Journal of Solid State Chemistry 184 (2011) 3329–3335

Contents lists available at SciVerse ScienceDirect

Journal of Solid State Chemistry

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

Intercalation of paracetamol into the hydrotalcite-like host

František Kovanda [a,*], Zuzana Maryšková [a], Petr Kovář [b]

[a] Department of Solid State Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague, Czech Republic
[b] Charles University in Prague, Faculty of Mathematics and Physics, Ke Karlovu 3, 121 16 Prague, Czech Republic

ARTICLE INFO

Article history:
Received 13 July 2011
Received in revised form
10 October 2011
Accepted 17 October 2011
Available online 25 October 2011

Keywords:
Hydrotalcite
Layered double hydroxide
Paracetamol
Intercalation
Molecular simulations
Drug release

ABSTRACT

Hydrotalcite-like compounds are often used as host structures for intercalation of various anionic species. The product intercalated with the nonionic, water-soluble pharmaceuticals paracetamol, *N*-(4-hydroxyphenyl)acetamide, was prepared by rehydration of the Mg–Al mixed oxide obtained by calcination of hydrotalcite-like precursor at 500 °C. The successful intercalation of paracetamol molecules into the interlayer space was confirmed by powder X-ray diffraction and infrared spectroscopy measurements. Molecular simulations showed that the phenolic hydroxyl groups of paracetamol interact with hydroxide sheets of the host via the hydroxyl groups of the positively charged sites of Al-containing octahedra; the interlayer water molecules are located mostly near the hydroxide sheets. The arrangement of paracetamol molecules in the interlayer is rather disordered and interactions between neighboring molecules cause their tilting towards the hydroxide sheets. Dissolution tests in various media showed slower release of paracetamol intercalated in the hydrotalcite-like host in comparison with tablets containing the powdered pharmaceuticals.

1. Introduction

Hydrotalcite-like compounds, which are known also as layered double hydroxides (LDHs) or anionic clays, represent a class of synthetic layered materials with a chemical composition expressed by the general formula $[M^{II}_{1-x}M^{III}_{x}(OH)_2]^{x+}[A^{n-}_{x/n}\cdot yH_2O]^{x-}$ where M^{II} and M^{III} are divalent and trivalent metal cations, respectively, A^{n-} is an n-valent anion and x ranges usually between 0.20 and 0.33. The ordering of hydroxide layers is similar to that of brucite, $Mg(OH)_2$, where each magnesium cation is octahedrally surrounded by six hydroxyl groups and the adjacent octahedra share edges to form infinite sheets. In the hydrotalcite-like compounds, the M^{II}/M^{III} isomorphous substitution in octahedral sites of the hydroxide sheets results in a net positive charge, which is compensated by anions localized together with water molecules in the interlayer. A weak bonding between the interlayer anions and hydroxide sheets is characteristic for these materials and the anions can be exchanged under suitable conditions. Therefore, the hydrotalcite-like compounds are often used as host structures for intercalation of various anionic species, especially the organic ones [1].

Hydrotalcite-like compounds can be prepared by various techniques. The most common method is coprecipitation, when solutions of M^{II} and M^{III} salts react with an alkaline solution. Other methods such as precipitation from "homogeneous" solution (urea method), induced hydrolysis, salt-oxide method, hydrothermal synthesis, or sol–gel method have been also reported [1–3]. The direct synthesis of a desired product is often not possible and other methods have to be applied for intercalation of anions into the host structure. Coprecipitated products containing easily exchangeable anions (e.g., NO_3^- or Cl^-) are commonly used as precursors in anion exchange reactions. An alternative procedure is rehydration of mixed oxides obtained after thermal decomposition of the products containing volatile interlayer anions (e.g., CO_3^{2-}). Such mixed oxides prepared at moderate heating temperatures can be rehydrated in aqueous solutions; the rehydration results in reconstruction of the layered structure containing intercalated anions from the solution. The versatility in chemical composition and physical–chemical properties of hydrotalcite-like compounds offer a great variety of applications of these materials, e.g., in heterogeneous catalysis, adsorption and decontamination processes, polymer processing, or in the preparation of new inorganic/organic hybrid materials [1,4,5].

Hydrotalcite-like hosts intercalated with pharmaceuticals or bioactive compounds can be very promising in various medical applications [6,7]; the intercalation of some nonsteroidal anti-inflammatory drugs [8–12], antihypertensives [13], antiparkinsonics [14], antibiotics [15,16], anticancer drugs [17–19], vitamins [20], or DNA fragments [6,21–24] has been reported in the last decade. The hydrotalcite-like hosts are nontoxic and biocompatible, and the intercalated substances are more stable to chemical, thermal, and light degradation. The active substances are

* Corresponding author. Fax: +420 224311082.
E-mail address: Frantisek.Kovanda@vscht.cz (F. Kovanda).

0022-4596/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.jssc.2011.10.029

intercalated mostly as water-soluble anions of carboxylic acids. By contrast, great numbers of active substances are nonionic or poorly soluble in water and common methods used for preparation of intercalated hydrotalcite-like compounds such as direct coprecipitation, anion exchange in aqueous solutions, or rehydration/reconstruction cannot be applied. Some hydrophobic drugs were intercalated after interaction with cholate micelles [16,19,25] or formation of complex with β-cyclodextrin [26,27]. Various sugar/LDH nanocomposites were obtained when non-ionized sugar molecules were intercalated into Mg–Al and Zn–Al LDH hosts during rehydration of calcined hydrotalcite-like precursors [28,29]. Rehydration reaction in water–ethanol solvent was used also for intercalation of nonionic drug camptothecin [30].

In the present work the preparation of Mg–Al hydrotalcite intercalated with paracetamol is reported. Paracetamol, *N*-(4-hydroxyphenyl)acetamide, is widely used as analgesic and antipyretic pharmaceuticals. It is soluble in water but after dissolution it does not form anions. The product obtained by rehydration reaction was characterized by powder X-ray diffraction and infrared spectroscopy; the molecular modeling was used to describe the arrangement of paracetamol molecules in the interlayer space. Dissolution tests were carried out to study the drug release in various media.

2. Experimental

2.1. Sample preparation

Magnesium nitrate, $Mg(NO_3)_2 \cdot 6H_2O$, aluminum nitrate, $Al(NO_3)_3 \cdot 9H_2O$, sodium hydroxide, NaOH, and paracetamol (4-acetamidophenol, Sigma-Aldrich) were used as purchased. Carbonate-free distilled water was used for preparation of solutions and washing the obtained products. The Mg–Al–NO_3 hydrotalcite-like precursor was prepared by coprecipitation under nitrogen. An aqueous solution (450 ml) of Mg and Al nitrates with Mg/Al molar ratio of 2 and total metal ion concentration of 1.0 mol l^{-1} was added with flow rate of 7.5 ml min^{-1} into 1000 ml batch reactor containing 200 ml of distilled water. The flow rate of simultaneously added NaOH solution (3 mol l^{-1}) was controlled to maintain the reaction pH = 9.5 ± 0.1. The coprecipitation was carried out under vigorous stirring at 75 °C. The resulting suspension was stirred under nitrogen for 2 h at 75 °C; the product was filtered off, washed thoroughly with distilled water, and dried at 105 °C. The dried sample was heated at 500 °C for 4 h in air and then cooled to room temperature in a desiccator. The Mg–Al mixed oxide obtained by precursor heating was dispersed in aqueous solution of paracetamol (400 ml, 0.075 mol l^{-1}, paracetamol excess of 35% with respect to the precursor anion exchange capacity (AEC) was applied) and stirred under nitrogen for 6 days at 30 °C. The rehydrated product was filtered off, washed with distilled water and methanol, and vacuum dried; the obtained sample was denoted as Mg–Al–parac.

2.2. Experimental techniques

Powder X-ray diffraction (XRD) patterns were recorded using a Seifert XRD 3000P instrument with Co Kα radiation ($\lambda = 1.79$ Å, graphite monochromator, goniometer with the Bragg–Brentano geometry) in the 2θ range from 3.5 to 80° with a step size of 0.05°.

Fourier-transform infrared (FTIR) absorption spectra were recorded using the KBr pellet technique on the spectrometer Nicolet 6700 in the range from 4000 to 400 cm^{-1} and the resolution of 4 cm^{-1}. The ATR technique was used for measuring the FTIR spectra of the paracetamol aqueous solution and the solution obtained by dissolution of the Mg–Al–parac sample in hydrochloric acid (2 mol l^{-1}).

Thermal analyses, including thermogravimetry, differential thermal analysis, and evolved gas analysis, were carried out using a Setaram Setsys Evolution 1750 instrument equipped with the mass spectrometer OmniStar (Pfeiffer Vakuum). The heating rate of 10 °C min^{-1}, air flow rate of 75 ml min^{-1}, and 20 mg of the sample were used. Gaseous products were continually monitored for chosen mass numbers m/z (18–H_2O^+ and 44–CO_2^+).

Dissolution tests were carried out using the Sotax USP apparatus 2 at 37.0 ± 0.5 °C in distilled water, aqueous HCl solution (pH = 1), and phosphate buffer (KH_2PO_4 aqueous solution (0.05 mol l^{-1}), whose pH was adjusted to 7.5 by addition of NaOH solution) with tablets containing 50 mg of paracetamol. The intercalated product (Mg–Al–parac sample) was mixed with cellulose and magnesium stearate, the resulting mixture was then compressed into tablets (10 mm in diameter and approximately 5 mm in length). For comparison, the tablets containing powdered paracetamol were prepared by the same way. Single tablets were placed in 1000 ml of the dissolution media and stirred by paddles (75 rpm); a photometric measurement at 249 nm was used for determination of the paracetamol concentration in solutions sampled at chosen time intervals.

2.3. Molecular modeling

Molecular mechanics and classical molecular dynamics were carried out in the Cerius^2 and Materials Studio modeling environment [31]. The host framework of Mg–Al hydrotalcite (Mg/Al molar ratio of 2) is a trilayered structure with trigonal cell in hexagonal axes. The space group is *R*-3*m* and the cell parameters used were $a = b = 3.046$ Å; the value was determined from the measured powder XRD patterns. The d_{003} basal spacing of the initial model was set to the experimental value of 19.9 Å. The hydroxide layer of the composition $[Mg_{32}Al_{16}(OH)_{96}]^{16+}$ was created by the linking of 48 individual cells to give the lattice parameters $A = 18.276$ Å and $B = 24.368$ Å, with Al cations distributed in the layers on the condition that the location of Al cations in the neighboring octahedra is excluded [32]. The geometry of paracetamol molecule was optimized in the compass force field [33]. The paracetamol molecules were placed as virtual anions into the interlayer space. A negative charge (calculated using the charge equilibration (QEq) method [34] in vacuum) in the paracetamol anion is located on oxygen atom of the OH group (−0.589 e) and on oxygen atom of the amidic group (−0.580 e). Two types of structure models with different orientations of paracetamol molecules in the interlayer space were examined: Type 1 with orientation of the paracetamol longitudal axis perpendicular to the hydroxide layers and the oxygen atoms of phenolic group located near the hydroxide layer and Type 2 with the longitudal axis of paracetamol tilted with respect to the hydroxide layers and amidic group localized near the hydroxide layers and oxygen atoms of phenolic group in the inner part of the interlayer space. We built a set of initial models with various mutual orientations of paracetamol and water molecules located in bulk arrangement near the hydroxide layers and randomly distributed in the interlayer space. Total composition of the three-layered supercell was $[Mg_{96}Al_{48}(OH)_{288}][(paracetamol)_{48} \cdot 202H_2O]$ with the space group set to *P*1. Layer charge and partial charges of the guest molecules were calculated by the QEq method [34]. The energy of the initial models was minimized in the Dreiding force field. All atomic positions in the interlayer space were variable and atomic positions in the hydroxide layers were fixed except the hydrogen atoms. The electrostatic and van der Waals energies were calculated by the Ewald summation method [35]. The dynamics simulations were carried out in an NVT statistical ensemble at 298 K. One dynamic

step was 0.001 ps, and dynamics of 150 ps were carried out. After molecular dynamics the models were optimized with variable cell parameters to obtain the final structure models.

3. Results and discussion

3.1. Characterization of the intercalated sample

The Mg/Al molar ratio of 1.96 in the host structure was determined by the atomic absorption spectroscopy after dissolution of the Mg–Al–NO_3 precursor in hydrochloric acid. Powder XRD pattern of the Mg–Al–NO_3 precursor showed well-crystallized hydrotalcite-like phase with d_{003} basal spacing of 8.8 Å. The Mg–Al–parac sample obtained after rehydration of the calcined precursor in the paracetamol-containing aqueous solution exhibited d_{003} basal spacing of about 20 Å (Fig. 1). The marked increase in basal spacing compared to the OH form of Mg–Al hydrotalcite (Mg–Al–OH sample, $d_{003}=7.7$ Å) obtained after rehydration of the calcined precursor in distilled water indicated successful intercalation of paracetamol into the hydrotalcite-like host. The photometric determination of paracetamol concentration in solutions used for rehydration reaction confirmed immobilization of paracetamol in the rehydrated product (about 80% with respect to AEC). Thermal analysis indicated relatively high content of interlayer water (about 20 wt%) in the Mg–Al–parac sample. Based on these results, an estimative chemical composition of the intercalated product corresponding to the empirical formula $Mg_4Al_2(OH)_{12}[(C_8H_9NO_2)_{1.6}(OH)_{0.4}]\cdot 8.4H_2O$ was considered and used for construction of the initial models in molecular simulations.

The characteristic vibrational bands of CO–NH group at 1656 and 1566 cm^{-1} corresponding to stretch vibration of C=O and bending vibration of C–N bonds were found in the FTIR spectrum of paracetamol (Fig. 2). The other vibrational bands at 1611 cm^{-1} (C–C bond in phenyl ring), 1507 cm^{-1} (C–C bond in phenyl ring and C–N bond), 1444 and 1374 cm^{-1} (CH_3 group), 1261 cm^{-1} (C–OH bond), and 1173 cm^{-1} (C–H bond in phenyl ring and C–OH bond) were also observed in the paracetamol FTIR spectrum. The paracetamol characteristic bands were identified in the FTIR spectrum of the intercalated Mg–Al–parac sample; changes in the positions and relative intensities can be explained by interaction of paracetamol with hydroxide layers of the host. No such bands were found in the FTIR spectrum of the Mg–Al–OH sample obtained after rehydration of the Mg–Al mixed oxide in distilled water. The sharp band at 1384 cm^{-1} can be ascribed to residual nitrate present in this sample. The change of paracetamol FTIR spectrum in basic environment can be documented in the spectrum of paracetamol aqueous solution, which pH was increased to 9 by addition of NaOH solution; in this spectrum measured by ATR technique the similar bands like in the spectrum of Mg–Al–parac sample were observed (Fig. 2). In both spectra the bands characteristic for CO–NH group were identified. Therefore, the intercalation of paracetamol molecules without elimination of acetyl group was expected. The spectrum of aqueous

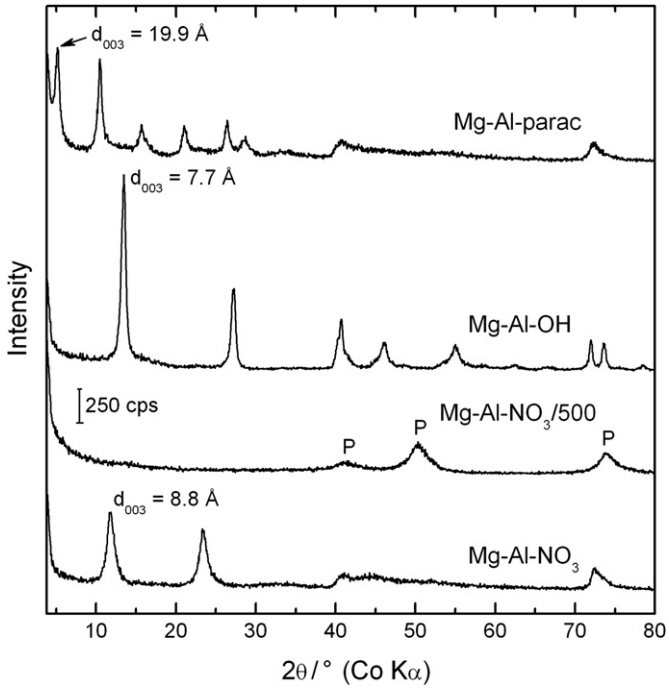

Fig. 1. Powder XRD patterns of the coprecipitated Mg–Al–NO_3 precursor, mixed oxide obtained by its heating at 500 °C, Mg–Al–OH samples obtained by rehydration of mixed oxide in distilled water, and Mg–Al–parac sample intercalated with paracetamol; *P*—periclase-like mixed oxide.

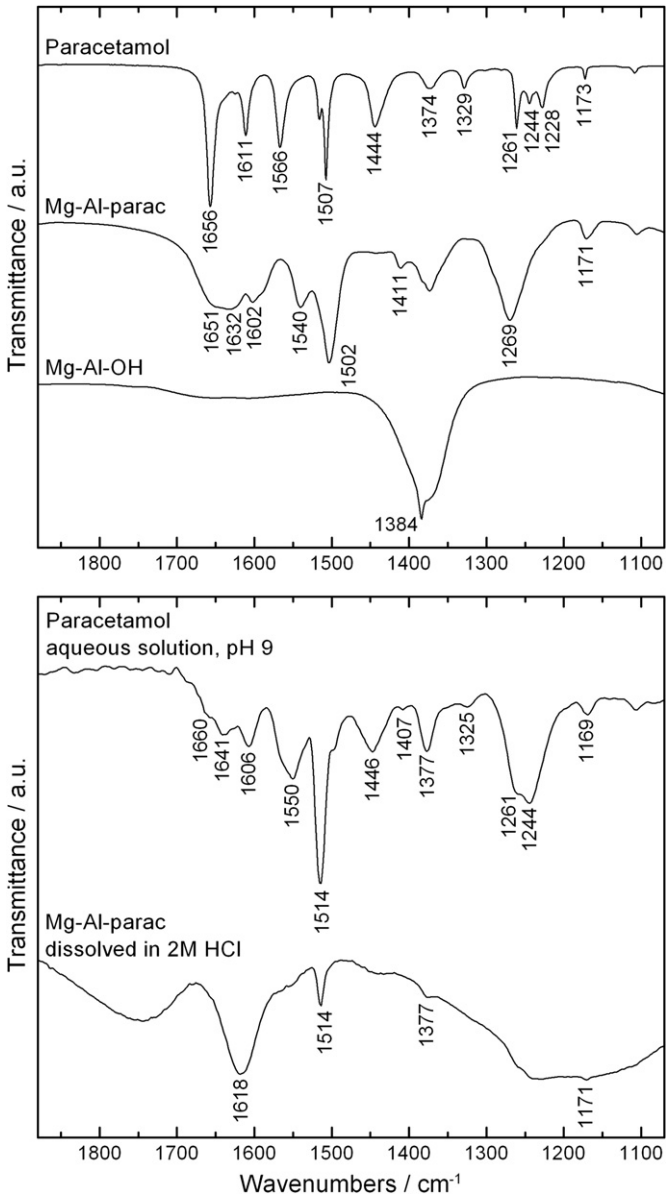

Fig. 2. FTIR spectra of the solid samples (paracetamol, intercalated Mg–Al–parac sample, and rehydrated Mg–Al–OH sample), paracetamol aqueous solution at pH=9, and aqueous solution obtained after dissolution of the Mg–Al–parac sample in hydrochloric acid.

solution obtained after dissolution of the Mg–Al–parac sample in 2M HCl showed some bands characteristic for paracetamol; it also proved the presence of paracetamol in the intercalated sample.

3.2. Results of the molecular modeling

Molecular simulations combined with XRD results give information on the potential arrangement of the guest molecules in the interlayer space. Decreasing intensities of the basal (00*l*) diffraction lines with increasing 2θ values represent a typical feature of perpendicular or tilted arrangement of the guest molecules with respect to the hydroxide layers of LDH hosts [36,37]. The XRD pattern calculated from the structure model presupposing the orientation of the paracetamol longitudal axis perpendicular to the hydroxide layers (Type 1) was in good agreement with the measured powder XRD pattern of the Mg–Al–parac sample (Fig. 3). The positions of basal (00*l*) diffraction lines in the measured and calculated powder XRD patterns corresponded to each other but some differences were observed. The intensity of (003) diffraction line was much lower compared to the calculated value; the low intensity of the measured (003) diffraction line can be explained by microabsorption due to sample surface roughness in the reflection geometry of the XRD experiment. The broadening of basal (00*l*) diffraction lines observed in the measured powder XRD pattern was likely caused by lattice imperfections, e.g., turbostratic disorder. The other examined model (Type 2 with the longitudal axis of paracetamol tilted with respect to the hydroxide layers and amidic groups localized near the hydroxide layers) showed different XRD pattern, in which only two basal diffraction lines, (003) and (009), appeared (not shown here). This model was in contradiction with the experimental data and, therefore, it was disregarded.

The calculated arrangement of paracetamol and water molecules in the interlayer space (Type 1 model) is shown in Fig. 4. It is evident that phenolic hydroxyl groups of paracetamol interact with hydroxide sheets via the hydroxyl groups of the positively charged sites of Al-containing octahedra. The water molecules are

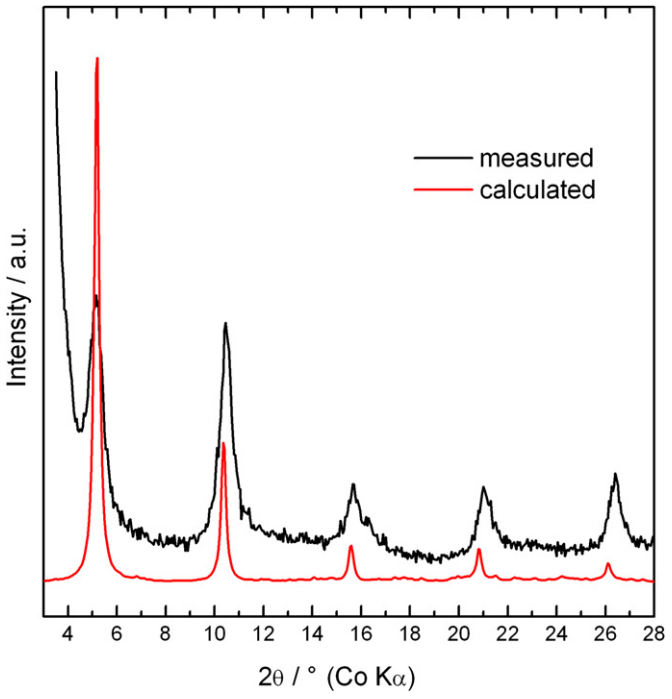

Fig. 3. Comparison of calculated and measured powder XRD patterns of the Mg–Al hydrotalcite intercalated with paracetamol.

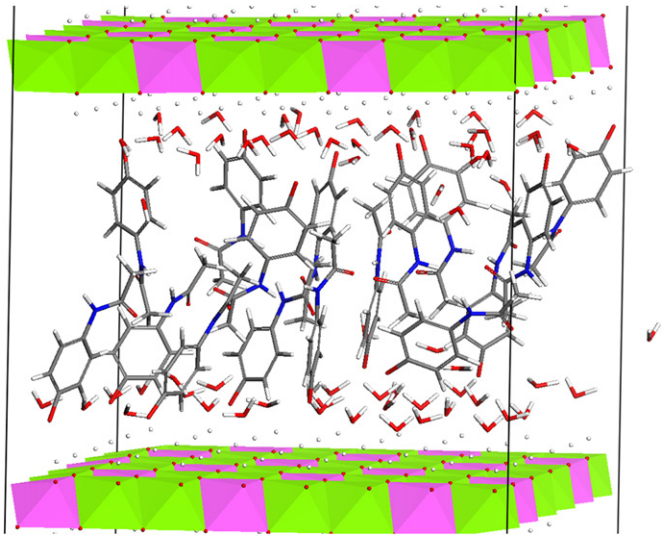

Fig. 4. Side view on arrangement of paracetamol and water molecules in the interlayer.

mostly located near the hydroxide sheets. The arrangement of paracetamol molecules in the interlayer is rather disordered and interactions between neighboring molecules cause their tilting towards the hydroxide sheets. The tilted angle is defined as the angle between the longitudal axis of the guest and the normal to the host layer and exhibits quite big variability. Some of the guest molecules exhibit nearly perpendicular orientation with tilted angle up to 10° (minimum value of 4° was found). Other molecules are much more tilted up to maximum angle of 58°. The average value of the tilted angle of 27° with standard deviation of 12° was calculated.

The tilted orientation of guest molecules with high variability in the tilted angle is very different compared to interlayer arrangement of LDHs intercalated with anions of carboxylic acids. For example, benzoate anions intercalated in the Mg–Al LDH host exhibit perpendicular or nearly perpendicular orientation with respect to the hydroxide layers [36]. It can be explained by the fact that the negative charge is located on the oxygen atoms of carboxyl groups whereas other parts of the guest anions are nearly neutral or slightly positive. On the contrary, the negative charge on the intercalated paracetamol is located on the oxygen atom of phenolic group (-0.8 e in average) and on the oxygen atom of amidic group (-0.6 e in average). Therefore, the amidic group can interact with the hydroxide layer via attractive electrostatic interactions and also with other guest species and water molecules in the interlayer space; it leads to deviations from the perpendicular orientation.

It is worth noting that positions of oxygen atoms of paracetamol phenolic groups do not occupy positions in the same planes (Figs. 4 and 5). The distance between the oxygen atoms of phenolic groups and hydrogen atoms of hydroxide layers ranges from 1.5 to 4.3 Å with the average value of 2.3 Å. The varying distances can be explained by interactions of amidic groups with the opposite layer leading to the shift of the paracetamol molecules towards this layer and also by a relatively high concentration of water molecules in the interlayer space ($4.2H_2O$ per $Mg_2Al(OH)_6$ unit). Both the calculated XRD patterns of the models with random distribution of water in the interlayer space and the models with bulk of water located near the hydroxide layers are in good agreement with the measured data. Despite of this, the total energy calculated for interlayer with water molecules located near the hydroxide layers is lower than that calculated for interlayer with random distribution of water

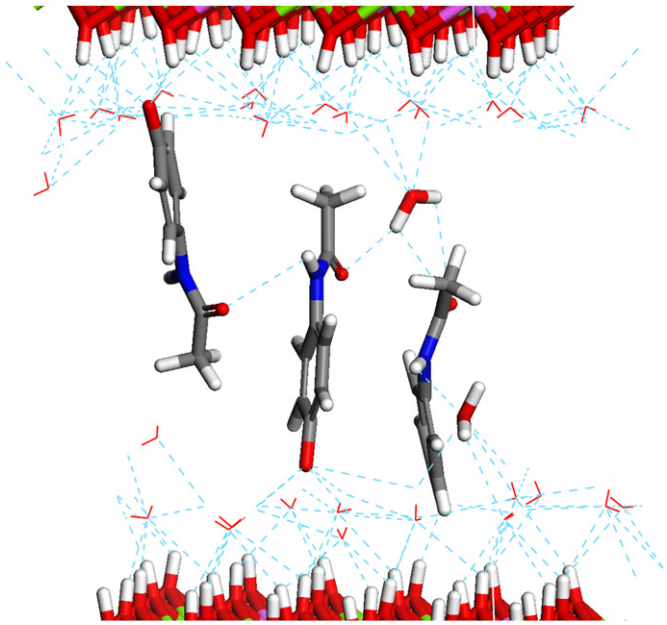

Fig. 5. Possible hydrogen bonding between the species in the interlayer space.

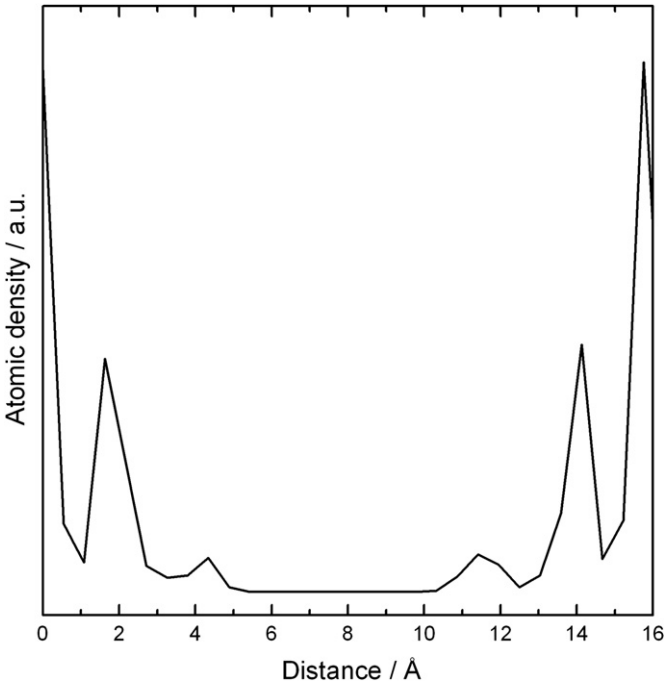

Fig. 6. Atomic density profile in 00*l* direction characterizing distribution of interlayer water.

molecules; the difference gives about 7%. Therefore, the interlayer arrangement, in which most of water molecules are located near the hydroxide layers, is more stable. The distribution of water in the interlayer is illustrated by atomic density profile in 00*l* direction (Fig. 6). The maxima at 0 and 16 Å represent the hydrogen atoms of the host hydroxide layers and the other peaks represent the oxygen atoms of interlayer water. It can be seen that water molecules are located mainly within the distance of 2–3 Å from the hydrogen atoms of the host hydroxide layers. A minor part of the water molecules (about 10–15%) can be located in longer distances (maximum 5 Å) from the hydroxide layers and interact with amidic groups of paracetamol via hydrogen bonds (Fig. 5).

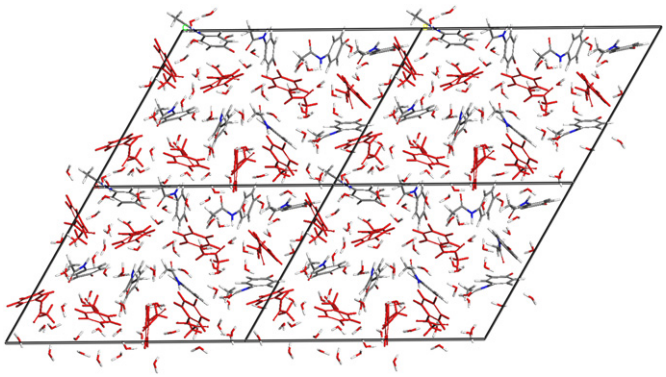

Fig. 7. Top view on the most ordered interlayer arrangement.

Top view of linked supercels showing the most ordered arrangement of guest molecules is demonstrated in Fig. 7. The common colors represent the same orientation of guests (oxygen atoms of paracetamol phenolic groups are oriented towards the same hydroxide layer). In this arrangement the equally oriented guests tend to be located in disordered rows and the orientations of paracetamol phenyl rings are randomly distributed with respect to each other. The mutual distance between oxygen atoms of phenolic groups ranges approximately from 4 to 6 Å (for each guest defined as the closest distance between its neighboring equally oriented guests). The orientation of amidic group with respect to the plane of phenyl ring is quite variable and can rotate around the longitudal axis of the paracetamol molecule. Due to the mutual interactions of the species in the interlayer space the absolute values of torsion angle range from 10° to 56°, with the average value of 37°.

3.3. Dissolution tests

The dissolution tests measured in vitro give useful information to predict release profiles of pharmaceuticals in vivo. The release rate is affected by pH value and, therefore, the dissolution tests were carried out in various media at different pH values; the carbonate-free distilled water (pH=6.7), 0.1 M HCl solution (pH=1.0), and phosphate buffer (pH=7.5) were used. The release of paracetamol from tablets containing Mg–Al–parac sample and powdered paracetamol was compared; each tablet contained the same amount of paracetamol (50 mg).

Results of the dissolution tests are shown in Fig. 8. The release profiles of paracetamol from the tablets containing powdered pharmaceuticals were similar to each other in all used media; the release rate was relatively high and not very influenced by pH value. Paracetamol is often used as a model soluble drug in studies of drug release from various materials [38–41]. Three steps can be distinguished in drug release from the matrix: liquid penetration into the matrix, dissolution of the drug, and diffusion. The release of paracetamol from polymeric matrices such as carboxymethylcellulose [38] or hydroxypropyl methylcellulose [39] was modeled by power function $q_t/q_e = kt^n$, where q_t means the amount of drug released at time t, q_e the amount of drug released at equilibrium, k the proportionality constant, and n the diffusional exponent; this equation was proposed by Peppas et al. [42] for swelling-controlled systems. The particle diffusion-controlled release can be tested by fitting the data with linearized equation developed by Bhaskar et al. [43]; the diffusion through the particle is the rate limiting step when the relationship between $\ln(1-q_t/q_e)$ and $t^{0.65}$ is linear. Applying this method to the measured paracetamol release data resulted in evidently non-linear dependences (not shown here).

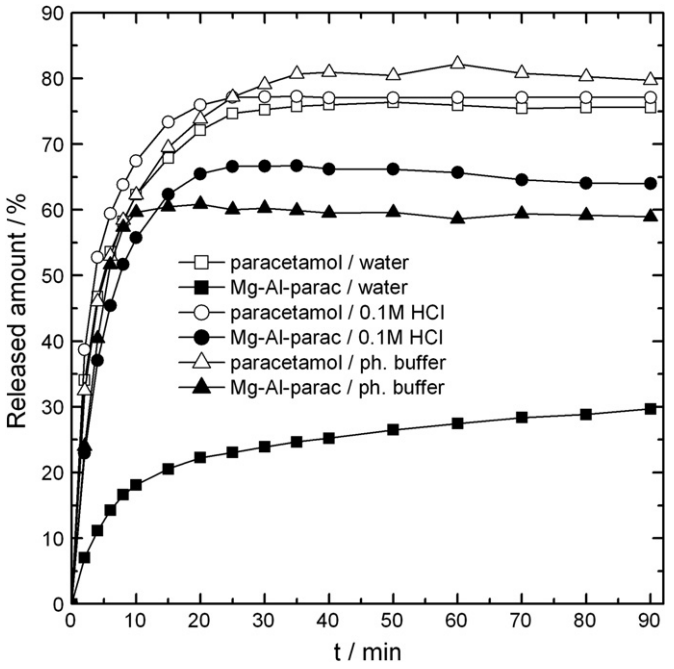

Fig. 8. Release profiles of paracetamol from tablets containing powdered paracetamol and the intercalated product (Mg–Al–parac sample) in various dissolution media.

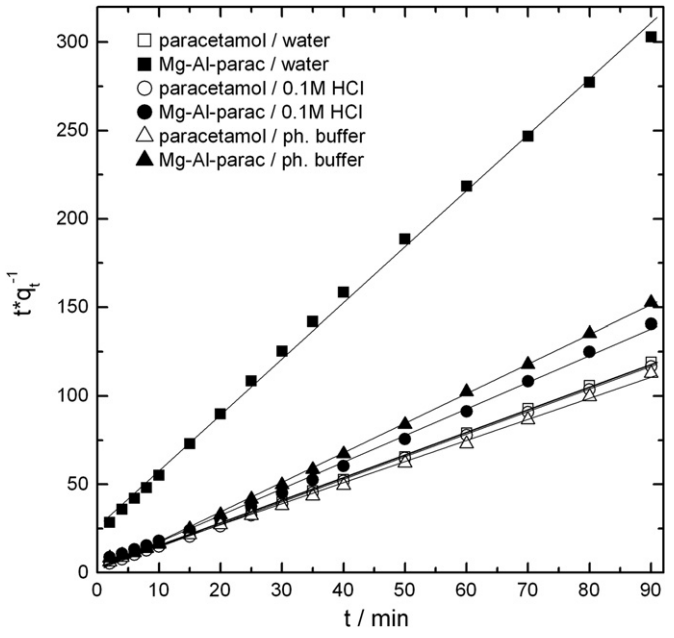

Fig. 9. Linearized release data fitted with the pseudo-second-order kinetic model.

The pseudo first-order and pseudo-second-order kinetic equations were tested to simulate the paracetamol release from the tablets. The pseudo-second-order kinetic model, $q_t=(q_e^2k_2t)/(1+q_ek_2t)$, showed very good agreement with the experimental data; the linearized data t/q_t vs. t are demonstrated in Fig. 9. The agreement of pseudo-second-order kinetic model with experimental data was reported also by Dong et al. [30] for release of camptothecin from its composites with Mg–Al LDH. The evaluated rate constants k_2, equilibrium release amounts q_e, and correlation coefficients r^2 are summarized in Table 1. Dissolution tests showed slower release of paracetamol intercalated in the hydrotalcite-like host; the slowest release rate was observed in distilled water. The paracetamol release from the intercalated product was increased both in acid and slightly basic media. In the acid HCl solution simulating the gastric fluid, the anion exchange for chloride together with gradual dissolution of the host structure can be expected [44,45]. Rapid release of the intercalated paracetamol in the phosphate buffer (simulating the conditions in an intestinal fluid) was likely caused by anion exchange of the weakly bonded paracetamol for the phosphate anions present in the solution. In the solutions simulating the body fluids (i.e., 0.1 M HCl and phosphate buffer), the difference in rate of paracetamol release from tablets containing powdered phramaceuticals and those containing the intercalated product was not significant. Therefore, the utilization of LDHs as drug carriers enabling the controlled release of paracetamol is questionable.

Table 1
Values of the rate constant k_2, equilibrium release amount q_e, and correlation coefficient r^2 obtained by fitting the measured paracetamol release data to the pseudo-second-order kinetic equation.

Sample[a]/medium	k_2/min^{-1}	q_e	r^2
Paracetamol/water	0.624	0.781	0.9997
Paracetamol/0.1 M HCl	0.917	0.788	0.9998
Paracetamol/phosphate buffer	0.435	0.839	0.9994
Mg–Al–parac/water	0.386	0.316	0.9991
Mg–Al–parac/0.1 M HCl	0.992	0.664	0.9988
Mg–Al–parac/phosphate buffer	2.641	0.598	0.9995

[a] Tablets containing powdered paracetamol or the intercalated Mg–Al–parac sample were used in the dissolution tests.

4. Conclusions

Paracetamol was successfully intercalated into the hydrotalcite-like host during rehydration of the mixed oxide obtained by thermal decomposition of the Mg–Al–NO_3 precursor. The intercalation of organic molecules was proven by the marked increase in basal spacing of the host structure and presence of the paracetamol characteristic vibrational bands in the FTIR spectrum of the Mg–Al–parac sample. Molecular simulations indicated interactions between hydroxide sheets and phenolic hydroxyl groups of paracetamol and rather disordered arrangement of paracetamol molecules in the interlayer space. The interactions between neighboring molecules cause their tilting towards the hydroxide sheets. The arrangement expecting the water molecules located near the hydroxide layers was found to be more stable. Dissolution tests carried out in the solutions simulating the body fluids indicated weak bonding of paracetamol in the hydrotalcite-like host. The release of paracetamol from tablets containing the Mg–Al–parac sample was slower in comparison with that from tablets containing the powdered pharamceuticals but the difference in release rate was not significant.

Acknowledgments

This work was supported by the Czech Science Foundation (P207/10/1447) and by the Ministry of Education, Youth and Sports of the Czech Republic (MSM 6046137302 and MSM 0021620835).

References

[1] C. Forano, T. Hibino, F. Leroux, C. Taviot-Guého, in: F. Bergaya, B.K.G. Theng, G. Lagaly (Eds.), Handbook of Clay Science, Developments in Clay Science, vol. 1, Elsevier, Amsterdam, 2006, pp. 1021–1095.

[2] F. Cavani, F. Trifiro, A. Vaccari, Catal. Today 11 (1991) 173–301.
[3] A. de Roy, C. Forano, J.P. Besse, in: V. Rives (Ed.), Layered Double Hydroxides: Present and Future, Nova Science Publishers, New York, 2001, pp. 1–37.
[4] F. Kovanda, K. Jirátová, R. Kalousková, in: F.L. Gerard (Ed.), Advances in Chemistry Research, vol. 1, Nova Science Publishers, New York, 2006, pp. 89–139.
[5] F. Li, X. Duan, in: X. Duan, D.G. Evans (Eds.), Layered Double Hydroxides, Structure and Bonding, vol. 119, Springer, Berlin/Heidelberg, 2006, pp. 193–223.
[6] J.H. Choy, M. Park, in: F. Wypych, K.G. Satyanarayana (Eds.), Clay Surfaces: Fundamentals and Applications, Elsevier, Amsterdam, 2004, pp. 403–424.
[7] C. del Hoyo, Appl. Clay Sci. 36 (2007) 103–121.
[8] C.R. Gordijo, C.A.S. Barbosa, A.M. da Costa Ferreira, V.R.L. Constantino, D. de Oliveira Silva, J. Pharm. Sci. 94 (2005) 1135–1148.
[9] J.-C. Dupin, H. Martinez, C. Guimon, E. Dumitriu, I. Fechete, Appl. Clay Sci. 27 (2004) 95–106.
[10] U. Costantino, V. Ambrogi, M. Nocchetti, L. Perioli, Micropor. Mesopor. Mater. 107 (2008) 149–160.
[11] M. del Arco, S. Gutiérrez, C. Martín, V. Rives, J. Rocha, J. Solid State Chem. 177 (2004) 3954–3962.
[12] M. del Arco, A. Fernández, C. Martín, V. Rives, Appl. Clay Sci. 36 (2007) 133–140.
[13] S.-J. Xia, Z.-M. Ni, Q. Xu, B.-X. Hu, J. Hu, J. Solid State Chem. 181 (2008) 2610–2619.
[14] M. Wei, M. Pu, J. Guo, J. Han, F. Li, J. He, D.G. Evans, X. Duan, Chem. Mater. 20 (2008) 5169–5180.
[15] W.-Z. Li, J. Lu, J.-S. Chen, G.-D. Li, Y.-S. Jiang, L.-S. Li, B.-Q. Huang, J. Chem. Technol. Biotechnol. 81 (2006) 89–93.
[16] M. Trikeriotis, D.F. Ghanotakis, Int. J. Pharm. 332 (2007) 176–184.
[17] J.-M. Oh, M. Park, S.-T. Kim, J.-Y. Jung, Y.-G. Kang, J.-H. Choy, J. Phys. Chem. Solids 67 (2006) 1024–1027.
[18] S.-J. Choi, J.-M. Oh, J.-H. Choy, J. Phys. Chem. Solids 69 (2008) 1528–1532.
[19] K.M. Tyner, S.R. Schiffman, E.P. Giannelis, J. Contr. Rel. 95 (2004) 501–514.
[20] S.-H. Hwang, Y.-S. Han, J.-H. Choy, Bull. Korean Chem. Soc. 22 (2001) 1019–1022.
[21] J.-H. Choy, S.-Y. Kwak, Y.-J. Jeong, J.-S. Park, Angew. Chem. Int. Ed. 39 (2000) 4042–4045.
[22] J.-H. Choy, S.-J. Choi, J.-M. Oh, T. Park, Appl. Clay Sci. 36 (2007) 122–132.
[23] K. Ladewig, M. Niebert, Z.P. Xu, P.P. Gray, G.Q.M. Lu, Biomaterials 31 (2010) 1821–1829.
[24] K. Ladewig, M. Niebert, Z.P. Xu, P.P. Gray, G.Q.M. Lu, Appl. Clay Sci. 48 (2010) 280–289.
[25] F. Li, L. Jin, J. Han, M. Wei, C. Li, Ind. Eng. Chem. Res. 48 (2009) 5590–5597.
[26] H. Nakayama, K. Kuwano, M. Tsuhako, J. Phys. Chem. Solids 69 (2008) 1552–1555.
[27] L. Jin, Q. Liu, Z. Sun, X. Ni, M. Wei, Ind. Eng. Chem. Res. 49 (2010) 11176–11181.
[28] S. Aisawa, H. Hirahara, K. Ishiyama, W. Ogasawara, Y. Umetsu, E. Narita, J. Solid State Chem. 174 (2003) 342–348.
[29] S. Aisawa, H. Hirahara, S. Takahashi, Y. Umetsu, E. Narita, Chem. Lett. 33 (2004) 306–307.
[30] L. Dong, Y. Li, W.-G. Hou, S.-J. Liu, J. Solid State Chem. 183 (2010) 1811–1816.
[31] Materials Studio Modeling Environment, Release 4.3 Documentation, Accelrys Software Inc., San Diego, 2003.
[32] P.J. Sideris, U.G. Nielsen, Z. Gan, C.P. Grey, Science 321 (2008) 113–117.
[33] H. Sun, D. Rigby, Spectrochim. Acta A 53 (1997) 1301–1323.
[34] A.K. Rappé, W.A. Goddard III, J. Phys. Chem. 95 (1991) 3358–3363.
[35] N. Karasawa, W.A. Goddard III, J. Phys. Chem. 93 (1989) 7320–7327.
[36] P. Kovář, K. Melánová, V. Zima, L. Beneš, P. Čapková, J. Colloid Interface Sci. 319 (2008) 19–24.
[37] E. Káfuňková, C. Taviot-Guého, P. Bezdička, M. Klementová, P. Kovář, P. Kubát, J. Mosinger, M. Pospíšil, K. Lang, Chem. Mater. 22 (2010) 2481–2490.
[38] J.S. Boateng, K.H. Matthews, A.D. Auffret, M.J. Humphrey, H.N. Stevens, G.M. Eccleston, Int. J. Pharm. 378 (2009) 66/72.
[39] P. Bustamante, J. Navarro-Lupión, M.A. Pena, B. Escalera, Int. J. Pharm. 414 (2011) 125–130.
[40] K. Campbell, D.Q.M. Craig, T. McNally, Int. J. Pharm. 363 (2008) 126–131.
[41] T. Mehling, I. Smirnova, U. Guenther, R.H.H. Neubert, J. Non-Cryst. Solids 355 (2009) 2472–2479.
[42] N.A. Peppas, P. Bures, W. Leobandung, H. Ichikawa, Eur. J. Pharm. Biopharm. 50 (2000) 27–46.
[43] R. Bhaskar, S.R.S. Murthy, B.D. Miglani, K. Viswanathan, Int. J. Pharm. 28 (1986) 59–66.
[44] B. Kostura, F. Kovanda, M. Valášková, J. Leško, Collect. Czech Chem. Commun. 72 (2007) 1284–1294.
[45] M.L. Parello, R. Rojas, C.E. Giacomelli, J. Colloid Interface Sci. 351 (2010) 134–139.