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Interference of 1:1 and 2:1 layered phyllosilicates as excipients with ranitidine

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ABSTRACT

As natural ingredients and excipients, kaolinite and talc were frequently studied for their interactions with drugs in pharmaceutical formulations. In this study, the uptake of ranitidine (RT) on these two minerals was studied under different physic–chemical conditions and the mechanism of RT uptake on these two minerals contrasted. Although the thermodynamic and kinetic RT uptake on these two minerals was similar and the RT uptake on both minerals were limited to the external surfaces only, drastic difference in RT uptake was found under different equilibrium solution pH and ionic strength conditions. As cation exchange process was strongly affected by solution pH and ionic strength, the RT uptake on kaolinite was dominated by cation exchange and electrostatic interactions, while the RT uptake on talc was more controlled by inter- and intra- molecular hydrogen bonding interactions. For kaolinite, the limiting factor for RT uptake was the specific surface area due to monolayer RT adsorption. In contract, multilayer RT uptake was found on talc surfaces. No matter which mechanism dominated RT uptake on these minerals, the interaction should not be neglected in pharmaceutical formulations should these minerals be used as additives and/or excipients.

1. Introduction

Kaolinite and talc are among the clay minerals used in pharmaceutical and cosmetic industries, either as active ingredients [1] or as excipients [2,3]. As a drug carrier kaolinite was demonstrated for its uptake of 5-fluorouracil on the external surfaces and in the interlayer spaces after modification with dimethyl sulfoxide [4]. Talc, is a suitable excipient for incorporation in crystallo-co-agglomeration technique, due to its hydrophobicity and preferential wetting with bridging liquid [5].

As excipients, minimal interactions with the drug should be anticipated. However, interactions between drugs and excipients were frequently found. Stronger inhibitory effect was found for rifampicin when bentonite was present as an excipient due to adsorption [6]. Kaolin was found to decrease chloroquine partitioning into the buccal membranes in three healthy volunteer subjects and was likely to decrease the effectiveness of chloroquine as an anti-rheumatic or anti-malarial drug if taken together with kaolin [7]. In cationic form at low pH, benzodiazepine diazepam was found to adsorb onto the negative sites of kaolin and talc [8]. Incorporation of kaolin in the formulation of chloroquine and chlorpheniramine tablets, and in amoxycillin/clavulanic acid and ampicillin/cloxacillin powder combinations significantly reduced the amount of the active drugs released into the dissolution; as such, its inclusion in such drug formulations should not be encouraged [9]. Although the adsorptive ability of kaolin was demonstrated for four drugs, it may also be possible that kaolin has affinities for other drugs [9]. An uptake of ciprofloxacin (CIP) as high as 6% was found on kaolinite [10].

For talc, a strong affinity for antibiotic CIP with a capacity of 0.74 mg/g was reported [11]. On the contrary, no interaction was found between talc and nateglinide [12]. These studies demonstrated that further work is still needed to study the effect of adsorption of drugs on talc and the interferences of drugs by talc [13].

Ranitidine (RT) is a selective H_2-receptor antagonist and powerful inhibitors of gastric acid secretion introduced for the treatment of peptic ulcers and related disorders [14]. Tests on its compatibility with several excipients showed that interactions were found

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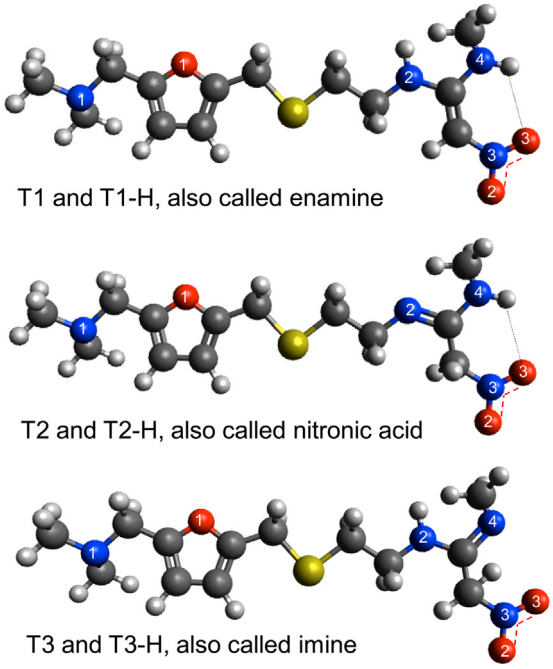

Fig. 1. Molecular structure of ranitidine with different tautomers. The yellow is S, red O, blue N, dark gray C, and light gray H. The top was considered as a thermodynamically stable form while the bottom as a kinetically stable form [24]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

under the storage conditions for 3 months for all excipients tested as conformed by the TG and FTIR analyses [15].

The goal of this study was to study and contrast the interactions between drugs and fillers/excipients using RT as a representative cationic drug and kaolinite and talc representing 1:1 and 2:1 layered clay minerals as the substrates. The results would provide information such as the types, degrees, and mechanisms of drug-excipient interactions for better drug formulation and minimization of drug-substrate interference.

2. Materials and methods

The representative 1:1 type clay used was KGa-2, a poorly crystallized kaolinite mineral obtained from the Clay Mineral Repository in Purdue University. The 2:1 type clay used was talc purchased from Acros. The specific surface area (SSA) was 21.7 [16] and 2.3 m^2/g for kaolinite and talc, respectively. The point of zero charge (pzc) was 4 and 7.7 for kaolinite and talc, respectively [17–19]. As the kaolinite was a standard clay mineral while the talc is relatively pure with only about 2% of clinochlore as determined by semiquantitative X-ray diffraction analyses, they were used as received without further treatments.

The ranitidine or *N*-[2-[[[5-1[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-*N′*-methyl-2-nitro-1,1-ethenediamine [20] used was in the HCl form (CAS# 66357-59-3). It has a molecular weight of 350.86 g/mol, a pK_a value of 8.2 [21,22], and an octanol–water partition coefficient close to 2 (logP∼0.3) [23]. It is freely soluble in water and is stable in aqueous solutions. It can exist as different tautomers T1–T3 [24] or enamine, nitronic acid, and imine [25] (Fig. 1).

In a typical experiment, 1.0 g of kaolinite or talc was combined with 10 mL of RT aqueous solution in 50 mL centrifuge tubes. The initial RT concentrations varied from 0 to 4 mmol/L for the isotherm study and were fixed at 1.2 or 1.0 mmol/L for all other tests using kaolinite and talc, respectively. The mixtures were shaken at 150 rpm for 24 h, with the exception of the kinetic study, and then centrifuged at 3500 rpm for 10 min. The supernatants were passed through 0.45 μm syringe filters before being analyzed for the equilibrium RT concentrations using a UV–vis method. For the kinetic study, the samples were shaken for 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 24 h, respectively. For the pH study, the equilibrium solution pH was adjusted to values between 2 and 12 using minute amounts of 1 M HCl or NaOH. For ionic strength tests, the solution was adjusted to reach NaCl concentrations of 0.001, 0.01, 0.1, and 1.0 M. For the temperature study, the mixing was maintained at 32, 42, and 52 °C in a Hybaid Micro-4 hybridization oven rotator incubator.

The equilibrium solution concentrations of RT were measured by the UV–vis method at a wavelength of 312 nm that was one of the two peak absorbance values [20,26] and was stable over pH 3.5–12 range [14]. In a separate study, 313 nm was used with a good linear calibration between 0 and 20 mg/L [27].

The FTIR spectra were acquired from 600 to 4000 cm^{-1} by accumulating 256 scans at a resolution 4 cm^{-1} using a Jasco FT/IR-4100 Spectrometer equipped with a ZnSe crystal and attenuated total reflection accessory. The powder X-Ray diffraction (XRD) analyses were conducted using a D8 ADVANCE diffractometer (Bruker Corp.) under a CuKα radiation at 40 kV and 40 mA. Samples were scanned from 2 to 20° 2θ with a scanning speed of 0.01°/s.

3. Results and discussion

3.1. RT uptake as affected by initial concentrations

For both minerals, the RT uptake increased as the initial RT concentrations increased (Fig. 2a). The experimental data were fitted to both Langmuir and Freundlich models. The Langmuir model has the formula:

$$C_S = \frac{K_L S_m C_L}{1 + K_L C_L} \quad (1)$$

where C_S is the amount of RT uptake at equilibrium (mmol/kg), S_m the apparent uptake capacity (mmol/kg), C_L the equilibrium RT concentration (mmol/L), and K_L the Langmuir coefficient (L/mmol), reflecting the affinity of solute for the substrate. The Fruendlich isotherm has the formula of:

$$C_S = K_f C_L^n \quad (2)$$

where K_f is the Freundlich coefficient (mmol^{1-n}-L^n/kg), representing the affinity of the solute for the surface, and n is the Freundlich exponent. The fitted results were S_m = 15 and 18 mmol/kg, and K_L = 2.8 and 1.4 L/mmol, for RT uptake on talc and kaolinite, respectively. When the Freundlich model was used, the fitted parameters were K_f = 9.8 mmol^{1-n}-L^n/kg and n = 0.45 for RT uptake on both minerals. Compared to the cation exchange capacity (CEC) value of 37 $mmol_c$/kg [28] for the kaolinite, the amount of RT uptake only accounted for half of the CEC value. In comparison, RT uptake on diosmectite resulted in a capacity of 610 mmol/kg [29]. Freundlich isotherm was used to model to uptake of RT on sucralfat with the K_f and n values of 6.7 and 0.99; 24 and 1.5; and 18 and 1.0 at pH 1.5, 3.6, and 5.0 [30].

3.2. Kinetics of RT uptake

RT uptake on both minerals was instantaneous even at the shortest contact time of 0.25 h (Fig. 2b). This quick uptake may indicate external sorption sites for RT on both minerals. In addition, a slight decrease in RT uptake with time was found for kaolinite. This may reflect a surface rearrangement of the sorbed RT molecules on kaolinite.