

# 1 Novel fluoride rechargeable dental composites containing MgAl and CaAl 2 layered double hydroxide (LDH)

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11 **Keywords:** Layered double hydroxide; dental composites; fluoride rechargeable; fluoride release; caries;  
12 dentistry; water uptake; mechanical properties.

## 13 Highlights

- 14 • 2:1 CaAl and MgAl LDH dental composites were developed with varying LDH loading.
- 15 • Fluoride absorption/release was studied (five recharge cycles) in DW and AS.
- 16 • Water uptake, solubility, cation release, and mechanical properties were studied.
- 17 • LDH-composites repeatedly absorbed/released fluoride maintaining a sustained release.
- 18 • Physico-mechanical properties of composites were maintained with LDH-composites.

## 19 Abstract

### 20 Objective

21 This study aims to incorporate 2:1 MgAl and 2:1 CaAl layered double hydroxides (LDHs) in  
22 experimental dental-composites to render them fluoride rechargeable. The effect of LDH on  
23 fluoride absorption and release, and their physico-mechanical properties are investigated.

### 24 Methods

25 2:1 CaAl and 2:1 MgAl LDH-composite discs prepared with 0, 10 and 30wt% LDH were charged  
26 with fluoride (48h) and transferred to deionised water (DW)/artificial saliva (AS). Fluoride  
27 release/re-release was measured every 24h (ion-selective electrodes) with DW/AS replaced daily,  
28 and samples re-charged (5min) with fluoride every two days. Five absorption-release cycles were  
29 conducted over 10 days. CaAl and MgAl LDH rod-shaped specimens (dry and hydrated; 0, 10 and  
30 30wt%) were studied for flexural strength and modulus. CaAl and MgAl LDH-composite discs (0,  
31 10, 30 and 45wt% LDH) were prepared to study water uptake (over seven weeks), water desorption  
32 (three weeks), diffusion coefficients, solubility and cation release (ICP-OES).

### 33 Results

34 CaAl LDH and MgAl LDH-composites significantly increased the amount of fluoride released in  
35 both media (P<0.05). In AS, the mean release after every recharge was greater for MgAl LDH-  
36 composites compared to CaAl LDH-composites (P<0.05). After every recharge, the fluoride  
37 release was greater than the previous release cycle (P<0.05) for all LDH-composites. Physico-

38 mechanical properties of the LDH-composites demonstrated similar values to those reported in  
39 literature. The solubility and cation release showed a linear increase with LDH loading.

40 Significance

41 LDH-composites repeatedly absorbed/released fluoride and maintained desired physico-  
42 mechanical properties. A sustained low-level fluoride release with LDH-composites could lead to  
43 a potential breakthrough in preventing early stage carious-lesions.

## 44 1. Introduction

45 The benefit of fluoride for controlling caries particularly in children and adolescents is widely  
46 known [1-3]. The potential application of fluoride released at low levels (~0.025 – 2 ppm), from  
47 dental materials in the oral environments, is the most effective method in preventing post-eruptive  
48 dental caries [1, 2, 4, 5]. The preventative action is due to the inhibition of demineralisation,  
49 promotion of remineralisation and, inhibition of bacterial growth and metabolism [6-8]. Due to the  
50 similar size of fluoride ions (1.36 Å) and hydroxide ions ( $\text{OH}^- = 1.40 \text{ \AA}$ ), fluoride ions are able to  
51 exchange with hydroxide ions in hydroxyapatite to form fluorapatite, which is more resistant to  
52 dissolution by an acid challenge [2].

53 Many studies have demonstrated the benefits of fluoride at a low concentration. As an example,  
54 Lynch *et al* [6] reported this effect *in vitro* with human teeth, by exposing them to a pH-cycling  
55 system while varying the fluoride concentration (0.009, 0.014, 0.025, 0.2 and 2.0 ppm). Significant  
56 changes in the reduction of demineralisation, determined through calcium released in acetic acid  
57 and image analysis of the exposed tooth section were observed. A small increase in fluoride  
58 concentration, from 0.009 to 0.2 ppm subsequently approached a plateau after increasing to 2 ppm.  
59 Furthermore, a 2-year clinical trial involving 174 children (mean age 8 years old) was reported by  
60 Toumba and Curzon [9]. A slow releasing fluoride dental device, in the form of a glass pellet, was  
61 attached to the tooth. The results showed an increase in the salivary fluoride concentration from  
62 0.03 ppm (control, physiological concentration) to 0.11 ppm and a 67% decrease in carious teeth  
63 after two years. In addition, Fan *et al* [10] showed that acid-etched enamel surfaces immersed in 1  
64 ppm fluoride for 16 h, produced a needle-like structure, indicating the formation of fluorapatite,  
65 which was further confirmed using pXRD.

66 Numerous consumer healthcare companies provide dentists with fluoride containing dental  
67 materials such as dental composites, fluoride varnishes, fissure sealants, glass ionomer cements  
68 (GICs) and resin modified glass ionomer cements (RMGICs) that are capable of releasing fluoride  
69 over time, in the oral cavity. However, fluoride release from these materials is not always well  
70 controlled and diminishes over time. Moreover, GICs have been reported to show an initial burst  
71 of fluoride, in a range from 5 – 155 ppm, within the first 24 h, depending on the different brands  
72 available [11, 12]. Although GICs have shown fluoride-recharging capabilities, the amount of  
73 fluoride re-released does not reach the initial concentration and substantially less is released with  
74 each successive recharge [13, 14]. It is worth acknowledging that high concentrations of fluoride  
75 in fluoridated water may lead to fluorosis, which causes mottling of enamel and may be  
76 aesthetically unpleasing [15]. A one year study conducted on 18755 children in the United States

77 with varying fluoride concentrations in drinking water, showed that an ideal fluoride concentration  
78 between caries prevention and fluorosis was around 0.7 ppm [16].

79 Fluoride is incorporated into composite resins in several forms such as water soluble salts (e.g.  
80 sodium fluoride, NaF), leachable glasses and/or matrix bound fluoride [17]. However, a study  
81 investigating the release of fluoride over 16 weeks (in 7 ml water, artificial saliva and lactic acid)  
82 from composites (containing a sparingly soluble ytterbium trifluoride [YbF<sub>3</sub>] salt), GICs and  
83 RMGICs, reported that fluoride release was significantly lower from composites. Also, the release  
84 of fluoride from composites containing fluoride salts resulted in voids in the structure (as the salts  
85 dissolved), which affected the mechanical properties such as wear resistance [18]. Composite resins  
86 also showed a burst of fluoride release however, it was less pronounced than from RMGICs and  
87 GICs. Yap *et al* [19], who investigated a range of dental fluoride releasing materials, demonstrated  
88 that composites (containing fluoride leachable glass) released less fluoride compared to GICs and  
89 RMGICs. Composites released 1.44 ppm within the first 24 h, which reduced to 0.22 ppm by day  
90 7 (replacing 1 ml of DW every 24 h), GIC released 8.78 ppm and RMGIC released 7.19 ppm  
91 fluoride in the first 24 h, which reduced to 1.51 and 3.18 ppm fluoride, respectively. Attar and  
92 Önen [20] studied fluoride release from commercial composite materials (Dyract, Dentsply,  
93 Germany containing strontium-aluminium-fluoro-silicate-glass and Tetric, Vivadent,  
94 Liechtenstein containing YbF<sub>3</sub>) over 60 days, and demonstrated a release of 0.04 - 0.55 ppm in the  
95 first 24 h (in 4 ml of de-ionised water); by the 60<sup>th</sup> day 0.02 - 0.03 ppm of fluoride was released.  
96 Even at this low fluoride concentration, fluoride containing composites have been shown to prevent  
97 the formation of secondary caries *in vitro*, in a one month study examining enamel demineralisation  
98 [21, 22]. The *in vitro* study also demonstrated that the composite materials were unable to recharge  
99 with fluoride. A satisfactory method for maintaining a sustained low concentration of fluoride in  
100 the oral environment is as yet an unsolved problem. This issue will therefore be the focus of this  
101 present paper. To achieve this, a material incorporating layered double hydroxides (LDH) will be  
102 investigated, which will also render it as fluoride rechargeable.

103 Layered double hydroxides, also known as hydrotalcites, consist of positively charged inorganic  
104 sheets, counterbalanced by negatively charged anions e.g. fluoride, chloride, carbonates etc. [23].  
105 These structures have been successfully proven to remove excess fluoride from drinking water  
106 [24]. They are also biocompatible since they have been studied in biological applications for  
107 controlled drug delivery. They are currently incorporated in commercially available antacids and  
108 anti-peptics, known as Talcid<sup>TM</sup> and Altacite<sup>TM</sup>, respectively, to neutralise the acidic environment  
109 [23-26]. The general formula for LDH is [M<sub>1-x</sub> M<sub>x</sub><sup>3+</sup> (OH)<sub>2</sub>][A<sub>x/n</sub><sup>n-</sup> · mH<sub>2</sub>O], consisting of  
110 divalent, M<sup>2+</sup> (Mg, Zn, Ni, Co, Mn, etc.) and trivalent cations, M<sup>3+</sup> (Al, Cr, Fe, Co, etc) in the  
111 positive sheets [27, 28].

112 Only a limited number of studies have reported the use of LDH (2:1 MgAl LDH) for dental  
113 applications. Perioli *et al* [29] performed a clinical study where LDH containing fluoride (at 1-4%  
114 wt./wt) was incorporated into a hydrophilic buccal mucoadhesive (2cm<sup>2</sup>) patch. This patch was  
115 attached to the gum of five healthy volunteers. Residence time, swelling capacity, salivary  
116 modification, fragment loss, acceptability and organoleptic properties were evaluated *in vivo*.  
117 These LDH patches released fluoride *in vitro* at a controlled rate, over 4 h, in 100 ml of water

118 containing 1.2 mM NaHCO<sub>3</sub> at 37 ±0.1°C. These results showed that fluoride release increased  
119 with an increase in LDH loading from 1 to 4 wt%. A further study by Yokogawa *et al* [30],  
120 investigated the release of fluoride from 0.1 g of 2.7:1 MgFe LDH powder alone (without  
121 incorporating into a matrix), immersed into hydrogen sulphide (H<sub>2</sub>S), for absorption of volatile  
122 sulphur compounds (VSC) to reduce halitosis (malodour). This LDH released 8 ppm fluoride and  
123 absorbed VSC completely over 8 h.

124 Calarco *et al* [31] incorporated 2:1 MgAl LDH into a commercial resin composite and  
125 demonstrated fluoride release over three weeks, which was compared to a fluoride-glass filled  
126 commercial dental resin. A lower, but controlled release rate of fluoride was achieved by the LDH-  
127 composite in comparison to the fluoride glass-filled composite (burst release). The former system  
128 increased the migratory response of human dental pulp stem cell subpopulation (STRO-1+) and  
129 indicated a complete odontoblast-like cell differentiation, an effect that was not observed with the  
130 fluoride-glass filled composite. Tamaro *et al* [32] pre-charged MgAl LDH powder with fluoride  
131 and incorporated this into a commercial resin composites as a filler, which improved the resins  
132 mechanical properties. However, the latter were only investigated prior to fluoride release (dry  
133 samples), and not after immersing in de-ionised water following fluoride release; this may have  
134 had an adverse effect on the materials properties, as it has been demonstrated that LDH also absorbs  
135 water within its interlayers [33]. *In vitro* studies have also shown differentiation and proliferation  
136 of human dental pulp stem cells (hDPSC). The authors claimed this was due to the release of  
137 fluoride at low concentrations (0.25-5 ppm) over the study period [32]. The authors did not  
138 recharge the LDH-composite with fluoride, and hence, it appears they did not incorporate LDH for  
139 recharging purposes, but merely as a filler that releases fluoride.

140 Recently, a study by Su *et al* [34] incorporated fluoride charged LiAl LDH at 3 and 5 wt% into  
141 dental composites (RX; Esthet-X Flow and CC; Dyract flow, Dentsply, USA) and investigated  
142 fluoride release in 3 ml of DW over 90 days, with a recharge (1000 ppm NaF solution 4 min) at  
143 day 30. After fluoride recharge, the fluoride release was increased by 0.07 - 0.2 ppm with the 5  
144 wt% LDH containing composite. The incorporation of LDH in commercial materials masks the  
145 effect of the LDH alone, since these materials also contain other sources of fluoride. Therefore, it  
146 is essential to incorporate LDH in an experimental dental composite of known composition. In  
147 addition, DW alone does not mimic the oral environment and therefore fluoride absorption and  
148 release experiments should be carried out in AS, which mimics the oral environment. There is also  
149 a requirement to assess whether the amount of fluoride released after every recharge is maintained  
150 by the LDH-composite and does not diminish as reported for GICs. These requirements fall within  
151 the scope of the research reported in this paper.

152 This present study aims to investigate the potential of MgAl and CaAl LDH incorporated into  
153 experimental composites, thus rendering them fluoride rechargeable, in DW and AS. These  
154 materials would act as dental LDH-composite fluoride reservoirs, with the potential of preventing  
155 early-stage carious lesions and secondary caries. The effect of the LDH on the composites physico-  
156 mechanical properties will also be assessed to understand whether the properties are maintained or  
157 enhanced for use as dental composites e.g. restorative materials.

## 158 **2. Materials and Methods**

### 159 **2.1 Materials**

160 Calcium chloride dihydrate ( $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ ; Sigma-Aldrich, UK), magnesium chloride ( $\text{MgCl}_2$ ;  
161 Sigma-Aldrich, UK) and aluminium chloride ( $\text{AlCl}_3$ ; Fluka Analytical) reagents, with a >99%  
162 purity, were used to produce LDH (see below). Fluoride absorption and release (over six cycles)  
163 was also compared from two commercial resin composites (Tetric and Tetric EvoCeram from  
164 Ivoclar Vivadent, Lichtenstein). These commercial products were selected as they closely matched  
165 the experimental composite matrix (see below). However, both commercial products additionally  
166 contained fillers (81 wt%). The full composition can be observed in the supplementary material).

### 167 **2.2 Immersion media**

168 Deionised water (DW) and artificial saliva (20 mM N-2-hydroxyethylpiperazine-N-2-  
169 ethanesulfonic acid [HEPES], 1.50 mM  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ , 0.90 mM potassium dihydrogen  
170 orthophosphate, 130 mM potassium chloride, pH 7.0) adopted from Lynch & ten Cate [35] was  
171 used as immersion media.

### 172 **2.3 Methods**

#### 173 **2.3.1 LDH powder synthesis**

174 Two LDH powders (2:1 calcium aluminium [CaAl LDH] and 2:1 magnesium aluminium [MgAl  
175 LDH]) were produced using a co-precipitation method which was adopted from Mandal &  
176 Mayadevi [24]. The LDH powders were co-precipitated (at room temperature;  $21 \pm 0.1^\circ\text{C}$ ) using a  
177 solution of metal chlorides with a 2:1 divalent ( $\text{Mg}^{2+}$  or  $\text{Ca}^{2+}$ ) to trivalent ( $\text{Al}^{3+}$ ) cations ratio; 0.667  
178 M concentration  $\text{CaCl}_2$  (or  $\text{MgCl}_2$ ) and 0.333 M  $\text{AlCl}_3$  aqueous solution at pH  $10 \pm 1$  for MgAl  
179 LDH and  $11.5 \pm 1$  for CaAl LDH. The pH for each LDH was maintained with the dropwise addition  
180 of 2 M sodium hydroxide (NaOH). The precipitate was aged for 24 h at room temperature, washed  
181 and centrifuged several times with DW until a neutral solution was obtained (using litmus paper)  
182 and then dried at  $80^\circ\text{C}$  for 36 h. The solid powder was ground with a mortar and pestle and sieved  
183 using a  $63\mu\text{m}$  analytical sieve (Endecotts, Ltd, London, UK), for 45 min on a Retsch VS1000 vibrating  
184 machine (Retch GmbH, Germany).

#### 186 **2.3.2 Composite sample preparation**

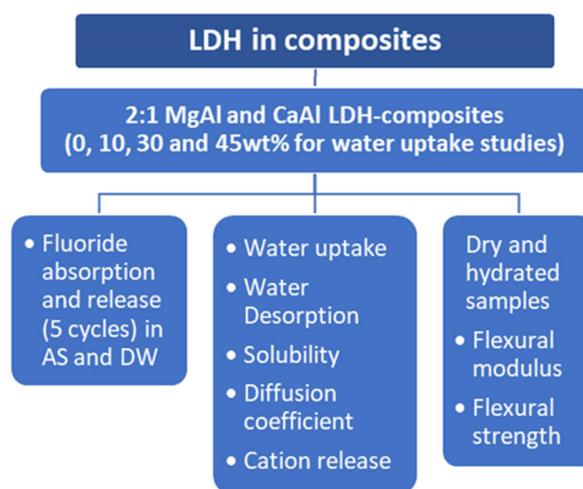
187 Light-curable experimental composites were produced from a prepared mixture of bisphenol A-  
188 diglycidyl methacrylate (Bis-GMA), urethane dimethacrylate (UDMA) and triethylenglycol  
189 dimethacrylate (TEGDMA) (35/35/30wt%), containing N,N-dimethyl-p-toluidine and  
190 camphorquinone (Sigma-Aldrich, UK). Seven mixtures were prepared; a control containing no  
191 LDH and three loadings (10, 30 and 45 wt%) of each LDH (2:1 CaAl and 2:1 MgAl). The refractive  
192 index of LDH (1.510 – 1.518) also closely matches the refractive index of the monomers used in  
193 the experimental composite (1.4703 - 1.5370), therefore a minimal effect on the curing depth of  
194 the LDH-composite can be considered [36, 37].

195 For fluoride absorption and release, circular discs of two loadings (10 and 30 wt%) of each LDH  
196 (2:1 CaAl and 2:1 MgAl) and an experimental resin control were studied (tested in DW and AS;  
197 n=6, 60 samples in total). A 45 wt% incorporation of LDH was not investigated since the water  
198 uptake studies showed unfavourable properties at this higher concentration (see section below).  
199 Two commercial composites (Tetric and Tetric Evoceram, Ivoclar Vivadent, Lichtenstein) were  
200 also studied in DW only (n=6), which were part of a previous pilot study and used for comparison  
201 purposes.

202 For water uptake studies, seven LDH mixtures (three loadings x two LDH: 10, 30 and 45 wt% and  
203 0% control; n=6, 42 samples in total) were used to prepare circular discs (measuring 1 mm x 10  
204 mm (n=6).

205 For mechanical properties (according to the ISO 4049 specifications [38]), rod-shaped samples  
206 were produced measuring 25 mm x 2.5 mm x 2.5 mm using 10 and 30 wt% of each LDH (2:1 CaAl  
207 and 2:1 MgAl) and two controls (tested dry and hydrated, n=10, 100 samples in total). Half of the  
208 samples were hydrated in 50 ml DW (37°C in an incubator shaker) for two weeks prior to testing.

209 For all studies, one sample was made at a time using a polytetrafluoroethylene (PTFE) mould. The  
210 mould was slightly overfilled with each mixture and was supported on both sides by glass slides  
211 covered with acetate sheets, the latter to prevent the resin from sticking to the glass slides. Whilst  
212 applying pressure over the slides for the circular discs, the samples were cured for 20 s using a  
213 light curing unit (3M ESPE Elipar™, USA; wavelength: 430-480 nm, 455 nm peak with 1200  
214 mW/cm<sup>2</sup> light intensity) on one side to complete curing (to mimic the materials' chairside  
215 application). For the rod-shaped samples, the samples were cured three times (slightly overlapping  
216 the light curing area each time) along the length of the specimen, in order to cure the whole length  
217 of the specimen. All samples were visually inspected and any sample with voids or defects were  
218 removed. All sample edges were smoothed by hand using silicon carbide abrasive paper (P600)  
219 (Buehler, IL, USA) to remove any flash or irregularities. Fig. 1 shows a flow chart of the work  
220 conducted with the LDH-composites in this report.



221

222 **Fig. 1 - Flow chart of the studies conducted with the LDH-composites. [Colour]**

### 2.3.3 Fluoride absorption and release

Each LDH-composite disc and commercial composite was immersed separately in 15 ml of 0.1 M sodium fluoride (NaF) solution in an incubator shaker (37°C and 60 rotations per minute, rpm) for two days (48 h) to absorb fluoride. The disc was then removed, blotted dry and transferred to 5ml of DW or AS (37°C and 60 rotations per minute, rpm) for 24 h. The amount of fluoride released in the immersion solution was measured every 24 h, using fluoride ion selective electrodes (NICO2000), following the addition of a total ionic strength adjustment buffer (TISAB, 5 ml) to break down any potential complexes formed in solution e.g. CaF<sub>2</sub> or AlF<sub>3</sub>. The immersion solution was then replaced with fresh DW or AS (every 24 h), to avoid saturation. After two days (48 h) of release the discs were immersed into tubes containing 15 ml NaF solution (0.05 M; 37°C and 60 rotations per minute, rpm) to absorb fluoride (recharge), for five minutes. The discs were then removed, blotted dry and placed back into fresh DW or AS (5 ml) to re-release fluoride. Fluoride recharge cycles were performed over 10 days (re-charging every 48 h), with two days of fluoride release between the recharges.

### 2.3.4 Water uptake

A similar method to that used by Agha *et al* [39] was used to conduct this study. All composite discs were firstly conditioned (dried) at 37±1°C in an incubator (Carbolite, Camlab, Cambridge, UK) over 72 h and then weighed separately (time 0, W<sub>0</sub>) and immersed in 100 ml DW at 37±1°C. At regular pre-determined time intervals over seven weeks the samples were removed from DW, blotted dry on filter paper (Fisherbrand, USA) and weighed (W<sub>t</sub>) to an accuracy of 0.0001 g (Mettler HK balance, USA), before returning to the bottle with DW in the oven. Several readings were recorded on the first day and then less frequently over seven weeks. Each sample was weighed in less than 30s to avoid any dehydration of the samples. The weight change (%) at each time point was calculated using Equation 1. W<sub>t</sub> was the weight at the time interval (t) and W<sub>0</sub> was the initial weight at time zero (time 0).

$$\text{Weight change (\% uptake)} = (W_t - W_0/W_0) \times 100 \quad \text{Equation 1}$$

The mean weight change was then plotted against time<sup>1/2</sup> (t<sup>1/2</sup>), with standard deviations for each interval.

### 2.3.5 Desorption, diffusion coefficient, solubility and cation release

After seven weeks of studying water uptake, the samples were removed from the solutions, blotted dry, weighed and transferred to a desorption oven (Carbolite, Camlab, Cambridge, UK) at 37±1°C. Similar to the water uptake method, the weight change (%) was calculated over three weeks and plotted against time<sup>1/2</sup>. W<sub>0</sub> was the weight at time 0 (at week 7 of absorbing water), and W<sub>d</sub> represents the constant minimum weight reached.

The solubility of the material was calculated by subtracting the weight after desorption (W<sub>d</sub>) from the initial weight (W<sub>0</sub>) and dividing by W<sub>0</sub> (Equation 2).

$$\text{Solubility (\%)} = (W_0 - W_d/W_0)/100 \quad \text{Equation 2}$$

260 For calculating the diffusion coefficients for the absorption (speed at which water enters the sample  
261 before equilibrating) and desorption (speed at which water is lost from the sample before  
262 equilibrating) processes, the weight change data for both were plotted in the form of  $M_t/M_\infty$  versus  
263 the square root of time (seconds). Where  $M_t$  is the weight at each time point,  $t$  (in seconds) and  $M_\infty$   
264 is the weight at equilibrium (i.e. where the linear part of % weight change versus  $t^{1/2}$  plots begin to  
265 equilibrate. Equation 3 was used to calculate the diffusion coefficients for the absorption and  
266 desorption processes:

$$267 \quad D = (S^2\pi L^2)/4 \quad \text{Equation 3}$$

268 Where,  $2L$ = the sample thickness,  $S$ = the slope of the graph ( $M_t/M_\infty$  plotted against  
269 time<sup>1/2</sup>, s<sup>1/2</sup>),  $M_t$  = the mass uptake at time ( $t$ ),  $M_\infty$  = the mass uptake at equilibrium.

270 The release of cations from the LDH-composite samples, for example  $Mg^{2+}$ ,  $Ca^{2+}$  and  $Al^{3+}$  from  
271 the water uptake DW solutions after the 7-weeks of water uptake, were also measured for each  
272 sample ( $n=3$ ), using inductively coupled plasma optical emission spectrometry (ICP-OES.)

### 273 **2.3.6 Flexural strength and flexural modulus**

274 The sample's height and thickness along three points, equally spaced along the specimen (at the  
275 centre and two ends), was measured using a digital micrometer (Mitutoyo, RS Components Ltd.,  
276 Corby, Northants, UK) to an accuracy of 0.001 mm. All samples were tested at room temperature  
277  $23 \pm 1^\circ\text{C}$ . A 3-point bending test was set up using a jig with a span of 20 mm (Instron 5567 -  
278 H1580, England). The test was performed by applying a gradual load (500 N calibrated load cell)  
279 to the specimen, at a cross-head speed of 0.75 mm/min, until the specimen reached the yield point,  
280 or fractured. The hydrated samples were also tested immediately after removing from DW. The  
281 data obtained was used to determine the flexural strength and modulus, via force and extension  
282 data obtained during testing, from the Instron machine. Flexural strength was calculated as per  
283 Equation 4 and flexural modulus was determined using Equation 5.

$$284 \quad \text{Flexural strength, } \sigma = \frac{3FL}{(2BH^2)} \quad \text{Equation 4}$$

285  $F$  is the maximum load,  $L$  is the span length,  $B$  is the width of the specimen and  $H$  is the thickness  
286 of the specimen.

$$287 \quad \text{Flexural modulus, } E = \frac{FL^3}{4BH^3D} \quad \text{Equation 5}$$

288  $D$  is the deflection of the specimen at a given linear region on a force/extension graph.

### 289 **2.3.7 Statistical methods**

290 To calculate the significance of the results where applicable, the means and standard deviations  
291 were calculated using Microsoft Excel. Data was subjected to a One-way ANOVA test and, where  
292 relevant, a post-hoc Tukey test was performed, with a statistical significance at  $p < 0.05$ .



## 293 3. Results

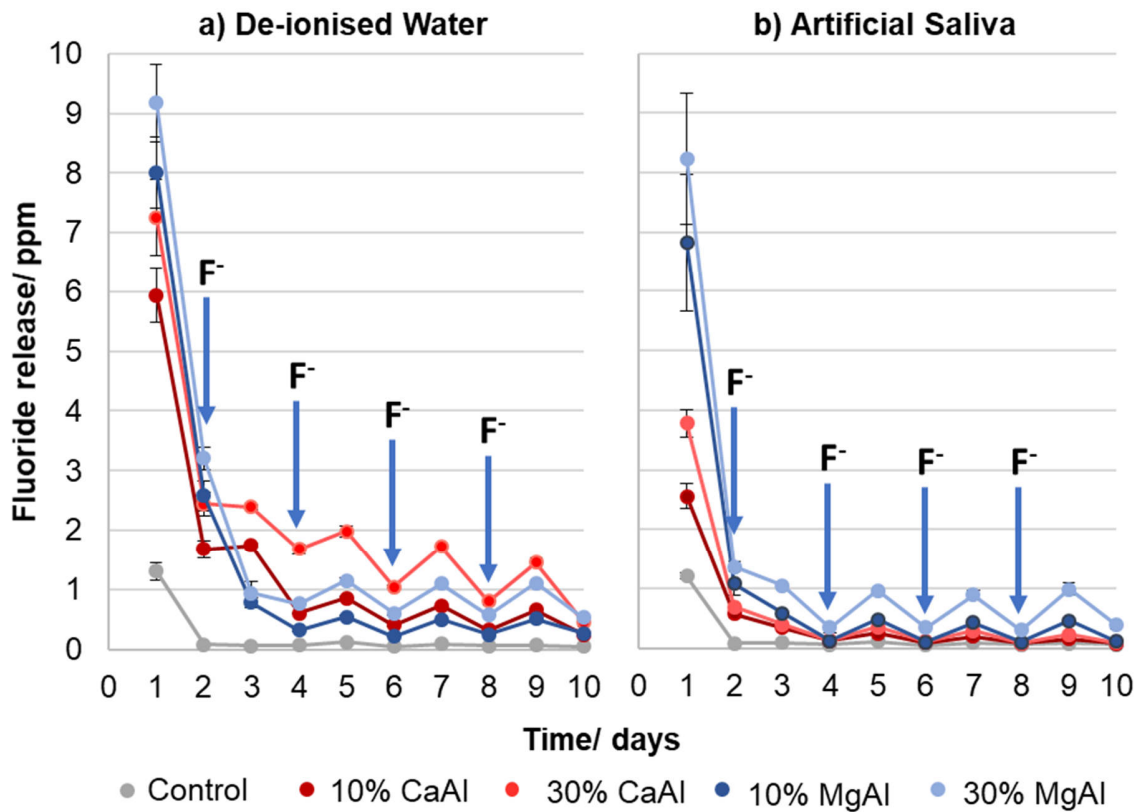
### 294 3.1 Fluoride uptake and release

295 The ability of the LDH containing composites to recharge with fluoride are shown in Figs 2a and  
296 b, in DW and AS, respectively. In DW (Fig 2a), the amount of fluoride released from the  
297 composites containing CaAl LDH or MgAl LDH, significantly increased compared to the control  
298 ( $P < 0.05$ ). 30 wt% CaAl LDH-composites released the greatest mean amount of fluoride 24 h after  
299 recharging with fluoride ( $1.89 \pm 0.37$  ppm), followed by 30 wt% MgAl ( $1.07 \pm 0.22$  ppm), 10 wt%  
300 MgAl ( $0.58 \pm 0.14$  ppm), 10 wt% CaAl LDH-composites ( $0.51 \pm 0.41$  ppm), and finally the  
301 experimental composite control ( $0.08 \pm 0.03$  ppm), shown in Table 1. In addition, the 10 wt% CaAl  
302 and MgAl LDH-composites were not statistically different from each other ( $P > 0.05$ ).

303 The CaAl LDH containing composites at both 10 and 30 wt% released less fluoride after every  
304 consecutive recharge. For example, with the 30 wt% CaAl LDH-composite,  $2.40 \pm 0.04$  ppm  
305 fluoride was released after the first recharge, however  $1.46 \pm 0.08$  ppm was released after the last  
306 recharge (Fig. 2a). In contrast, the MgAl LDH containing composites at both 10 and 30 wt%  
307 released similar amounts of fluoride throughout all recharge cycles. For example, the fluoride  
308 release after the first recharge and after the last recharge for 30 wt% MgAl LDH-composite was  
309  $0.94 \pm 0.21$  ppm and  $1.10 \pm 0.03$  ppm respectively, with a mean value of  $1.07 \pm 0.22$  ppm after all  
310 recharge cycles. Overall, after every recharge there was an increase in fluoride release. For  
311 example, 30 wt% CaAl LDH-composite released  $0.80 \pm 0.06$  ppm before the last recharge (at day  
312 8) and released  $1.46 \pm 0.06$  ppm after recharging in Fig. 1a. Therefore, a potential recharge of  $\sim 0.66$   
313 ppm was achieved by this LDH-composite. The enhanced release of fluoride obtained initially was  
314 probably due to the initial charging time (48 h; Fig. 2a and 2b), in comparison to subsequent five-  
315 minute recharges.

316 As with fluoride release in DW, the amount of fluoride released in AS from the composites  
317 containing CaAl and MgAl LDH, increased significantly compared to the control ( $P < 0.05$ , Fig.  
318 2b). Comparing the fluoride released after every recharge in DW and AS (Fig. 2a and 2b) overall,  
319 less fluoride was released in AS ( $P < 0.05$ ) from both the MgAl and CaAl LDH containing  
320 composites. However, the difference between the fluoride released for MgAl LDH-composites at  
321 both 10 and 30 wt%, demonstrated no significant differences ( $P > 0.05$ ) between DW and AS. In  
322 AS, the mean fluoride release after every recharge was greater for the MgAl LDH-composite (10  
323 and 30 wt%;  $0.49 \pm 0.08$  ppm and  $0.97 \pm 0.15$  ppm) compared to the CaAl LDH-composites (10  
324 and 30 wt%;  $0.24 \pm 0.10$  ppm and  $0.31 \pm 0.07$  ppm). After every recharge, the fluoride release was  
325 greater than the previous release cycle ( $P < 0.05$ ) from all the LDH-composites. All composites  
326 containing MgAl and CaAl LDHs released more fluoride after every recharge ( $P < 0.05$ , Table 1) in  
327 comparison to the two commercial Ivoclar composites (Ivoclar Vivadent, Lichtenstein).

328 As previously observed with samples in DW, the CaAl LDH-composites gradually released less  
329 fluoride after every consecutive recharge in AS (Fig. 2b). For example, the 30 wt% CaAl LDH-  
330 composite released  $0.39 \pm 0.01$  ppm fluoride after the first recharge, however this gradually  
331 reduced after every recharge, releasing  $0.26 \pm 0.03$  ppm after the final fluoride recharge.



332  
 333 **Fig. 2 - Mean fluoride release every 24 h over 10 days from 10 and 30 wt% 2:1 MgAl and**  
 334 **CaAl LDH-composites in a) DW and b) AS. The arrows indicate fluoride recharging for five**  
 335 **minutes in a 0.05 M NaF solution. [Colour]**

**Table 1 - Mean fluoride release 24 h after each of the four fluoride recharges for 10 and 30 wt% 2:1 MgAl and CaAl LDH-composites, control and commercial materials in DW and AS from Fig. 2.**

Composite sample	Av. fluoride release after every recharge (DW)	Av. fluoride release after every recharge (AS)
Control	0.08 (0.02)	0.08 (0.03)
CaAl 10 wt%	0.51 (0.41)	0.24 (0.10)
CaAl 30 wt%	1.89 (0.37)	0.31 (0.07)
MgAl 10 wt%	0.58 (0.14)	0.49 (0.08)
MgAl 30 wt%	1.07 (0.22)	0.97 (0.14)
Tetric	0.13 (0.05)	-
Tetric Evoceram	0.12 (0.03)	-

336

### 337 **3.2 Flexural strength and modulus**

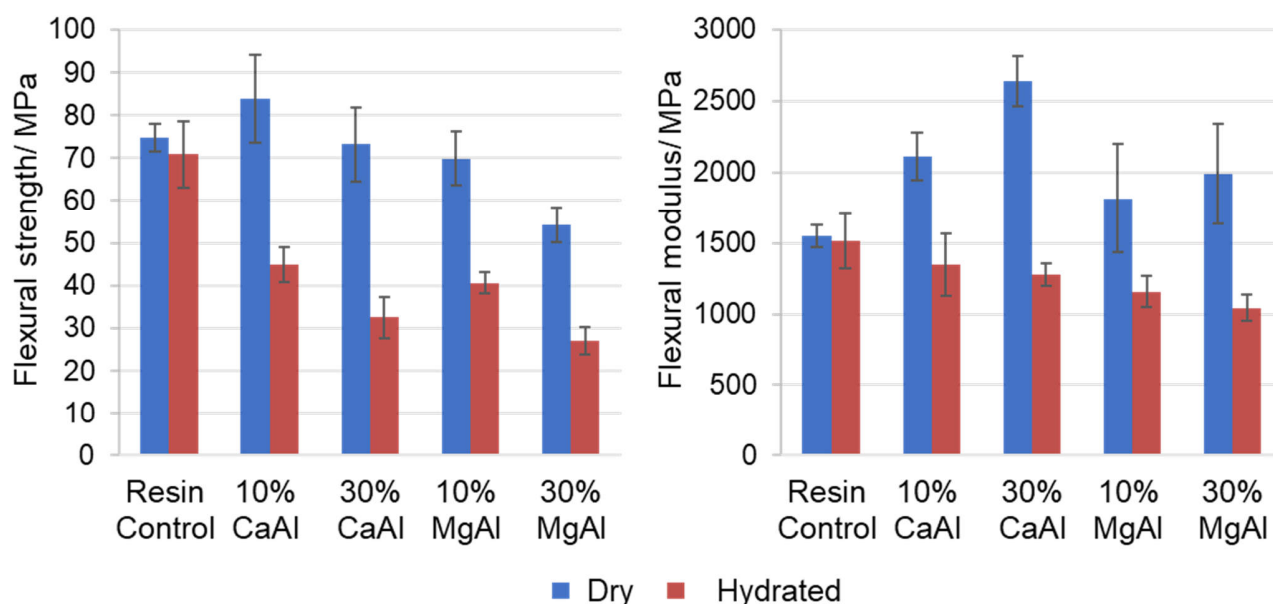
338 Fig. 3 illustrates the flexural strength of composite resins, containing CaAl and MgAl LDH at 0  
339 (control), 10 and 30 wt % in their dry and hydrated (2 weeks in DW) state. It was evident from the  
340 data that in the dry state, the 10 wt% 2:1 CaAl LDH-composites significantly increased in flexural  
341 strength by ~12% compared to that of the dry control group ( $P<0.05$ ). 30 wt% CaAl LDH-  
342 composite showed no significant difference in flexural strength to the control in the dry state.

343 Once hydrated for two weeks, the composite samples containing the CaAl and MgAl LDH showed  
344 a significant reduction in flexural strength compared to their dry state and to the resin control group  
345 (Fig. 3). The CaAl LDH-composites showed a greater reduction in comparison to the MgAl LDH-  
346 composites; CaAl 10 wt% ~46% reduction, CaAl 30 wt% ~56% reduction, MgAl 10 wt% ~42%  
347 reduction and MgAl 30 wt% ~50% reduction. The resin control showed no significant difference  
348 in flexural strength between the dry and hydrated state ( $P>0.05$ ).

349 Although the 2:1 CaAl LDH-composites demonstrated a greater reduction in flexural strength  
350 when comparing the dry state to the hydrated state, it had a significantly higher flexural strength in  
351 comparison to the 2:1 MgAl LDH composite rods. It was also evident that with an increase in either  
352 MgAl or CaAl LDH loading, from 10 to 30 wt%, (for both dry and hydrated samples), the flexural  
353 strength decreased.

354 Fig. 3 shows the mean flexural modulus data for the same LDH-composite groups analysed for the  
355 flexural strength ( $n=10$ ). The addition of either 2:1 CaAl or MgAl LDH powder to experimental  
356 resin composites significantly increased the flexural modulus in the dry state in comparison to the  
357 dry resin control group.

358 With an increase in the 2:1 CaAl LDH powder in the resin material, the data showed that the  
359 flexural modulus increased significantly from  $1549 \pm 79$  MPa (control) to  $2113 \pm 164$  MPa (10 wt%  
360 CaAl LDH-composite and  $2642 \pm 176$  MPa (30 wt% CaAl LDH-composites) ( $P<0.05$ ). 10 wt%  
361 MgAl and CaAl LDH-composites, and 30 wt% MgAl LDH-composites showed no significant  
362 difference between each other ( $P>0.05$ ). After immersing the samples for two weeks in DW, it was  
363 clear from the data (Fig. 3) that there was no significant difference in flexural modulus between  
364 the control group and 10 wt% CaAl LDH-composite. The 10 and 30 wt% CaAl- LDH showed no  
365 significant difference with each other after hydration ( $P>0.05$ ).



366  
 367 **Fig. 3 - Mean flexural strength and flexural modulus for the resin control (no LDH), 2:1 CaAl**  
 368 **or MgAl LDH-composites 10 and 30 wt%, tested dry and hydrated in DW for two weeks**  
 369 **(n=10; total 100 samples). [Colour]**

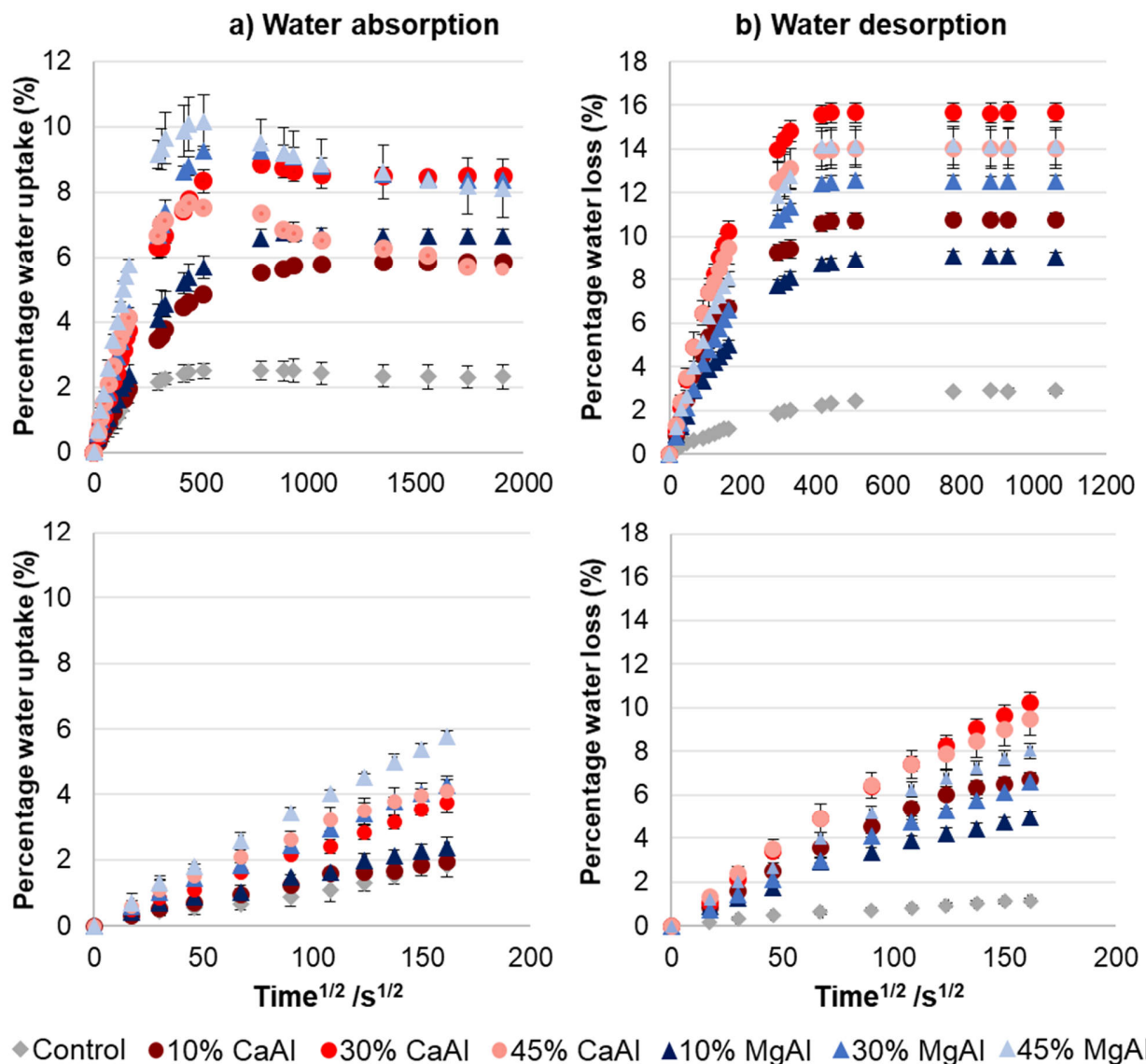
### 370 3.3 Water uptake and desorption

371 This section analyses the results on water uptake, water desorption and % solubility of the  
 372 composite samples containing 2:1 MgAl and 2:1 CaAl LDH at different concentrations (10, 30 and  
 373 45 wt% LDH). Fig. 4a represents the percentage weight change (water uptake) against the square  
 374 root of time (in seconds, s) and the initial water uptake for up to 8 h, to demonstrate the relationship  
 375 during the initial stages, which were linear for all samples. Water uptake equilibrium was reached  
 376 much sooner for the control  $\sim 779 \text{ s}^{1/2}$  ( $\sim 7$  days), whereas with both MgAl and CaAl LDH  
 377 incorporated at 10 wt%, equilibrium occurred at  $\sim 930 \text{ s}^{1/2}$  ( $\sim 10$  days), at 30 wt% LDH, at  $1347 \text{ s}^{1/2}$   
 378 ( $\sim 21$  days) and at 45 wt%, equilibrium did not occur throughout the seven weeks (Fig. 4a). The  
 379 percentage water uptake decreased after reaching a maximum water uptake at  $510 \text{ s}^{1/2}$  ( $\sim 3$  days) for  
 380 the 45 wt% MgAl and CaAl LDH-composites.

381 Fig. 4a also demonstrates that as the amount of both MgAl and CaAl LDH increased in the  
 382 composites from 0 to 45 wt%, the amount of water taken up significantly increased ( $P > 0.05$ ;  
 383 maximum water uptake, control  $2.50 \pm 0.24\%$ , 10 wt% MgAl and CaAl LDH  $6.76 \pm 0.26\%$  and  
 384  $5.84 \pm 0.20\%$  respectively, 30 wt% MgAl and CaAl LDH  $9.25 \pm 0.21\%$  and  $8.74 \pm 0.17\%$   
 385 respectively, and 45 wt% MgAl and CaAl  $10.14 \pm 0.84\%$  and  $7.66 \pm 0.85\%$  respectively). An  
 386 increase in water uptake when increasing the LDH loading from 30 to 45 wt% CaAl LDH-  
 387 composites was however not observed. For all LDH weight percentages, the MgAl LDH-composite  
 388 absorbed a statistically significant greater amount of water in comparison to the corresponding  
 389 CaAl LDH-composites.

390 The water desorption was faster in comparison to water uptake, with the samples reaching  
391 equilibrium at  $442-510 \text{ s}^{1/2}$  (~2 - 3 days, Fig. 4b). Fig. 4b demonstrates that the amount of water  
392 desorbed from the composite discs containing 10, 30 and 45 wt% 2:1 CaAl and MgAl LDH, was  
393 significantly greater, in comparison to the composite control ( $P < 0.05$ ). With an increase in LDH  
394 weight percent in the composite discs, from 0 to 45 wt%, the amount of water desorbed increased  
395 e.g. for MgAl LDH-composites; control  $2.89 \pm 0.11\%$ , 10 wt%  $9.09 \pm 0.21\%$ , 30 wt%  $12.55 \pm$   
396  $0.25\%$  and 45 wt%  $14.17 \pm 0.88\%$ . However, as in the water uptake study, only the 45 wt% CaAl  
397 LDH-composite did not follow this increase in trend (between 30 to 45 wt% CaAl LDH-  
398 composites).

399 Although the MgAl LDH-composites absorbed more water in comparison to the CaAl LDH-  
400 composite discs, the MgAl LDH-composites lost less water than the CaAl LDH-composites during  
401 water desorption (see Discussion).



402 ◆ Control ● 10% CaAl ● 30% CaAl ● 45% CaAl ▲ 10% MgAl ▲ 30% MgAl ▲ 45% MgAl  
 403 Fig. 4 - a) Percentage water uptake for up to seven weeks and the early stages (over ~8 h, 162  
 404 s<sup>1/2</sup>), b) percentage water desorption up to three weeks and early stages (over ~8 h, 162 s<sup>1/2</sup>)  
 405 from the resin composite discs, containing either 2:1 CaAl or MgAl LDH at 0 (control), 10,  
 406 30 and 45 wt% (n=6) in DW. [Colour]

407 **3.4 Diffusion coefficients and solubility%**

408 All materials from both experiments (absorption and desorption) showed a linear relationship when  
 409 plotted as  $M_t/M_\infty$  against  $t^{1/2}$ , which was confirmed with trendlines fitted with a regression of ( $R^2$ )  
 410  $>0.99$  (see supplementary material). However, for the LDH composites, it should be noted that  
 411 these samples reached a maximum before losing weight and then virtually equilibrating. Therefore,  
 412 the maximum uptake value was taken as the  $M_\infty$  value, in order to calculate apparent diffusion  
 413 coefficients. A  $M_t/M_\infty$  value of 0.5 was used to determine the slope of the linear region and was  
 414 used to calculate the diffusion coefficient of absorption ( $D_{abs}$ ) using Equation 3.

415 The  $D_{\text{abs}}$  for the control ( $(3.67 \pm 0.52) \times 10^{-12} \text{ m}^2/\text{s}$ ) was significantly higher compared to  $D_{\text{abs}}$  for  
 416 the 10, 30 and 45 wt% 2:1 CaAl LDH-composite(s) (which ranged from  $(0.89 \pm 0.08) \times 10^{-12}$  to  
 417  $(2.13 \pm 0.22) \times 10^{-12} \text{ m}^2/\text{s}$ ) and the MgAl LDH-composite (ranging from  $(0.96 \pm 0.19) \times 10^{-12}$  to  
 418  $(2.16 \pm 0.13) \times 10^{-12} \text{ m}^2/\text{s}$ ) (Table 2). This confirms that the control discs absorbed water much  
 419 faster than the LDH-composite samples ( $P < 0.05$ ). With an increase in LDH (in either 2:1 CaAl and  
 420 MgAl) from 10 to 45 wt% the  $D_{\text{abs}}$  increased, therefore absorbing water faster due to the more  
 421 hydrophilic nature of the LDH in comparison to the polymer matrix in the composites. There was  
 422 no significant difference in  $D_{\text{abs}}$  between the CaAl and MgAl LDH-composites at 10 and 45 wt%,  
 423 although at 35 wt%, the MgAl LDH-composites demonstrated a higher  $D_{\text{abs}}$  in comparison to the  
 424 CaAl LDH-composites ( $P < 0.05$ ).

425 The diffusion coefficients for desorption ( $D_{\text{des}}$ ) were significantly greater for the samples  
 426 containing 2:1 CaAl or MgAl LDH-composites compared to the control ( $P < 0.05$ ), e.g. for 10 wt%  
 427 LDH; CaAl LDH-composite ( $4.69 \pm 0.44) \times 10^{-12} \text{ m}^2/\text{s}$ , MgAl LDH-composite ( $3.42 \pm 0.31) \times 10^{-12}$   
 428  $\text{m}^2/\text{s}$  and the control ( $1.16 \pm 0.16) \times 10^{-12} \text{ m}^2/\text{s}$ . Therefore, these samples were losing water at a  
 429 faster rate than the control samples, and yet they took longer to equilibrate. For all weight  
 430 percentages, the 2:1 MgAl LDH had a significantly lower value in comparison to the 2:1 CaAl  
 431 LDH (Table 2).

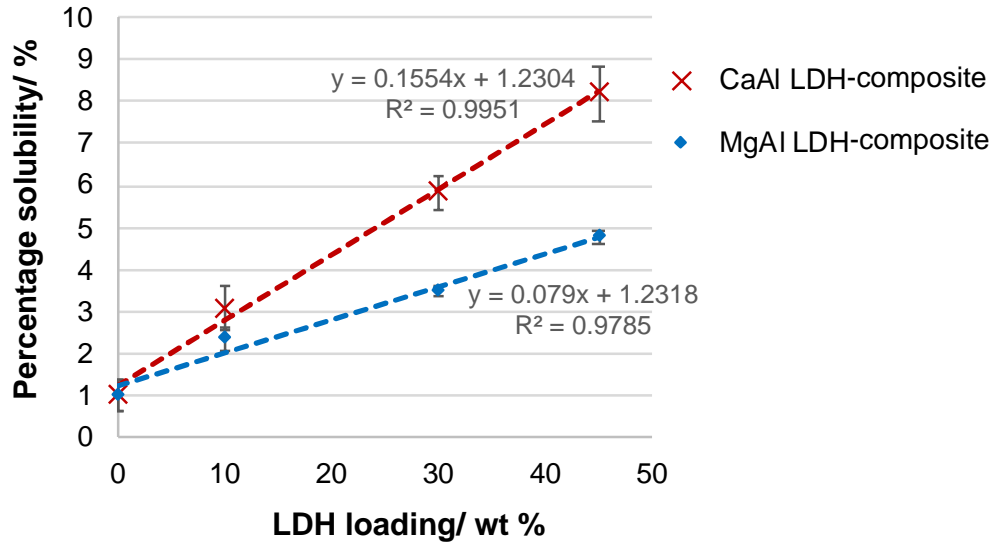
432  $D_{\text{des}}$  for all the LDH-composites were greater than their corresponding  $D_{\text{abs}}$  ( $P < 0.05$ ), however the  
 433 opposite was observed for the control. Table 2 shows the differences between  $D_{\text{abs}}$  and  $D_{\text{des}}$ , which  
 434 are discussed further in the discussion. The calculations and data spreadsheets for the above  
 435 percentage uptake, loss,  $D_{\text{abs}}$  and  $D_{\text{des}}$  are in the Supplementary material.

**Table 2 – Diffusion coefficients for water absorption ( $D_{\text{abs}}$ ) and desorption ( $D_{\text{des}}$ ) for the resin composite discs, containing CaAl or MgAl LDH at 0 (control), 10, 30 and 45 wt%.**

Composite sample	$D_{\text{abs}}$ $\times 10^{-12} (\text{m}^2 \text{s}^{-1})$	$D_{\text{des}}$ $\times 10^{-12} (\text{m}^2 \text{s}^{-1})$
Control	3.67 (0.52)	1.16 (0.16)
MgAl 10 wt%	0.96 (0.19)	3.42 (0.31)
MgAl 30 wt%	1.45 (0.11)	3.07 (0.20)
MgAl 45 wt%	2.16 (0.13)	3.85 (0.54)
CaAl 10 wt%	0.89 (0.08)	4.70 (0.43)
CaAl 30 wt%	1.09 (0.15)	4.63 (0.37)
CaAl 45 wt%	2.13 (0.22)	5.15 (0.30)

436  
 437 The solubility of the samples containing LDH was significantly greater than the control, therefore  
 438 the samples lost more mass ( $P < 0.05$ ). Fig. 5 also demonstrates that the solubility of the 2:1 CaAl  
 439 LDH-composite samples was significantly greater than the 2:1 MgAl, therefore more LDH ions

440 and/or residual monomers were leaching out from the CaAl LDH discs. As the wt% of both 2:1  
 441 CaAl and 2:1 MgAl LDH incorporated in experimental composites, increased, the solubility also  
 442 increased linearly (Fig 5).



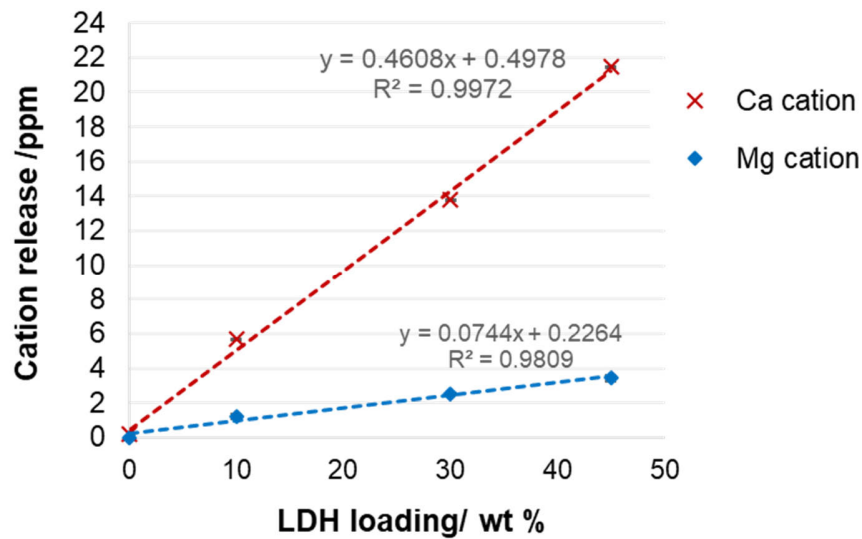
443  
 444 **Fig. 5 - Percentage solubility of the resin composite discs, containing CaAl or MgAl LDH at**  
 445 **0 (control), 10, 30 and 45 wt% (n=6) after immersion in DW for seven weeks and drying at**  
 446 **37°C for three weeks. [Colour]**

### 447 3.5 Cation release

448 Fig. 6 shows cations ( $Mg^{2+}$  and  $Ca^{2+}$ ) released from the MgAl and CaAl-LDH composites in DW,  
 449 during water uptake over seven weeks. A significantly greater amount of calcium ions was released  
 450 from the CaAl-LDH composites, in comparison to the magnesium ions released from MgAl LDH-  
 451 composites and the composite control ( $P < 0.05$ ). For example, at 10 wt% loading, the CaAl LDH-  
 452 composites released  $5.680 \pm 0.002$  ppm calcium, the MgAl LDH-composite released  $1.21 \pm 0.14$   
 453 ppm magnesium.

454 The release of both calcium and magnesium cations from the two LDHs increased linearly with an  
 455 increase in LDH loading in the composite (Fig. 6). For example, the calcium release from the CaAl  
 456 LDH-composite increased from  $5.680 \pm 0.002$  ppm for the 10 wt% loading to  $21.45 \pm 0.02$  ppm  
 457 for the 45 wt% loading ( $P < 0.05$ ). The release of aluminium from all samples was minimal  $\sim 0 -$   
 458  $0.33$  ppm (Data in supplementary material). 45 wt% CaAl LDH-composite released the greatest  
 459 amount of aluminium:  $0.33 \pm 0.20$  ppm over the seven weeks.





460  
 461 **Fig. 6 - Cation release from the resin composite discs, containing CaAl or MgAl LDH at 0**  
 462 **(control), 10, 30 and 45 wt% (n=6) after immersion in DW for seven weeks. [Colour]**

463 **4. Discussion**

464 **4.1 Fluoride absorption and release**

465 Since the development of a material with a controlled and prolonged delivery of fluoride is a  
 466 necessity to the dental field to reduce the prevalence of dental caries, this paper was focussed on  
 467 developing LDH-composites capable of absorbing and releasing fluoride repeatedly to maintain a  
 468 sustained release of fluoride.

469 Experimental composites were prepared in this present report, in order have knowledge of all  
 470 ingredients used, so that the results obtained for fluoride absorption and release, were not affected  
 471 by any other source of fluoride (e.g. from fillers). Commercial composites do contain a source of  
 472 fluoride (e.g. glass filler – strontium-alumino-fluoro-silicate and/ or ytterbium trifluoride [40]), and  
 473 therefore after incorporating in LDH, the source of fluoride (or any other ion release) cannot be  
 474 attributed to the LDH alone.

475 LDH was successfully incorporated into the experimental composite, which was able to absorb and  
 476 release fluoride over five cycles. The fluoride absorption and release was studied in both DW and  
 477 AS, since previous studies have demonstrated that other ions such as phosphates, which are also  
 478 present in AS, interfere and reduce fluoride absorption by LDH powders (not incorporated into any  
 479 resin)[41].

480 Both MgAl and CaAl LDH-composites (at 10 and 30 wt%) significantly increased the amount of  
 481 fluoride released in comparison to the control and the two commercial composites (Tetric and  
 482 Tetric Evoceram, Ivoclar Vivadent, Lichtenstein). Both commercial composites, contain ytterbium  
 483 trifluoride, from which fluoride was released and the amount decreased significantly after each  
 484 consecutive recharge (five fluoride recharges), in comparison to the 2:1 MgAl LDH-composites,

485 which maintained a similar amount of fluoride release throughout the study. This amount of  
486 fluoride release by the 2:1 MgAl-LDH composite resides in the desired optimal therapeutic level  
487 range from ~0.1 - 1 ppm for caries prevention [2, 42, 43], and so it has potential use in the oral  
488 cavity.

489 Although 2:1 MgAl LDH-composite released similar amounts of fluoride after every fluoride  
490 recharge, the 2:1 CaAl LDH-composites released less. This may be due to the formation of CaF<sub>2</sub>  
491 forming, as a result of its low solubility product ( $K_{sp}=3.45\times 10^{-11}$ ) compared with Ca(OH)<sub>2</sub> ( $K_{sp}$   
492  $=5.02\times 10^{-6}$ ). This would require further analysis, by for example, analysing the surface of the CaAl  
493 LDH-composites after fluoride charging. MgF<sub>2</sub> (from MgAl LDH) may not form after fluoride  
494 absorption since it has a higher solubility product than its hydroxide derivatives ( $K_{sp}(\text{MgF}_2)=$   
495  $5.16\times 10^{-11}$  compared to  $K_{sp}(\text{Mg}(\text{OH})_2)=5.61\times 10^{-12}$ ) [44]. The formation of CaF<sub>2</sub> has been shown  
496 to be unfavourable in the oral environment, as it remains insoluble, and therefore would result in a  
497 reduction in fluoride release [45].

498 Further, in DW, CaAl LDH-composite released more fluoride than MgAl LDH-composites. In AS,  
499 an opposite relationship was observed. In addition, the MgAl LDH-composites showed no  
500 significant difference in the amount of fluoride released in AS and DW, whereas the CaAl LDH-  
501 composites released significantly less fluoride in AS, and again, after each consecutive cycle. It  
502 appears that the 2:1 MgAl LDH-composite was less affected by the presence of other ions in  
503 solution, compared to the 2:1 CaAl LDH-composite. As mentioned above CaF<sub>2</sub> may be forming on  
504 the surface of the LDH-composite and thus hindering fluoride release. A previous study reported  
505 that fluoride release may be modified due to the formation of CaF<sub>2</sub> [46]. Hence, the 2:1 MgAl LDH  
506 has potential to be used in dental composites where it would recharge, since it released a therapeutic  
507 level (~1 ppm) of fluoride in AS, where the latter was used to mimic the condition of the oral  
508 environment. It appears that 2:1 CaAl LDH in dental composites would not be suitable as a  
509 rechargeable system, but it could be used as a fluoride releasing dental material, since it released a  
510 therapeutic level initially.

511 As mentioned in the introduction, Su *et al* [34] who incorporated LiAl LDH into commercial  
512 composites, showed less fluoride release (~0.2 ppm) compared to the amount released from 2:1  
513 MgAl and CaAl LDH-composites (10 and 30 wt%) in this present study. Su *et al* [34] investigated  
514 fluoride release in 3 ml of DW, rather than 5 ml, as used in this present study. The sample disc  
515 sizes were smaller (6 mm x 2 mm compared to 10 mm x 1mm) and charging occurred over 4 min  
516 in 1500 ppm rather than for 5 min in 950 ppm (0.05 M), at 37°C, used in this present study.  
517 Therefore, the results obtained from the current study cannot be directly compared with that of Su  
518 *et al* [34]. However, the results obtained from this current study are promising with sustained  
519 release achieved after five recharge cycles, particularly with MgAl LDH.

520 Other studies that have incorporated LDH into commercial composites also used different protocols  
521 e.g. fluoride release in 15 ml AS (~2 ppm in 24 h from 14 mm x 1 mm discs) and release in 50 ml  
522 0.9% w/v NaCl aqueous solution (~0.1 ppm in 24 h from 20 mm x 1 mm discs) [31, 32]. However,  
523 no fluoride recharges were investigated in these studies. A further study, which incorporated LDH  
524 (1-4 wt%) into a mucoadhesive strip, investigated fluoride release in 100 ml 1.2 mM NaHCO<sub>3</sub>

525 water (~0.2 mg F/cm). Hence, due to the differences in the various release protocols, LDH  
526 compositions, and carrier matrices, the studies could not be compared to each other or to the results  
527 reported in the present study.

528 Experiments performed in the present paper and those in published literature were conducted in a  
529 static environment (e.g. DW or AS). This does not directly mimic the fluoride concentration levels  
530 in the oral environment, since a salivary flow exists in the cavity, and therefore fluoride equilibrium  
531 may not be reached. Considering the release method protocol further, having a salivary flow system  
532 for future studies, to obtain a maintained therapeutic level of 0.1-1 ppm, would be of greater  
533 advantage [47, 48].

## 534 4.2 Mechanical properties

535 The addition of either 2:1 CaAl or MgAl LDH powder to experimental resin composites  
536 significantly increased the flexural modulus in the dry state, in comparison to the resin control  
537 group, as also reported in the published literature [32]. Also, the flexural strength of the CaAl LDH-  
538 composites was greater than the MgAl LDH-composites. Tammaro *et al* [32] used a dynamic  
539 mechanical thermo-analyser at temperatures varying from -50 to 150°C. Their method only  
540 provides an elastic modulus, and it does not reflect how tough the samples were to failure (flexural  
541 strength). Flexural strength and modulus are more relevant and are described in ISO 4049 [38].  
542 Tammaro *et al* [32] also only studied the samples in their dry state, and it is clear from the literature  
543 that water uptake affects the materials physical properties. For example the water uptake of  
544 RMGICs, after immersion in DW (3 months), was shown to decrease the physical properties  
545 compared to dry RMGICs samples, e.g. flexural strength (20-80% reduction), elastic modulus (50-  
546 80% reduction), Vickers hardness (50% reduction) [49]. Although, once CaAl LDH and MgAl  
547 LDH-composites were hydrated (two weeks in DW) the former demonstrated a greater % reduction  
548 in strength (CaAl LDH-composite: ~46 – 56 % compared to MgAl LDH-composites: ~42 – 50 %.).  
549 This decrease could be related to the greater solubility of the CaAl LDH-composites. Compared to  
550 the flexural strength reduction of RMGIC (80% reduction) after hydration, both CaAl LDH and  
551 MgAl LDH-composites strength were well below a 80% reduction.

552 The flexural modulus of the CaAl-LDH was greater than the MgAl-LDH composites. There were  
553 no significant differences in the flexural modulus before and after hydrating both CaAl and MgAl  
554 LDH-composites at 10 wt% loading. Several factors have been reported to affect the flexural  
555 strength and modulus of dental composites e.g. the degree of conversion (how well cured) [50],  
556 type of filler particle [51] sample size during testing [52] and chemical composition of the  
557 composite [53]. In addition, silane coupled inorganic fillers for example have proven to improve  
558 mechanical properties of composites, although LDH was not silane treated, the mechanical  
559 properties were still acceptable [54]. If the LDH was silane treated the mechanical properties may  
560 have not reduced as much after hydration. Yap & Teoh [52], reported on the disadvantages of using  
561 the three-point bend test. These included large variations in the results obtained due to flaws/cracks  
562 present on the samples during preparation, the degree of cure of the samples may not be  
563 homogeneous, due to the overlapping of irradiation (light curing) for curing the large beam length.

564 In this present study, a large sample size was used but samples with defects were rejected, curing  
565 by overlapping was standardised, and therefore large standard deviations were not obtained.

### 566 4.3 Water uptake/ desorption/ solubility

567 Water uptake studies with composites containing LDH have not been previously reported in the  
568 published literature. From the results obtained, it was evident that the 2:1 MgAl LDH-composites  
569 (~6.5-10%) absorbed a greater amount of water in comparison to the 2:1 CaAl LDH-composites  
570 (~5.7-8.5%) and the control (~2.3 %; experimental composite with no LDH). Due to LDHs  
571 hydrophilic nature, and its ability to absorb water molecules within the interlayers, the water uptake  
572 of the LDH-composites was observed to increase. **Hydrophilic fillers in commercial composites  
573 are usually silane treated and this reduces their water uptake [55]. In the present study the LDH  
574 was not silane treated in order to understand LDHs properties prior to any other treatment.**

575 The CaAl LDH-composite samples appeared to lose weight after reaching a maximum, in  
576 comparison to the MgAl LDH-composites. Therefore, this value is not the true water uptake of this  
577 material. The loss in weight may be due to the loss of divalent cations ( $\text{Ca}^{2+}$ ) ions, as shown by the  
578 ICP-OES study (Fig. 5), as well as leaching of residuals. The linear increase in solubility, as the  
579 amount of LDH was increased in the composite was directly related to a linear increase in cation  
580 release. A significant increase in water absorption was also observed, with an increase in the  
581 loading of LDH (MgAl and CaAl) in the composites, apart from the 45 wt% CaAl LDH-composite.  
582 Again, the CaAl LDH did not follow this trend, due to residuals/ions leaching from the composite  
583 during water uptake.

584 Water uptake values ranging between 1-4 % have been reported in the literature for Bis-  
585 GMA/TEGDMA composites, with varying ratios of each [56, 57]. Although water absorption may  
586 be beneficial for a dental composite to compensate for polymerisation shrinkage and improve the  
587 marginal seal, a value much greater than the shrinkage (reported volume shrinkage range: 0.06-  
588 9%) would not be favoured [58, 59]. Based on the water uptake results obtained, the lower weight  
589 loading (10 wt%) of LDH in composites is the more favourable option.

590 The initial stages of water absorption were linear to  $t^{1/2}$  for LDH-composites, thus demonstrating a  
591 diffusion-controlled process during water uptake [55, 60, 61]. The  $D_{\text{abs}}$  for the control was  
592 significantly higher compared to the 10, 30 and 45 wt% 2:1 CaAl LDH-composites or 2:1 MgAl  
593 LDH-composites. The  $D_{\text{abs}}$  values obtained are in agreement with those reported in studies for  
594 dental composites [55, 56, 61]. Braden *et al* [62, 63] reported that when water diffused into  
595 polymers at a faster rate, higher diffusion coefficient values (e.g.  $< \times 10^{-8} \text{ m}^2/\text{s}$ ) were obtained,  
596 whereas low diffusion coefficient values (e.g.  $> \times 10^{-14} \text{ m}^2/\text{s}$ ) refer to water diffusing slowly into  
597 (or out of) the polymer matrix. Therefore, the control discs absorbed water much faster, reaching  
598 equilibrium sooner than the LDH-composite samples. A possible reason for the lower  $D_{\text{abs}}$  for  
599 LDH-composites can be explained by the fact that water was clustering at impurity sites (e.g. LDH  
600 impurities) within the polymer matrix, and this probably affected the rate of water absorption [64].  
601 With an increase in LDH (2:1 CaAl and MgAl) from 10 to 45 wt% the  $D_{\text{abs}}$  increased, therefore  
602 absorbing water faster due to the more hydrophilic nature of the LDH, in comparison to the

603 composite polymer matrix. There was no significant difference in  $D_{abs}$  between the CaAl and MgAl  
604 LDH-composites at 10 and 45 wt%, although at 35 wt%, the MgAl LDH-composites demonstrated  
605 a higher  $D_{abs}$  in comparison to the CaAl LDH-composites.

606 The  $D_{des}$  of all LDH-composites were greater than their corresponding  $D_{abs}$  ( $P < 0.05$ ), however the  
607 opposite was observed for the control. Generally, the  $D_{des}$  are usually higher than the  $D_{abs}$ , as during  
608 drying there are no interfering/leaching monomers hindering the movement of water [63]. The  $D_{des}$   
609 for the CaAl-LDH samples was significantly greater than for the MgAl LDH-composites and there  
610 was no significant relationship between  $D_{des}$  and increasing the LDH loading in the composites.

611 The solubility reflected the amount of weight loss (e.g., leaching residual monomers or the release  
612 of cations) from the LDH-composites. Solubility levels were generally higher for the CaAl LDH-  
613 composites in comparison to the MgAl-LDH composites, which reflects the data obtained for water  
614 uptake, since the CaAl LDH-composites overall weight reduced after reaching a maximum weight  
615 during water absorption (as mentioned above). As the loading of the LDH for both 2:1 CaAl and  
616 2:1 MgAl LDHs increased, the solubility also increased. This may be attributed to the increased  
617 LDH loading interfering with the curing of the actual discs and therefore increasing the amount of  
618 unreacted material.

619 ICP-OES demonstrated that the CaAl LDH-composites released a significantly greater amount of  
620 the divalent cation ( $Ca^{2+}$ ) in comparison to the amount of  $Mg^{2+}$  released from MgAl LDH-  
621 composites. This amount continued to increase with an increase in LDH loading for both LDH-  
622 composites. This finding confirms that the greater solubility of the CaAl LDH-composite was due  
623 to the release of  $Ca^{2+}$  ions from the samples in addition to residuals. The release of trivalent cation  
624 ( $Al^{3+}$ ) was surprisingly very low (, ~0.3 ppm, ~0.03mg released), over the seven weeks of  
625 immersion in DW. In accordance to the safety of aluminium, this is well below the recommended  
626 daily intake (0.1-0.12 mg Al/kg/day) [65, 66].

## 627 **5. Conclusion**

628 The 2:1 MgAl and 2:1 CaAl LDHs incorporated in experimental composites demonstrated no  
629 adverse effect on the composites' curing time and its physico-mechanical properties. LDH  
630 increased the composites flexural modulus and strength in the dry state. These LDH-composites  
631 were able to absorb and release fluoride over five cycles. 2:1 MgAl LDH-composites were able to  
632 maintain a sustained release, after each consecutive fluoride recharge cycle, whereas the 2:1 CaAl  
633 LDH-composites released less fluoride each time. The LDHs ability to absorb and release a  
634 sustained low-level fluoride from experimental composite materials, demonstrates their potential  
635 to prevent carious-lesions and secondary caries from developing. These findings are promising,  
636 leading to a potential breakthrough in preventing early stage carious-lesions, and open the pathway  
637 for fruitful research in the field of dental materials.

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643

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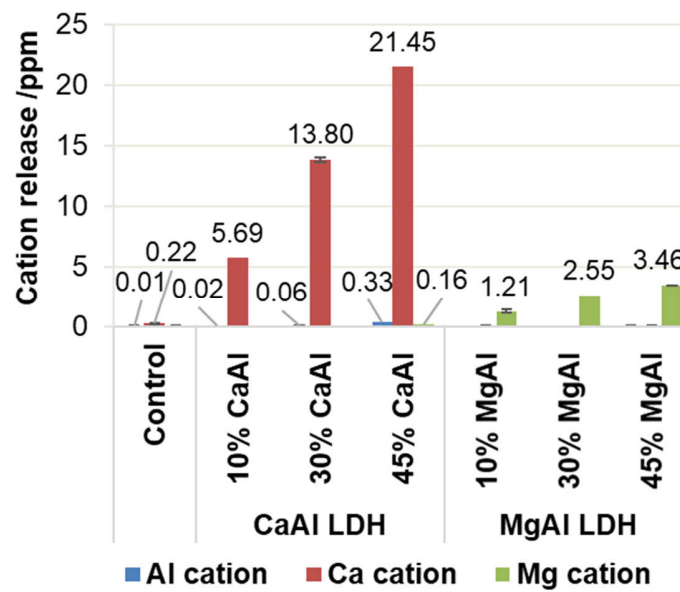
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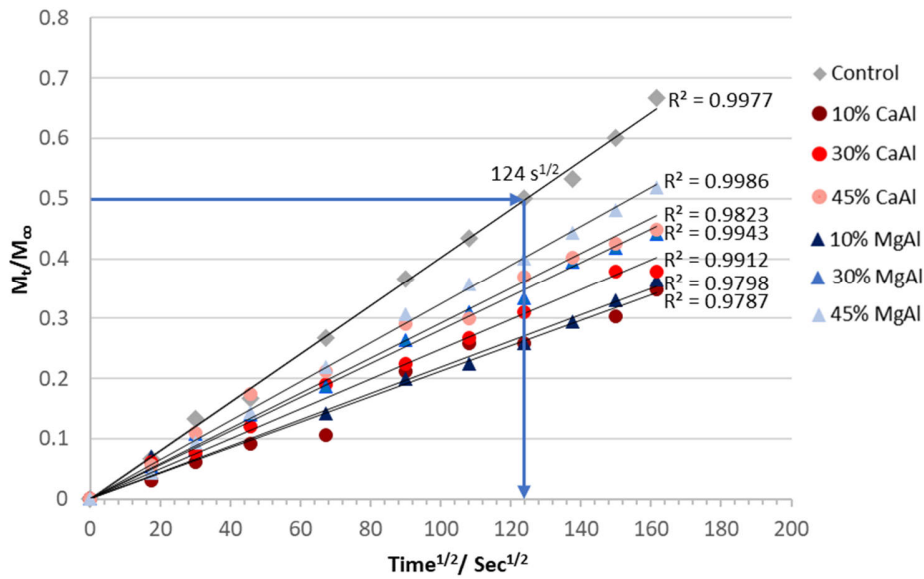


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795 **Supplementary material**



796  
797 **Fig. A - Cation release from the resin composite discs, containing CaAl or MgAl LDH at 0**  
798 **(control), 10, 30 and 45 wt% (n=6) after immersion in DW for seven weeks.**



799  
 800 **Fig. B - The linear region of  $M_t/M_\infty$  against the square root of time for each sample (10, 30**  
 801 **and 45 wt% CaAl LDH-composite, 10, 30 and 45 wt% MgAl LDH-composite and the**  
 802 **experimental control), with a line of regression  $R^2 > 0.99$ . Trendline fitted only for the early**  
 803 **stages of water uptake.**

804 **Table A - Thickness values and diffusion coefficient calculations for water absorption from**  
 805 **the 45 wt% MgAl LDH-composite.**

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6		
Av. thickness	1.0538	1.0954	1.094	1.1682	1.1542	1.0484		
Mt	162	165	159	180	167	153		
$M_t/M_\infty$	0.5	0.5	0.5	0.5	0.5	0.5		
s	0.00308642	0.003030303	0.003144654	0.002777778	0.002777778	0.003267974		
L	0.0005269	0.0005477	0.000547	0.0005841	0.0005771	0.0005242	Average	SD
D	2.07709E-12	2.16345E-12	2.32386E-12	2.06757E-12	2.01831E-12	2.30484E-12	2.15919E-12	1.29099E-13

806  
 807  $D = s^2 \pi L^2 / 4 = s^2 \pi (4L^2) / 16$  in excel:  $D = ((S^2) * 3.14159265 * (4 * (L^2))) / 16$

808 **Table D - Typical water desorption data for the 45 wt% MgAl LDH-composite over 3**  
 809 **weeks.**

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6		
Av. thickness	1.0538	1.0954	1.094	1.1682	1.1542	1.0484		
Mt	135	125	128	127	120	115		
$M_t/M_\infty$	0.5	0.5	0.5	0.5	0.5	0.5		
s	0.003703704	0.004	0.00390625	0.003937008	0.004166667	0.00434783		
L	0.0005269	0.0005477	0.000547	0.0005841	0.0005771	0.0005242	Average	SD
D	2.99102E-12	3.7696E-12	3.58579E-12	4.15333E-12	4.54119E-12	4.0797E-12	3.85344E-12	5.36017E-13