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Intercalation and controlled release of pharmaceutically active compounds from a layered double hydroxide†

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A series of pharmaceutically active compounds including diclofenac, gemfibrozil, ibuprofen, naproxen, 2-propylpentanoic acid, 4-biphenylacetic acid and tolfenamic acid can be reversibly intercalated into a layered double hydroxide, initial studies suggest that these materials may have application as the basis of a novel tuneable drug delivery system.

In order for drug therapy to be most effective the desired pharmacological response must be obtained at the target without harmful interactions at other sites.[1] This requires the correct amount of drug to be absorbed into the body and transported to the target with control of the drug rate input in order to produce the correct dosage. Ideally the delivery of the drug to other tissues should be minimised or prevented, however this is rarely achieved owing to the complex nature of these processes.[2] Modern controlled release systems are usually polymer based with mechanisms of release regulated by diffusion, bioerosion, degradation and swelling or the production of osmotic pressure. Exposing the polymer–drug mixture to the gastrointestinal fluid results in the diffusion of the drug from the tablet or capsule and the polymers are excreted. Certain polymer–drug complexes undergo bio-erosion or degradation when they pass through the gastrointestinal tract. Swelling or the generation of osmotic pressure occurs with other polymer–drug formulations upon contact with gastrointestinal fluid resulting in the release or expulsion of the drug.[3]

Controlled release systems have many advantages but also have disadvantages. The main advantage is the decreased fluctuation in drug concentration resulting in reduced toxicity. In addition, the reduction in the number of doses may lead to lower patient care time and also to the use of a smaller amount of drug. However, disadvantages include the increased amount of time required to achieve therapeutic blood concentrations, dose dumping and usually an increase in the cost.[3] Not all drugs are suitable for controlled release systems—those not suitable are drugs with very short or very long half lives, poor absorption through the gastrointestinal tract and low solubility.[4] Controlled release systems are most useful for drugs that are taken on an extended basis such as drugs used to treat cardiovascular disorders and arthritis. Layered double hydroxides (LDHs) represented by the general formula $[M^{II}_{(1-x)}M^{III}_{x}(OH)_2]$-$[A^{n-}_{x/n}]\cdot zH_2O$ or $[M^{I}M^{III}_2(OH)_6][A^{n-}_{1/n}]\cdot zH_2O$, where M^{I}, M^{II} and M^{III} are mono-, di- and tri-valent metal cations, respectively, are now well established as excellent anion-exchange materials and their extensive intercalation chemistry has widespread applications in areas such as heterogeneous catalysis,[5,6] optical materials,[7,8] biomimetic catalysis,[9,10] separation science[11,12] and as DNA reservoirs.[13,14]

Here we report the reversible intercalation of a number of active cardiovascular and anti-inflammatory agents into a layered double hydroxide and the results of an initial study into the use of these drug–inorganic hybrid materials as a novel tuneable drug delivery system.

As a number of well known cardiovascular, anti-inflammatory and analgesic agents are either carboxylic acids or carboxylic derivatives we were interested in investigating whether these compounds could be ion-exchange intercalated in a layered double hydroxide. $[LiAl_2(OH)_6]Cl\cdot H_2O$ reacts with 2 equivalents of either the sodium salts of diclofenac, gemfibrozil, ibuprofen, naproxen, 2-propylpentanoic acid, 4-biphenylacetic acid or tolfenamic acid (Table 1) in H_2O at 60 °C for 1–2 h to give a LDH–drug intercalation compound. The solid products are isolated by filtration and then washed with an excess of deionised water and then acetone. In each case full anion exchange of the interlayer Cl^- anions and intercalation of these pharmaceutically active compounds has taken place. In each case the products are first stage intercalation compounds and they have all been fully characterised using X-ray powder diffraction (XRD), elemental microanalysis, IR spectroscopy and thermogravimetric analysis. The observed interlayer spacings for the drug–LDH intercalates are shown in Table 1, the values are consistent with the formation of bilayer arrangement for all the drug molecules with the positively charged $[LiAl_2(OH)_6]^+$ layers of the host lattice. In all cases the intercalated anions can be quantitatively recovered from the host lattice by treatment of the intercalates with either an aqueous solution of M_2CO_3 (M = Na or Li) or addition of dilute HCl. In the case of treatment with an alkali metal carbonate, the alkali metal salt of the organic guest ions goes into solution and

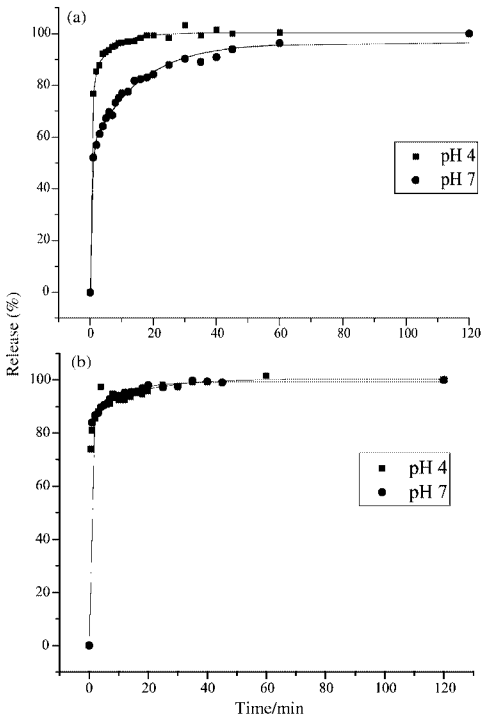

Fig. 1 Release profiles for (a) diclofenac at pH 4 and pH 7 and (b) gemfibrozil at pH 4 and pH 7.

† Electronic supplementary information (ESI) available: Fig. S1: X-ray diffraction patterns of (a) $[LiAl_2(OH)_6]Cl\cdot H_2O$ and (b) LDH/Ibuprofen intercalate. See http://www.rsc.org/suppdata/cc/b1/b106465g/

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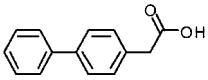
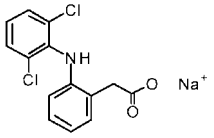
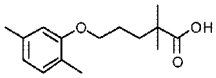
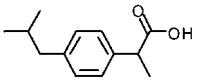
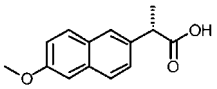
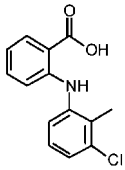
Table 1 Summary of the guest molecule used and the analytical and structural data of the LDH–drug intercalation compounds

Guest	Molecular structure of guest[a]	Interlayer spacing/Å[b]	Elemental analysis: found (calc.)[c]
4-Biphenylacetic acid ($C_{14}H_{12}O_2$)		20.4	C, 30.77 (30.77); H, 5.16 (5.20); $x = 0.58$, $y = 2$
Diclofenac ($C_{14}H_{10}Cl_2NaNO_2$)		22.3	C, 30.91 (30.92); H, 4.12 (3.91); N, 2.60 (2.58); $x = 0.72$, $y = 1$
Gemfibrozil ($C_{15}H_{22}O_3$)		23.2	C, 35.35 (35.36); H, 6.56 (6.65); $x = 0.69$, $y = 1$
Ibuprofen ($C_{13}H_{18}O_2$)		22.7	C, 31.92 (31.98); H, 6.15 (5.99); $x = 0.75$, $y = 3$
Naproxen ($C_{14}H_{14}O_3$)		21.5	C, 27.91 (28.08); H, 4.98 (4.99); $x = 0.48$, $y = 1$
2-Propylpentanoic acid ($C_8H_{16}O_2$)		18.7	C, 14.78 (14.82); H, 5.77 (6.04); $x = 0.35$, $y = 1$
Tolfenamic acid ($C_{14}H_{12}ClNO_2$)		21.9	C, 23.24 (23.18); H, 5.25 (5.29); N, 1.90 (1.93); $x = 0.46$, $y = 3$

[a] Neutral guest molecules were converted to the sodium salt prior to intercalation. [b] Based on hexagonal cell: $\alpha = \beta = 90$, $\gamma = 120°$, $a = b = 5.1$ Å and $c = 2 \times d_{(002)}$ [c] Based on the general formula $Li_xAl_2(OH)_6[drug]_x \cdot yH_2O$

the solid phase is quantitatively converted to $[LiAl_2(OH)_6](CO_3)_{0.5}\cdot H_2O$ as indicated by the XRD data which shows a series of 00*l* reflections corresponding to an interlayer spacing of 7.51 Å. Addition of dilute aqueous HCl solution to the LDH–drug complex results in dissolution of the inorganic host and precipitation of the neutral form of the guest acid.

Given that these ions could be recovered intact from the LDH host we were interested to see if this could form the basis of a drug reservoir and controlled release system. Therefore, we performed a series of experiments in order to quantitatively monitor the kinetics of release of the guest ions under conditions which would resemble physiological conditions. Deintercalation of the drugs from the LDH was performed by the addition of the drug–LDH complex to 250 ml of phosphate buffer solution at 37 °C of pH 7 or pH 4. A mass of 0.025 g of the LDH–drug complex was used for 4-biphenylacetic acid, diclofenac and tolfenamic acid and a larger amount of 0.1 g for naproxen and gemfibrozil. Aliquots were removed from the reaction mixture at regular intervals and solution UV–Vis absorption spectroscopy was used to quantify the concentration of the de-intercalated ions in the aqueous phase. Fig. 1 shows release profile plots for the deintercalation of diclofenac and of gemfibrozil on addition of phosphate buffer at pH 4 and pH 7. At pH 4 the measured release of diclofenac and gemfibrozil is very fast with almost full deintercalation observed in less than 10 min. Surprisingly, the release curve for gemfibrozil at pH 7 is almost identical to the profile recorded at pH 4. At pH 7 the release of diclofenac is much slower and only after 28 min is 90% of the drug released into solution. Table 2 is a summary of the release profiles for all the different guest ions that we have intercalated in $[LiAl_2(OH)_6]Cl\cdot H_2O$.

In summary, the results show that the intercalation of pharmaceutically active compounds that form stable anions is a feasible approach for the storage then subsequent controlled release of bioactive agents. We anticipate that there will be tremendous scope for fine tuning the intercalation and de-intercalation kinetics in these materials by employing different LDHs with differing charge densities and basicities.

Table 2 Release profile data

	Release times/min[a]			
	pH 4		pH 7	
Guest molecules	t_{50}[b]	t_{90}[b]	t_{50}[b]	t_{90}[b]
Diclofenac (λ_{max} = 279 nm)	1	4	1	28
Naproxen (λ_{max} = 317, 330 nm)	1	9	1	17
Gemfibrozil (λ_{max} = 275 nm)	1	5	1	5
Tolfenamic acid (λ_{max} = 290 nm)	1	21	1	23
4-Biphenylacetic acid (λ_{max} = 290 nm)	1	2	1	35

[a] Release (%) = $(I_t/I_{max}) \times 100$, at λ_{max}. [b] t_{50} and t_{90} are the times for 50 and 90% release, respectively.

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