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# EVALUATING A NOVEL CLASS OF BIOMATERIALS: MAGNESIUM-CONTAINING LAYERED DOUBLE HYDROXIDES

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***Abstract:*** *Metallic magnesium and compounds such as magnesium hydroxide $Mg(OH)_2$ have been shown to have osteoconductive properties under experimental conditions and are gaining an increasing interest in the field of degradable biomaterials. The application of the compounds as implant coatings could support implant incorporation, resulting in an increased period of use of the implants. A variety of Mg-containing Layered Double Hydroxides (Mg-LDHs) has been synthesized and examined. These materials have been tested in various in vitro and in vivo studies; the latter took place in different sites like in the middle ear or in the condyle of New Zealand White Rabbits. In the latest study newly formed bone could be found around the Mg-Al-$CO_3$-LDH pellets, making it a promising compound for bone-healing applications.*

***Keywords:*** *Osteoproliferation, Magnesium hydroxide, Layered Double Hydroxides, Drug delivery*

## Introduction

The osteoproliferative properties of $Mg(OH)_2$ were shown by Janning *et al.* in 2010 [1]. Most properties of this single compound are fixed, which reduces the number of possible applications. A way to adjust some properties of a single compound such as $Mg(OH)_2$ is to vary particle sizes and morphology during the synthesis or with post-synthesis modifications. The composition nonetheless cannot be altered.

Mg-LDHs can be derived from $Mg(OH)_2$ by substituting $Mg^{2+}$ ions ($M^{II}$) with a certain amount of trivalent cations ($M^{III}$) such as $Al^{3+}$ and $Fe^{3+}$, respectively. The surplus positive charge is balanced by anions such as $CO_3^{2-}$ ($A^{n-}$) which leads to the general formula [2]

$[Mg_{1-x}M^{III}_x(OH)_2^{x+}][A^{n-}]_{x/n}{\cdot}yH_2O$.

An impression of the structure is given in Figure 1 [3].

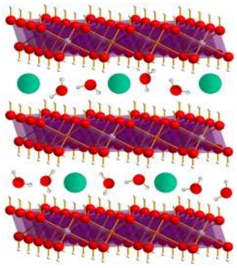

Figure 1: Structure of Layered Double Hydroxides $[M^{II}_{1-x}M^{III}_x(OH)_2^{x+}][A^{n-}]_{x/n}{\cdot}yH2O$.

Also anionic dyes and pharmaceuticals can be chosen as anions to be intercalated in this class of material. Besides the choice of anions and cations, the ratios of the ions can be varied, making this class of materials tailorable for different purposes.

## Methods

LDHs can be obtained by the precipitation of metal salt solutions with bases. The intercalation of a desired anion can be performed either at the precipitation step during the formation of the compound or post synthetic, for instance by an anion exchange. In order to obtain a nano-suspension the application of a suitable after treatment is necessary. With the suspensions obtained, samples such as middle ear implants can be coated by dip or spray coating.

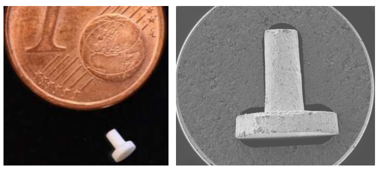

Figure 2: Images of middle ear implants as used for *in vivo* studies.

For the latest *in vivo* study cylindrical pellets (3x3 mm) were prepared from Mg-Al-$CO_3$-LDH, Mg-Fe-$CO_3$-LDH, commercially available $Mg(OH)_2$ and specifically synthesized $Mg(OH)_2$, respectively. Pellets made of the LDHs are shown in Figure 3.

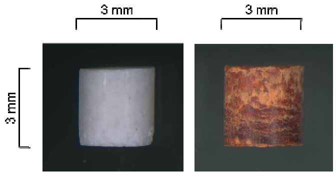


Figure 3: Cylindrical pellets made of LDHs (left: Mg-Al-$CO_3$-LDH, right: Mg-Fe-$CO_3$-LDH).

These pellets were inserted into the medial and lateral condyles of the left femur of New Zealand White Rabbits and remained in place for six weeks. For a non-destructive *in vivo* study, micro-computed tomography was applied. In order to examine the implant-bone contact and the formation of new bone, histological investigations were performed.

## Results

A variety of Mg-Al- and Mg-Fe-LDHs could be synthesized. For some LDHs a suitable after-treatment was developed, allowing the synthesis and long-term storage of LDH nanosuspensions. Also coating of the different substrates (glass, titanium, silicon and others) was established.

In order to test the biocompatibility of LDHs, titanium discs were coated with Mg-Al-LDHs ($CO_3^{2-}$, $NO_3^{-}$ and $SO_4^{2-}$) and seeded with NIH3T3 cells. Excellent biocompatibility in these cell culture tests was observed for all LDH coatings investigated.

In an *in vitro* study, a mixture of Mg-Al-$SO_4$-LDH and Ciprofloxacin was tested as a drug delivery system. The release of antibiotic could be delayed sufficiently to provide an efficacious amount of the drug to thwart bacterial infection (*P. aeruginosa*) for over two weeks [3].

In another *in vivo* study, implants coated with the mixture were inserted into the middle ear of New Zealand White Rabbits. One group was infected with *P. aeruginosa* directly after surgery, another group one week later. A strong antimicrobial activity could be detected for the first group, an attenuated effect for the second group [3]. The *in vivo* stability of LDH coatings in the middle ear was investigated in a subsequent study.

According to CT and histological data of the latest study, newly formed bone was found tightly around the Mg-Al-$CO_3$-LDH pellet (Figure 4). In the case of the Mg-Fe-LDH pellet a more advanced decomposition and no improvement of the surrounding bone growth could be observed.

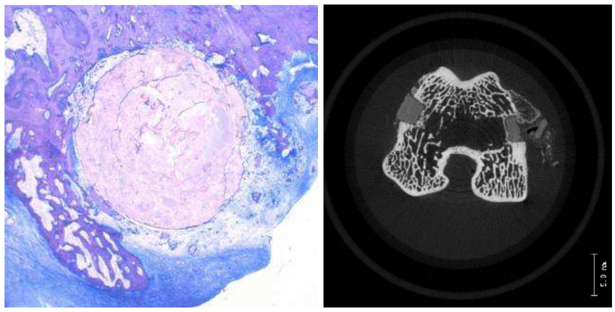

Figure 4: Left: Toluidine blue stained bone sections of the lateral Mg-Al-$CO_3$-LDH pellet. Right: CT image of implanted Mg-Al-$CO_3$-LDH.

In the case of the $Mg(OH)_2$ pellets it was observed that altering the synthesis conditions and processing led to different degrees of degradation and bone-response, although the formula was $Mg(OH)_2$ for all implants.

## Discussion

Mg-LDHs are a novel class of biomaterials that provide the possibility to vary the composition widely and therefore to adapt many properties such as degradation rates. They show osteoproliferative properties and are biocompatible in cell culture tests as well as *in vivo* in animal models.
Furthermore LDHs are a promising for controlled drug delivery systems. For bone-healing purposes the Mg-Al-$CO_3$-LDH appeared to be the most strongly osteoconductive LDH.
The variation of the synthesis conditions and processing of $Mg(OH)_2$ pellets give a change to alter the properties of this $Mg^{2+}$ source without changing the chemical composition.

## Acknowledgement

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