.

indicated that not all the Na^+ ions were exchanged with DOD.

The product was then converted in the microporous material by removing the organic fraction by means of calcination. The XRDP (Fig. 3) show that even in the calcined product, the three-dimensional network was retained. The specific surface area and the pore size distribution of the calcined compound were also characterized. The nitrogen adsorption–desorption isotherms are shown in Fig. 4. The calculated BET surface area of the sample was 1014 m^2/g. From *t*-plot analysis it was found that only 118 m^2/g were attributable to the external surface, while the estimated micropore volume was about 0.44 cm^3/g (Fig. 5). The pore size distribution performed by the MP method indicated that the mean hydraulic radius was lower than 0.55 nm. From BJH analysis too, some pores with dimensions in the range of 3–30 nm and a volume of 0.11 cm^3/g were found.

The loading of diphenydramine hydrochloride in the microporous material was obtained by equilibrating this material with an aqueous solution of the drug for 1 day. The diphenydramine content was evaluated after

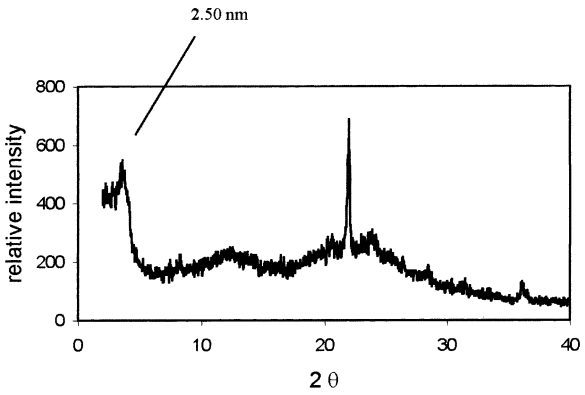

Fig. 6. XRDP of the intercalated compound.

decomposition of the inorganic fraction with HF and drug determination with UV spectroscopy. The drug content in the inclusion product was determined to be 0.216 g/g.

The intercalation of diphenydramine in kanemite, due to the ionic exchange Na^+/diphenydramine hydrochloride, was performed by equilibrating a solution of the drug with kanemite (molar ratio 10:1). As a consequence of diphenydramine intercalation, the interlayer distance of the host increased from 1.03 nm, the interlayer distance of kanemite, to 2.50 nm as shown by the X-ray powder diffraction (Fig. 6). From elemental analysis and UV drug determination, the intercalation compound (Kanemite-DIF) composition was determined to be $H_{1.44}Si_2O_5DIF_{0.56}{\cdot}1H_2O$. The drug content was determined to be 0.428 mg of diphenydramine per 1 g of intercalation compound.

Both the microporous material and the intercalation compound were submitted to in vitro release at pH 7.5. The drug release profiles are illustrated in Fig. 7. The release of diphenydramine from the physical mixture was already complete after 30 min. Dissolution of the drug from the microporous material was at first fast, so that within 5 min, 60% of the drug was released, and then slow and the release was complete after 180 min. The release of diphenydramine from the intercalation compound had a different profile. It was gradual but not complete and only 30% of the drug was released at all. In this case the drug is released by a process of de-intercalation, due to ionic exchange between the intercalated diphenydramine ions and the Na^+ present in the medium. In order to explain why a large amount of drug was retained, a hypothesis can be drawn. When small species (in this case Na^+) exchange bigger ions (intercalated drug), a consequent decrease of the interlayer distance occurs. The exchange of ions begins from the external part of the layer and usually causes the formation of an external phase with a smaller distance [7] that could obstruct the exit of the big intercalated ions.

In the case of the microporous material different considerations can be drawn. From this material the drug is released by diffusion and the size, the length and the tortuosity of the pores play an important role. From our studies of a specific surface area and porosity it was found that kanemite microporous material shows pores with different sizes. The part of the drug adsorbed on the larger pores (3–30 nm) was released fast, whereas the other part of the drug, which occupies the micropores with a lower mean hydraulic radius, was released slowly.

Other studies are in progress in order to prepare a microporous material with a lower pore size and to obtain a slower drug release.

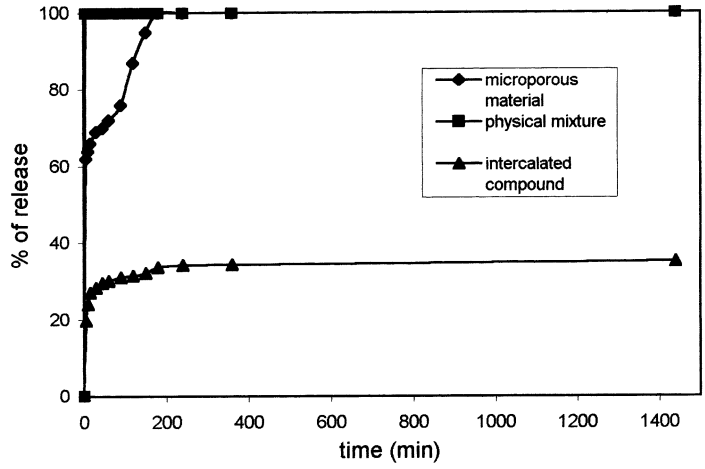

Fig. 7. In vitro drug release at pH 7.5.

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