

Mixed Oxides as Successful Sorption Materials for Some Active Pharmaceutical Ingredients



This work is licensed under a Creative Commons Attribution 4.0 International License

E. Vrbková,* E. Vyskočilová,
A. Semrádová, L. Sekerová, and L. Červený
University of Chemistry and Technology Prague,
Technická 5, 16628 Prague, Czech Republic

<https://doi.org/10.15255/CABEQ.2020.1774>

Original scientific paper
Received: January 16, 2020
Accepted: April 2, 2020

Mixed oxides based on Mg-Al, Mg-Fe, Zn-Al, and Ni-Mg-Al were prepared, characterized and used as sorption materials for different types of active pharmaceutical ingredients (APIs)– nicotinic acid, salicylic acid, ibuprofen, paracetamol and ascorbic acid. Immobilization of APIs on solid supports was confirmed using X-Ray diffraction and infrared spectroscopy. Overall, the best sorption material for mentioned substances showed to be mixed Mg-Al oxides (>80 % of immobilized substance after 4 h except ascorbic acid). On the other hand, Mg-Fe and Mg-Ni-Al materials did not possess high sorption capacity (max. 59 % after 4 h). From studied substances, the immobilization amount was the lowest in the case of ascorbic acid (max. 44 % immobilized after 4 h), the highest amount was immobilized in the case of salicylic and nicotinic acids (>95 %, 4 h). The discussion regarding the structure of substances and properties of sorption materials is also offered.

Keywords:

API immobilization, sorption, mixed oxides

Introduction

Structure of hydrotalcite (hydrated mixed oxide, HTC) is based on the structure of brucite ($\text{Mg}(\text{OH})_2$). Magnesium atoms and hydroxyl groups create octahedral structure, individual octahedral units share edges and create endless neutral structure. In this structure, bivalent magnesium atoms can be exchanged for e.g. trivalent aluminum atoms, which cause origination of positive charge. The positive charge has to be compensated by the negative charge of anions situated in the space between the layers of hydrotalcite. Remaining interlayer space is occupied by water molecules. A ratio of bivalent and trivalent atoms in the structure of hydrotalcite can be simply varied by conditions of synthesis. Calcination of hydrotalcite provides mixed oxide, monolayer mesoporous material. Mixed oxides can be rehydrated back to hydrotalcite. The rehydration of mixed oxide with a water solution of active compound results in hydrotalcite-like material, which contains active compound intercalated in interlayer space (intercalation into hydrotalcite structure).

Usage of hydrotalcites in drug delivery systems can offer a large number of advantages compared to traditional materials. Among them, it is worth men-

tioning the low preparation costs and low toxicity, stability, high surface area, and biocompatibility^{1–4}. Hydrotalcite materials containing pharmaceutical substances are widely studied. They can be used to support active pharmaceutical ingredients which are poorly water-soluble (indomethacin, ketoprofen, tiaprofenic acid)⁵. Intercalation of active pharmaceutical ingredient (API) can also be used for the controlled release of intercalated substance (diclofenac, gemfibrozil, ibuprofen, naproxen, paracetamol, ascorbic acid)^{4,6–10}. Hydrotalcites can also stabilize nonstable molecules like ascorbic acid, tocopherol or retinoic acid⁴.

Despite many mentioned benefits, some disadvantages are also connected with the use of these interesting materials – (i) For intercalation of API, materials with nitrate anions in interlayer are usually used. Nitrate-loaded hydrotalcite-like materials must be performed without air access to prevent loading of carbonates into interlayers. (ii) Calcination and hydration of material are necessary prior to use of hydrotalcite-like materials. In this work, we would also like to show that different types of mixed oxides (Mg-Al, Zn-Al, Mg-Fe, and Mg-Ni-Al) as possible HTC precursors may be successfully used for loading of chosen APIs – paracetamol, ascorbic acid, nicotinic acid, ibuprofen and salicylic acid. To our best knowledge, the usage of at least Ni-Mg and Fe-Mg mixed oxides has not been described in the literature.

*Corresponding author: eva.vrbkova@vscht.cz

Materials and methods

Materials

Several types of mixed oxides – Mg-Al¹¹, Zn-Al¹², Mg-Fe¹³ and Mg-Ni-Al¹⁴ were prepared according to literature by coprecipitation method at constant pH and temperature. After preparation, the materials were calcined and used as prepared without hydration. Magnesium nitrate hexahydrate, aluminum nitrate nonahydrate, zinc nitrate hexahydrate, ferric nitrate nonahydrate, nickel nitrate hexahydrate, potassium hydroxide, potassium carbonate, sodium hydroxide, and sodium carbonate (all Penta, p.a.) were used for the synthesis of mixed oxides. Nicotinic acid (NA, Sigma Aldrich, >98 %), salicylic acid (SA, Lachema, >98 %), ibuprofen (IB, Sigma Aldrich, >98 %), paracetamol (PA, Sigma Aldrich, >99 %), ascorbic acid (AA, Sigma Aldrich, 99 %) and methanol (Penta, p.a.) were used for immobilization.

Immobilization

Different amounts of immobilized substance were used. In the case of ascorbic acid and paracetamol, 100 mg of substance was dissolved in 10 cm³ of demineralized water, then 100 mg of mixed oxide (pretreated at 450 °C/17 h/air) was added. In the case of nicotinic acid, salicylic acid, and ibuprofen 20 mg of substance was dissolved in 10 cm³ of demineralized water, in the case of ibuprofen in 10 cm³ of mixture methanol:demineralized water (1:1 vol.) and 50 mg of mixed oxide was added (pretreated at 450 °C/17 h/air). This mixture was stirred at 900 rpm for 4 h. After the desired time, materials were filtered using vacuum and glass sintered filter S4, and dried (40 °C/air/18 h). The concentration of the substance in solution was monitored using UV-VIS spectrophotometer Perkin Elmer Lambda 35 (used wavelengths: SA: 231 nm, NA: 262 nm, AA: 269 nm, PA: 243 nm, IB: 220 nm). Selected experiment was repeated 5 times to determine measurement deviation – it was shown to be 5 %.

Characterization

X-ray fluorescence analysis (spectrometer ARL 9400 XP Thermo Scientific) was used to analyze composition of prepared mixed oxides. X-ray diffraction (X Pert Pro PAN analytical) was used for characterization of prepared mixed oxides and mixed oxides modified with different substances. Infrared spectrometer (Nicolet 6700 Thermo Scientific) was used to measure diffuse reflectance to confirm immobilization of substances on mixed oxides. Specific surface area was measured using Pulse Chemisorb (Micromeritics). UV-VIS spectrophotometer Perkin Elmer Lambda 35 was used to monitor the concentration of substances in solutions.

Results and discussion

Characterization of materials

X-Ray fluorescence, specific surface area

X-ray fluorescence (Table 1) confirmed the composition of prepared mixed oxides, which corresponds to expected values. The highest specific surface areas were observed at Ni-Mg-Al materials, the lowest at Zn-Al mixed oxide. Values are in accordance with literature^{12,15}. No specific trend was observed following the increase of Mg-Al ratio in this type of material.

X-Ray diffraction

X-Ray diffractograms of prepared materials

In diffractograms of Mg-Al materials (Fig. 1) the lines typical for hydrotalcite Mg_{0.83}Al_{0.17}(CO₃)_{0.08}(OH)₂(H₂O)_{0.75} (2 theta° 11, 23, 35, 39, 46, 61, 62) and pure magnesium oxide (2 theta° 43, 65, 74, 79)^{16,17} were identified. The lines at 11.7° 2 theta corresponding to (003) reflection can be assigned to the interlayer distance of 0.77 nm, which is in agreement with the presence of carbonate cation.

Table 1 – Composition (X-ray fluorescence) and specific surface area of prepared materials

Material	MgO (wt.%)	Al ₂ O ₃ (wt.%)	ZnO (wt.%)	NiO (wt.%)	Fe ₂ O ₃ (wt.%)	other (wt.%)	S _{BET} (m ² g ⁻¹)
Mg-Al 2:1	51.9	47.8	–	–	–	0.3	134
Mg-Al 3:1	62.5	37.4	–	–	–	0.1	101
Mg-Al 4:1	65	34.3	–	–	–	0.7	141
Mg-Fe 2:1	48.4	–	–	–	51.3	0.3	135
Mg-Fe 3:1	58.3	–	–	–	41.5	0.2	87
Zn-Al 3:1	–	20.5	79.4	–	–	0.1	73
Ni-Mg-Al 1.5:2.5:1	35.8	22.0	–	42.1	–	0.1	170
Ni-Mg-Al 1.5:1:1	17.7	26.4	–	55.7	–	0.2	181

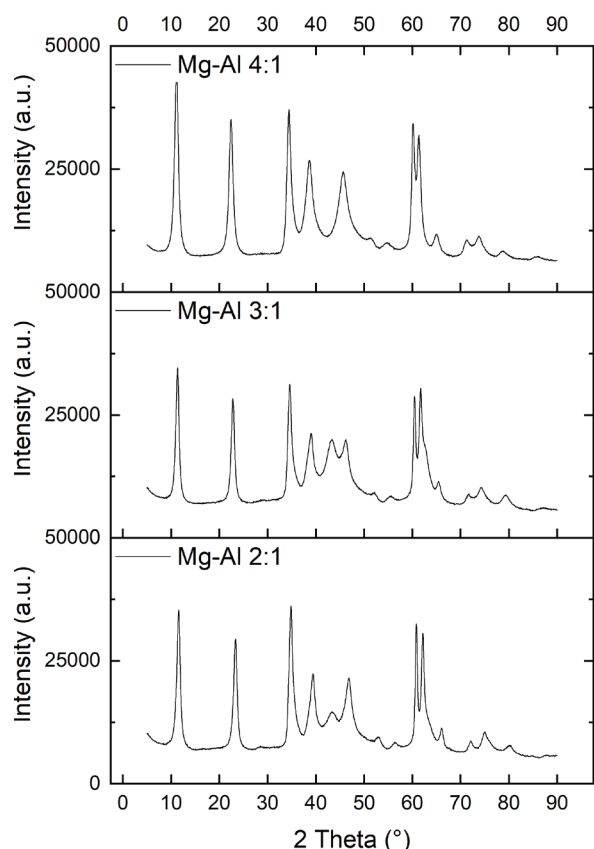


Fig. 1 – X-ray diffractogram of prepared Mg-Al materials

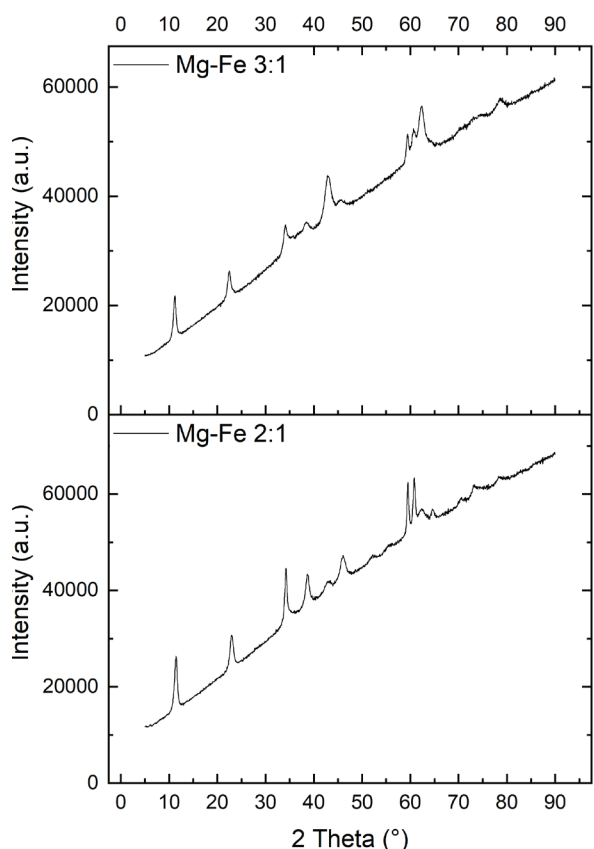


Fig. 2 – X-ray diffractogram of prepared Mg-Fe materials

The presence of hydrotalcite lines of only calcined materials is, in the cases of all prepared materials, connected with its storage at air atmosphere, and no rehydration was performed prior to measurement and use. The ratio between rehydrated and oxide form cannot be calculated, especially due to the amorphous form of aluminum oxide.

Mg-Fe mixed oxides contained phases of $\text{Mg}_{0.78}\text{Fe}_{0.22}(\text{CO}_3)_{0.11}(\text{OH})_2(\text{H}_2\text{O})_{0.7}$ (2 theta° 11, 23, 34, 59, 61) and, again, magnesium oxide (2 theta° 39, 43, 62, 78)^{16,18} (Fig. 2). The increase of baseline is typical for materials containing iron in its structure¹⁹.

Diffractogram of Zn-Al oxide contains phases for $\text{Zn}_{0.65}\text{Al}_{0.35}(\text{OH})_2(\text{CO}_3)_{0.167}(\text{H}_2\text{O})_{0.49}$ (2 theta° 12, 23, 35, 39, 46, 60, 61), and for zinc oxide (2 theta° 34, 36, 37, 48, 57, 63, 65, 67, 69)^{20,21}. Diffractogram of Ni-Mg-Al oxides contains two phases of mixed carbonate hydroxide hydrate – $\text{Mg}_{0.83}\text{Al}_{0.17}(\text{CO}_3)_{0.08}(\text{OH})_2(\text{H}_2\text{O})_{0.75}$ and $\text{Ni}_{1.869}\text{Al}_{1.131}(\text{OH})_6(\text{CO}_3)_{1.020}$ (2 theta° 11, 23, 35, 61, 62) and two phases of pure oxides – nickel and magnesium oxide. Lines of nickel and magnesium oxides are overlapping, therefore, they are listed together (2 theta° 35, 43, 62, 75, 79)^{15–17,22,23} (Fig. 3).

X-Ray diffractograms of Mg-Al 2:1 after sorption of active substances

XRD diffractogram of modified Mg-Al 2:1 (Fig. 4) confirms preservation of hydrotalcite structure after modification with APIs in the case of all modified materials. Lines typical for hydrotalcite (described in Fig. 1) are present. In the case of material modified with paracetamol, typical lines for this substance are also present (2 theta° 9, 18, 24 and 27), meaning that this API was not homogeneously distributed. As described below, its adsorbed amount was not the lowest of all material, although the pKa of this API is the highest of all studied (pKa = 9.86). In the case of ascorbic acid and salicylic acid, the intensity of hydrotalcite lines significantly decreased (especially visible is this fact in the case of ascorbic acid). These two compounds were the most acidic of all used APIs (pKa NA = 2.2 and SA 3.0), and the hydrotalcite-like materials suffered from dissolution in acidic media.

In all loaded materials, the decrease or disappearance of lines attributed to magnesium oxide was observed – especially the disappearance of line at 43° 2 theta and significant decrease of line at 65° 2 theta. This meant that mixed oxide was hydrated in the loading process.

The intercalation of compounds to the structure of hydrotalcite-like materials may be evaluated by the shift of (003) reflection to lower 2 theta values²⁴. But in our case, this detection was not possi-

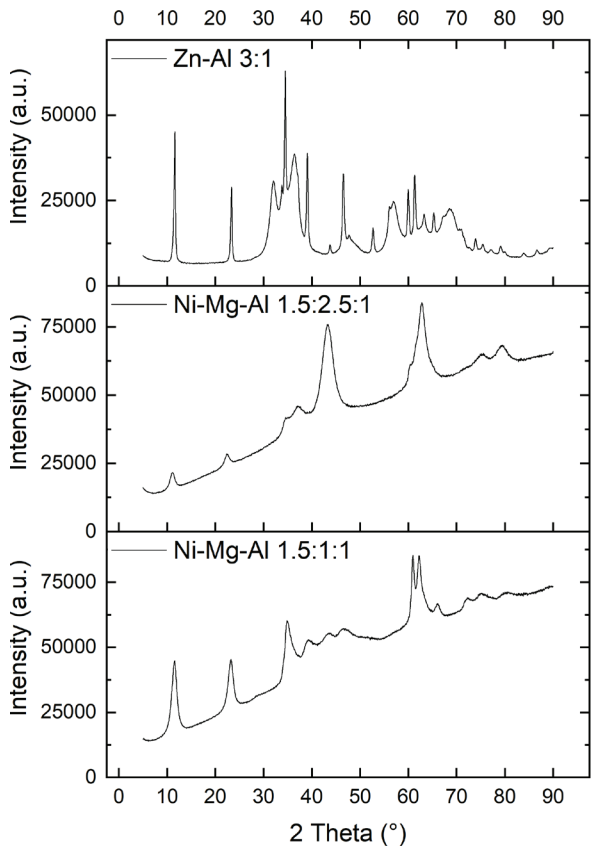


Fig. 3 – X-ray diffractogram of prepared Ni-Mg-Al and Zn-Al materials

ble due to two facts: 1) used sorption materials were predominantly HTC like in carbonate form (which is not very convenient for ion exchange), and 2) the largest size of used APIs was, in most cases, smaller or similar to the interlayer distance of carbonate material, so the increase in this distance could not be observed. The size of APIs was measured using Gaussian 03 software (nicotinic acid 0.70 nm, salicylic acid 0.71 nm, ascorbic acid 0.79 nm, paracetamol 0.81 nm, ibuprofen 1.04 nm). The only case when formation of a new line that may be connected to the increase in size of interlayer distance was observed, was in the case of the largest molecule – ibuprofen. Line at 9° 2 theta was visible and may be calculated as interlayer distance 0.99 nm. Nevertheless, we presume the simple adsorption of chosen APIs on materials surface. This was also confirmed by the fact that crystal structure of paracetamol was observed after loading on this material.

Infrared characterization of modified materials

Characterization using infrared spectroscopy – diffuse reflectance was performed to confirm immobilization of API's on Mg-Al 2:1 mixed oxide (Fig. 5). In the case of paracetamol (Fig. 5a), present were characteristic lines for this substance (1650 , 1500 , 1360 and 1270 cm^{-1}). In the case of

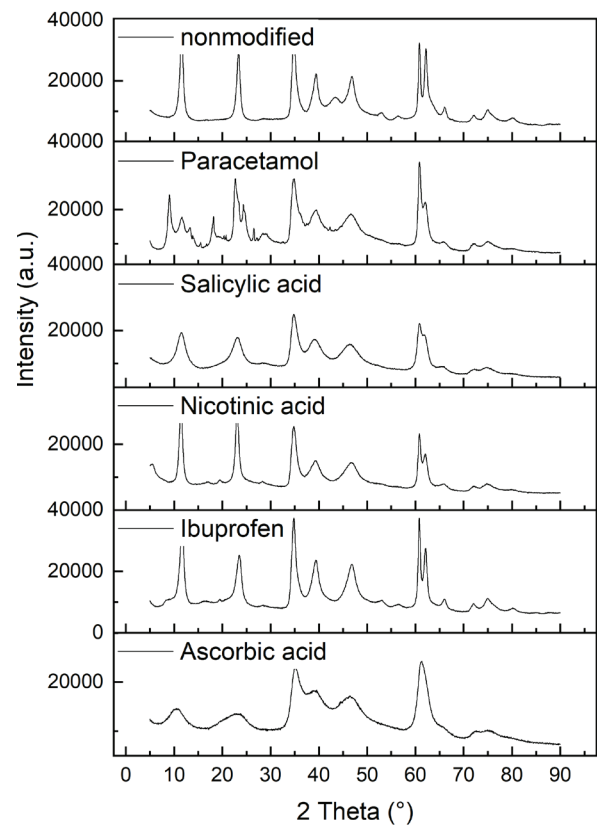


Fig. 4 – X-ray diffractograms of Mg-Al 2:1 material modified with different APIs

ascorbic acid (Fig. 5b), two characteristic lines were identified – 1640 and 1380 cm^{-1} . Material modified with salicylic acid (Fig. 5c) contained typical lines for this substance (1570 , 1460 , 1370 , 1260 and 750 cm^{-1}). Lines found in ibuprofen-modified material (Fig. 5d) overlapped with lines typical for original nonmodified material (1560 , 1410 and 1370 cm^{-1}). Lines identified in material modified with nicotinic acids (Fig. 5e) were 1600 , 1550 , 1400 and 1370 cm^{-1} . With longer adsorption time, the increase in API typical lines intensity was obvious.

Course of immobilization

Comparison of immobilization course of different substances and materials is depicted in Fig. 6 and summarized in Table 2. Maximal theoretical amount of API on supporting material was either 100 mg/100 mg material in the case of PA and AA or 40 mg/100 mg material in the case of SA, IB and NA. At least 90 % of these values were obtained after 4 h in the case of SA (Mg-Al 3:1 and 4:1) and NA (all Mg-Al materials). Comparing immobilization of PA and AA, the course was considerably faster in the case of PA (exception in first 15 min was Ni-Mg-Al 1.5:1:1). These substances have in common the fact that one of the less efficient supports for immobilization were the materials contain-

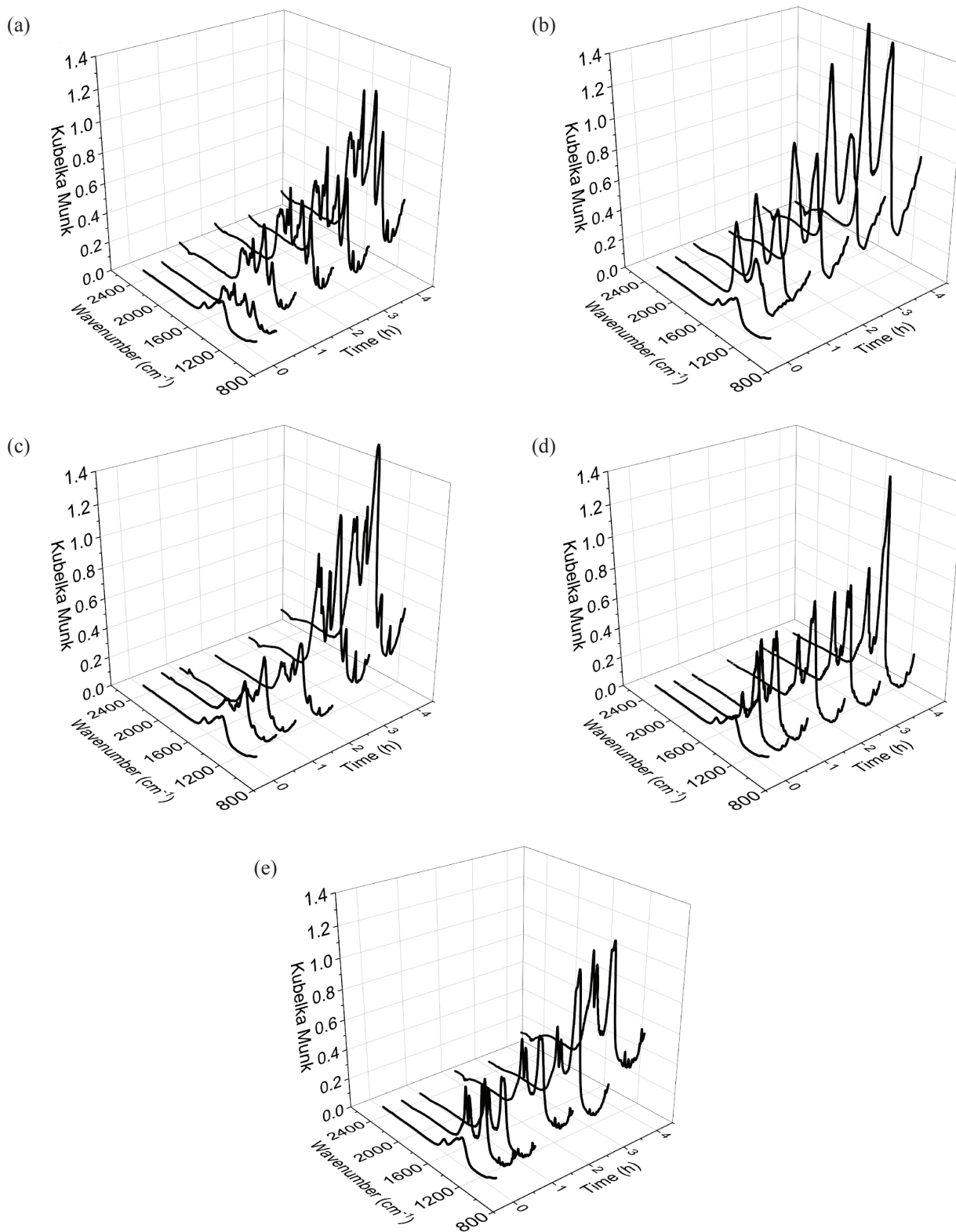


Fig. 5 – Infrared spectra of Mg-Al 2:1 material modified with different APIs – paracetamol (a), ascorbic acid (b), salicylic acid (c), ibuprofen (d), and nicotinic acid (e)

Table 2 – Immobilized amounts during immobilization (AA, PA: 100 mg substance, 100 mg mixed oxide; NA, SA, IB: 20 mg substance, 50 mg mixed oxide; 10 mL of demineralized water; 900 rpm, 4 h)

Material	Immobilized amount in 15 min (mg/100 mg _{mat.})					Immobilized amount in 4 h (mg/100 mg _{mat.})				
	PA	AA	SA	IB	NA	PA	AA	SA	IB	NA
Mg-Al 2:1	17	0	9	19	15	82	15	33	35	40
Mg-Al 3:1	27	4	4	23	18	78	44	40	34	39
Mg-Al 4:1	19	0	11	20	20	70	42	37	34	37
Mg-Fe 2:1	13	2	11	8	12	39	25	17	14	25
Mg-Fe 3:1	10	0	9	5	11	31	41	18	11	24
Zn-Al 3:1	14	0	13	14	14	34	28	18	21	35
Ni-Mg-Al 1.5:1:1	7	9	11	17	16	15	13	12	19	20
Ni-Mg-Al 1.5:2.5:1	10	0	10	13	14	29	11	12	20	18

ing nickel. Immobilization of AA was the less efficient from all API's, which could be caused by its structure (more hydroxyl groups than other tested substances). This is also in correlation with decreased intensity of lines of hydroxalite material observed in XRD diffractograms.

Paracetamol (N-(4-hydroxyphenyl)acetamide, PA)

The course of paracetamol immobilization is depicted in Fig. 6a. The highest immobilized amount was obtained using pure Mg-Al oxides (70 – 82 %), a material with the lowest magnesium content immobilized the highest PA amount. Zn-Al, Mg-Fe, and Ni-Mg-Al 1.5:2.5:1 mixed oxides behavior in PA immobilization was similar –29 – 39 % PA immobilized amount after 4 hours. The less efficient material was in this case Ni-Mg-Al 1.5:1:1 oxide, which adsorbed only 15 % of PA after 4 hours. In case of all materials, immobilized amount increased with immobilization time. Higher adsorbed amounts on Mg-Al samples could be caused by its higher specific surface area (Table 1) compared to materials Mg-Fe and Zn-Al. Materials containing nickel also had higher specific surface, but the nickel content in material significantly decreased PA immobilized amount. Nickel in this type of material replaces aluminum in the structure. As aluminum bears Lewis acidity probably convenient for the sorption of such slightly basic API, its replacement with less acidic nickel is disadvantageous.

Ascorbic acid ((5R)-[(1S)-1,2-Dihydroxyethyl]-3,4-dihydrofuran-2(5H)-one, AA)

In comparison with immobilization of PA, immobilization of AA took place significantly more slowly (Fig. 6b). The highest immobilized amounts (42–44 %) were obtained using Mg-Al 3:1, Mg-Al 4:1 and Mg-Fe 3:1 oxides. Zn-Al 3:1 and Mg-Fe 2:1 exhibited the same behavior –approx. 25 % of

immobilized AA after 4 h. The lowest amount (11–15 %) of AA was immobilized on both Mg-Ni-Al oxides and on Mg-Al 2:1 oxide. In the case of Ni-Mg-Al 1.5:1:1 oxide, all AA was immobilized in 15 min, and no further increase of immobilized amount was observed. In case of all other oxides, immobilized amount increased with time of adsorption. Ascorbic acid contains, in comparison with other tested substances, higher number of hydroxyl groups, which could cause higher affinity to polar immobilization media (water), and therefore, overall lower absorbed amount. Moreover, the interaction of AA with materials caused the deepest impact on the materials structure as visible from XRD (Fig 4).

Salicylic acid (2-hydroxybenzoic acid, SA)

The highest immobilized amount was obtained using Mg-Al oxides (82–99 %, Fig. 6c). In case of Mg-Al oxide, magnesium content did not influence the amount of immobilized SA. Mg-Al 3:1 mixed oxide proved to be the best immobilization support, but the difference between 3:1 and 4:1 was not very significant. This is in correlation with the fact that Mg-Al oxides are the most basic of all tested materials, and SA was the second most acidic API used. Mg-Fe and Zn-Al oxides gave similar results, after 4 hours of immobilization, 43–45 % of SA was immobilized. Materials containing nickel showed to be the least efficient immobilization materials – only 29–30 % of SA immobilized after 4 hours. In the case of Mg-Al oxides, the immobilization course was gradual, in the case of other oxides almost all SA was immobilized during first 30 min.

Ibuprofen ((RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid, IB)

In the case of ibuprofen (Fig. 6d), the highest immobilized amount was again obtained using Mg-Al oxides – the most basic ones and with high spe-

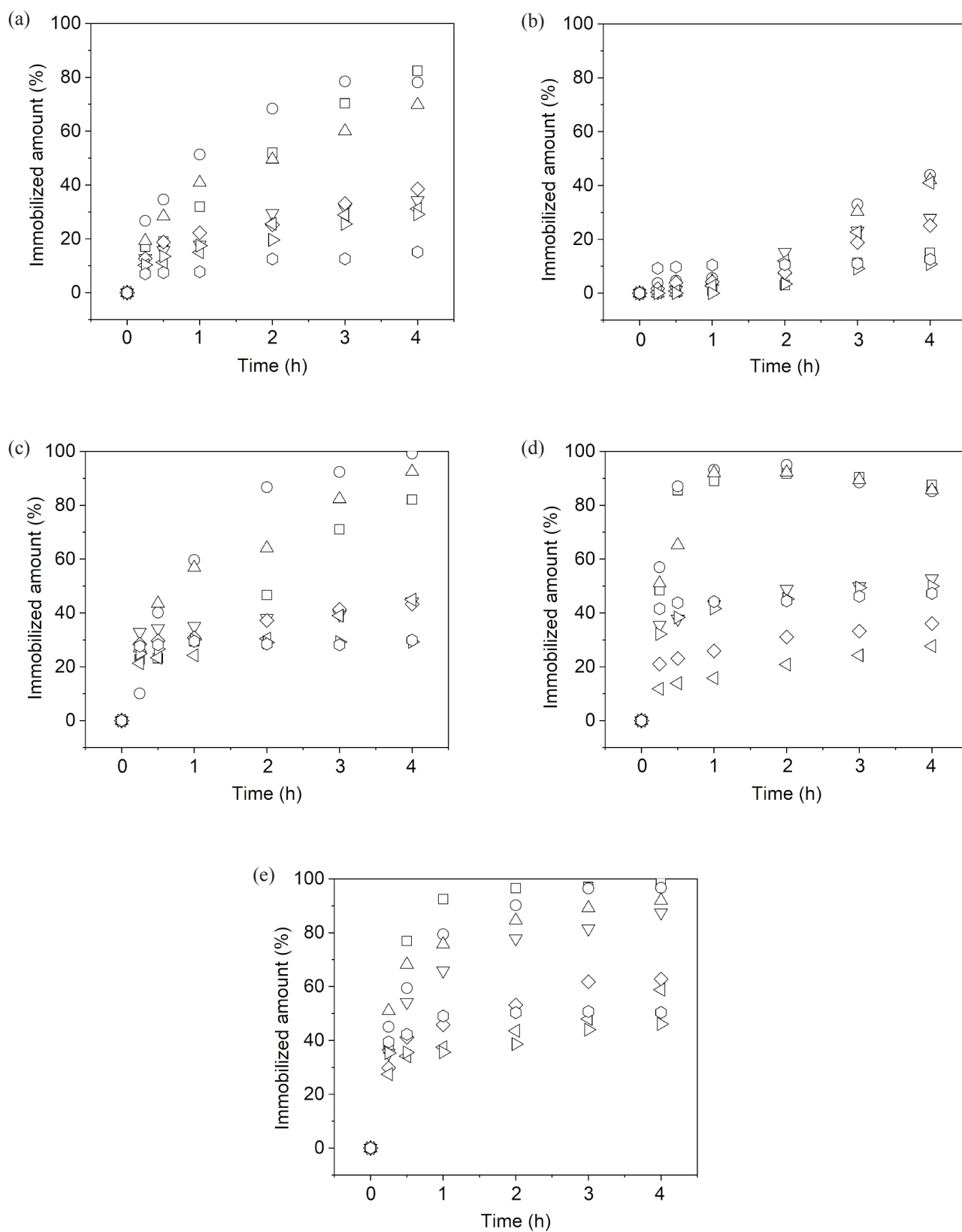


Fig. 6 – Immobilization course of different substances and materials – paracetamol (a), ascorbic acid (b), salicylic acid (c), ibuprofen (d), and nicotinic acid (e); Mg-Al 2:1 (square), Mg-Al 3:1 (circle), Mg-Al 4:1 (triangle), Zn-Al 3:1 (bottom triangle), Mg-Fe 2:1 (diamond), Mg-Fe 3:1 (left triangle), Ni-Mg-Al 1.5:2.5:1 (right triangle), Ni-Mg-Al 1.5:1:1 (hexagon)

cific surface. In this case, the highest immobilized amount (93–95 %) was obtained at 2 h of immobilization, and with increasing time, the immobilized amount slightly decreased (86–87 %). This behavior was not observed using other oxides, where the immobilization gradually increased with immobilization time. The lowest immobilized amount (28–37 %) was obtained using Mg-Fe materials (probably due to low specific surface).

Nicotinic acid (pyridin-3-carboxylic acid, NA)

Immobilization of nicotinic acid (the most acidic of all APIs used, Fig. 6e), in cases of using any mixed oxide, was very fast from the beginning (more than 80 % of total immobilized amount in first 30 minutes) except with Mg-Fe oxides, which exhibited more gradual immobilization of NA. Mixed Mg-Al oxides immobilized the highest amounts of NA (92–99 %), and similar amount (88 %) was immobilized also using Zn-Al oxide. In the case of Mg-Al oxides, more NA was immobilized with lower magnesium content in material. Analogously, in the case of Mg-Fe and Ni-Mg-Al oxides, more NA was immobilized on material with lower magnesium content. Materials containing nickel immobilized the lowest NA amounts (46–50 %). The course of immobilization was very similar to paracetamol. The high rate of NA adsorption was probably caused by the affinity of carboxylic group to a particularly basic character of all studied materials and the highest acidity of NA among all studied APIs.

Release of API from material was monitored using paracetamol, salicylic acid, and ibuprofen on Mg-Al 3:1 material in three dissolution media – pH = 2, 4.5, and 7. The highest released amount (29 %, 4 h) in the case of paracetamol was observed using solution pH = 2. Dissolution medium pH = 2 was also the most efficient in the case of salicylic acid – 39 % of API released at 4 h. In contrast, the most efficient dissolution media for ibuprofen release were pH = 4.5 and 7 (14 % for both, 4 h).

Conclusion

Immobilization on different types of mixed oxides was performed using five APIs – paracetamol, ascorbic acid, salicylic acid, ibuprofen, and nicotinic acid in water media. In case of paracetamol, Mg-Al mixed oxide showed to be the best solid support – increasing immobilized amount with decreasing Mg-Al ratio (70–82 % immobilized amount, 4 h) is attributed to decreasing material basicity, as well as to low basicity of this API. Other types of materials exhibited lower immobilized amount (15–38 %, 4 h). Overall, the immobilization of ascorbic acid was

less efficient than any other API, which could be caused by its higher affinity to polar immobilization media because of its structure containing a number of hydroxyl groups (in the best case only 44 % was immobilized at 4 hours (Mg-Al 3:1). In the case of salicylic acid, again the most efficient solid supports were Mg-Al mixed oxides (82–99 %, 4 h), and Ni-Mg-Al materials showed to be the least efficient (29–30 %, 4 h). Mg-Al mixed oxides were the best supports also in the case of ibuprofen and nicotinic acid immobilization (IB 82–86 %, NA 92–99 %, 4 h). The lowest immobilized amount in the case of ibuprofen (28–36 %, 4 h) was observed using Mg-Fe materials, in the case of nicotinic acid using Ni-Mg-Al materials (46–50 %, 4 h – the most acidic materials). Immobilization of APIs to solid supports was confirmed using X-ray diffraction and infrared spectroscopy. Overall, the most efficient sorption properties were observed for Mg-Al materials – the most basic ones and with relatively high specific surface. These readily available and cheap mixed oxides might be promising for the sorption of all chosen APIs for the treatment of, e.g., wastewaters.

ACKNOWLEDGEMENTS

The authors would like to thank Iva Paterová, Ph.D., for providing samples of Ni-Mg-Al mixed oxides, and Michaela Dvořáková, Ph.D., for enabling preparation of Mg-Fe mixed oxides (both UCT Prague). We also thank Jan Sedláček from Charles University for enabling measurement of FTIR spectra.

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- Burzlauff, A., Brethauer, S., Kasper, C., Jackisch, B. O., Scheper, T., Flow cytometry: Interesting tool for studying binding behavior of DNA on inorganic layered double hydroxide, (LDH), *Cytometry A* **62** (2004) 65. doi: <https://doi.org/10.1002/cyto.a.20085>
- Meyn, M., Klaus, B., Lagaly, G., Anion-exchange reaction of layered double hydroxide, *Inorg. Chem.* **29** (1990) 5201. doi: <https://doi.org/10.1021/ic00351a013>
- Barahuie, F., Hussein, M., Fakurazi, S., Zainal, Z., Development of drug delivery systems based on layered hydroxides for nanomedicine, *Int. J. Mol. Sci.* **15** (2014) 7750. doi: <https://doi.org/10.3390/ijms15057750>
- Choy, J., Choi, S., Oh, J., Park, T., Clay minerals and layered double hydroxides for novel biological applications, *Appl. Clay Science* **36** (2007) 122. doi: <https://doi.org/10.1016/j.clay.2006.07.007>
- Ambrogi, V., Fardella, G., Grandolini, G., Nocchetti, M., Perioli, L., Effect of hydroxalate-like compounds on the aqueous solubility of some poorly water-soluble drugs, *J. Pharm. Sci.* **92** (2003) 1407. doi: <https://doi.org/10.1002/jps.10411>

6. Ambrogì, V., Fardella, G., Grandolini, G., Perioli, L., Intercalation compounds of hydrotalcite-like anionic clays with anti-inflammatory agents – I. Intercalation and *in vitro* release of ibuprofen, *Int. J. Pharm.* **220** (2001) 23. doi: [https://doi.org/10.1016/S0378-5173\(01\)00629-9](https://doi.org/10.1016/S0378-5173(01)00629-9)
7. Ambrogì, V., Fardella, G., Grandolini, G., Perioli, L., Tiralti, M. C., Intercalation compounds of hydrotalcite-like anionic clays with anti-inflammatory agents, II: Uptake of diclofenac for a controlled release formulation, *AAPS Pharm. Sci. Tech.* **3** (2002) 77. doi: <https://doi.org/10.1208/pt030326>
8. Kovanda, F., Maryšková, Z., Kovář, P., Intercalation of paracetamol into the hydrotalcite-like host, *J. Solid State Chem.* **184** (2011) 3329. doi: <https://doi.org/10.1016/j.jssc.2011.10.029>
9. Gasser, M. S., Inorganic layered double hydroxides as ascorbic acid (vitamin C) delivery system—Intercalation and their controlled release properties, *Colloids Surf. B Biointerfaces* **73** (2009) 103. doi: <https://doi.org/10.1016/j.colsurfb.2009.05.005>
10. Vyskočilová, E., Luštická, I., Paterová, I., Machová, L., Červený, L., Modified MCM-41 as a drug delivery system for acetylsalicylic acid, *Solid State Sci.* **38** (2014) 85. doi: <https://doi.org/10.1016/j.solidstatesciences.2014.10.004>
11. Vrbková, E., Tišler, Z., Vyskočilová, E., Kadlec, D., Červený, L., Aldol condensation of benzaldehyde and heptanal: A comparative study of laboratory and industrially prepared Mg–Al mixed oxides, *J. Chem. Technol. Biotechnol.* **93** (2018) 166. doi: <https://doi.org/10.1002/jctb.5336>
12. Tišler, Z., Vrbková, E., Kocik, J., Kadlec, D., Vyskočilová, E., Červený, L., Aldol condensation of benzaldehyde and heptanal over zinc modified mixed Mg/Al oxides, *Cat. Lett.* **148** (2018) 2042. doi: <https://doi.org/10.1007/s10562-018-2416-2>
13. Tahir, N., Abdelssadek, Z., Halliche, D., Saadi, S., Chebout, R., Cherifi, O., Bachari, K., Mg-Fe-hydrotalcite as catalyst for the benzylation of benzene and other aromatics by benzyl chloride reactions, *Surf. Interface Anal.* **40** (2008) 254. doi: <https://doi.org/10.1002/sia.2695>
14. Sikander, U., Sufian, S., Salam, M. A., Synthesis and structural analysis of double layered Ni–Mg–Al hydrotalcite like catalyst, *Procedia Eng.* **148** (2016) 261. doi: <https://doi.org/10.1016/j.proeng.2016.06.559>
15. Dėbek, R., Motak, M., Duraczyska, D., Launay, F., Galvez, M. E., Grzybekand, T., Da Costa, P., Methane dry reforming over hydrotalcite-derived Ni–Mg–Al mixed oxides: The influence of Ni content on catalytic activity, selectivity and stability, *Catal. Sci. Technol.* **6** (2016) 6705. doi: <https://doi.org/10.1039/C6CY00906A>
16. Nemade, K. R., Waghuley, D. S., Synthesis of MgO nanoparticles by solvent mixed spray pyrolysis technique for optical investigation, *Int. J. Met.* **2014** (2014) 1. doi: <https://doi.org/10.1155/2014/389416>
17. Macala, G. S., Robertson, A. W., Johnson, C. L., Day, Z. B., Lewis, R. S., White, M. G., Iretskii, A., Ford, P. C., Transesterification catalysts from iron doped hydrotalcite-like precursors: Solid bases for biodiesel production, *Cat. Lett.* **122** (2008) 205. doi: <https://doi.org/10.1007/s10562-008-9480-y>
18. Kang, D., Yu, X., Tong, S., Ge, M., Zuo, J., Cao, C., Song, W., Performance and mechanism of Mg/Fe layered double hydroxides for fluoride and arsenate removal from aqueous solution, *Chem. Eng. J.* **228** (2013) 731. doi: <https://doi.org/10.1016/j.cej.2013.05.041>
19. Sekerová, L., Vyskočilová, E., Fantova, J. S., Paterová, I., Krupka, J., Červený, L., Preparation of 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol via Prins cyclization using Fe-modified silica, *Res. Chem. Intermed.* **43** (2017) 4943. doi: <https://doi.org/10.1007/s11164-017-2922-7>
20. Talam, S., Karumuri, S. R., Gunnam, N., Synthesis, characterization, and spectroscopic properties of ZnO nanoparticles, *ISRN Nanotechnol.* **2012** (2012) 1. doi: <https://doi.org/10.5402/2012/372505>
21. Liu, Y., Yang, Z., Intercalation of sulfate anions into a Zn–Al layered double hydroxide: Their synthesis and application in Zn–Ni secondary batteries, *RSC Adv.* **6** (2016) 68584. doi: <https://doi.org/10.1039/C6RA09096F>
22. Li, C., Liu, S., Preparation and characterization of Ni(OH)₂ and NiO mesoporous nanosheets, *J. Nanomater.* **2012** (2012) 1. doi: <https://doi.org/10.1155/2012/648012>
23. Lu, H., Li, Q., Xiao, H., Wang, E., Xie, D., Effect of non-thermal plasma modified NiAl layered double hydroxides on the removal of fluoride from aqueous solution, *Am. J. Anal. Chem.* **5** (2014) 547. doi: <https://doi.org/10.4236/ajac.2014.59062>
24. Kovář, P., Pospíšil, M., Káfuňková, E., Lang, K., Kovanda, F., Mg–Al layered double hydroxides intercalated with porphyrin anions: Molecular simulations and experiments, *J. Mol. Model.* **16** (2010) 223. doi: <https://doi.org/10.1007/s00894-009-0537-7>