THE USE OF SURFACE MODIFIED NATURAL ZEOLITES (SMNZs) IN PHARMACEUTICAL SECTOR

FRANCESCO IZZO

Dipartimento di Scienze e Tecnologie, Università del Sannio, Via Port'Arsa 11, 82100 Benevento

INTRODUCTION

Thanks to their properties, natural zeolites have been widely investigated in various contexts, such as environment (Bowman 2003; Langella *et al.*, 2000; Cappelletti *et al.*, 2011; Misaelides 2011; de Gennaro *et al.* 2014), pedotechnique (Buondonno *et al.,* 2013), animal feed (Mercurio *et al.*, 2012, 2016a) and oenology (Mercurio *et al.*, 2010, 2016b).

Recently, these tectosilicates have featured as excipients in pharmaceutical preparations and biomedical applications due to their adsorptive and ion exchange capacities (de Gennaro *et al.*, 2015; Cerri *et al.*, 2016; Pasquino *et al.*, 2016; Cappelletti *et al.*, 2017; Serri *et al.*, 2017; Mercurio *et al.*, 2018; Izzo *et al.*, 2019).

The aim of this research consists in a feasibility study about the use of some natural zeolite-rich rocks as carriers in the drug delivery. The so called Surface Modified Natural Zeolites (SMNZs) were obtained by interaction with some selected cationic surfactants that can replace the native cations in order to improve the adsorption of drug molecules.

MATERIALS AND METHODS

For this research, four zeolite-rich rocks from Southern Italy (PHI_SAV and CHA_SM), Slovakia (CLI_SK) and California (CLI_CA) were selected for SMNZ preparation using cationic surfactants as cetylpyridinium chloride (CC), benzalkonium chloride (BC), hexadecyltrimethylammonium chloride (HC) and hexadecyltrimethylammonium bromide (HB) (Fig. 1). SMNZs were subsequently tested for loading and *in vitro* release of non-steroidal anti-inflammatory drugs (NSAIDs) as ibuprofen (Fig. 2) and (partially) diclofenac.

Selected starting materials were characterized from mineralogical and technological point of views by means of several analytical techniques and methods (details in Cappelletti *et al.*, 2017). Further investigations on starting materials (as well as surfactants and drugs) and SMNZs were carried out by means of Simultaneous Thermal Analyses coupled to Evolved Gas Analysis and Fourier Transform Infrared spectroscopy (Izzo *et al.*, 2017, 2018; Mercurio *et al.*, 2018).

Despite the presence of non-adsorbent and non-dangerous minerals (such as feldspar, quartz and pyroxene), zeolite contents of starting materials were significantly high: ~77 wt.% in PHI_SAV), ~76 wt.% in CHA_SM, and ~80 wt.% in CLI_CA. The lowest amount of zeolite (~56 wt.%) was observed in CLI_SK. From a chemical point of view, Cappelletti *et al.* (2017) performed leaching tests according to Mercurio *et al.* (2012) in order to determine the concentration of noxious elements as nickel, arsenic, cadmium and lead. Values never exceeded 20 mg/kg. As far as cation exchange capacities (CECs) of selected samples were concerned, experimental values were 2.47 mEq/g for PHI_SAV, 2.39 mEq/g for CHA_SM, 1.49 mEq/g for CLI_SK and 1.97 mEq/g for CLI_CA, whereas external cation exchange capacity of zeolite-rich rock (ECECs) were 0.144 mEq/g for PHI_SAV, 0.229 mEq/g for CHA_SM, 0.119 mEq/g for CLI_SK and 0.477 mEq/g for CLI_CA (Cappelletti *et al.*, 2017).

Functionalization of zeolite-rich rocks consisted in an interaction under continuous stirring between powdered zeolite-rich rock and surfactant solution (solid-to-liquid ratio = 1 g/50 mL) (de Gennaro *et al.*, 2016), generally using a high-speed disperser (IKA T25 digital ULTRA TURRAX), and varying mixing speed (from 3000 to 8000 rpm), contact time (from 15 to 90 minutes) and the initial concentration of surfactant (from 15% to 200% of ECEC).

Name: Cetylpyridinum chloride
CAS number: 123-03-5
Molecular Weight, MW: 358 g/mol
Critical Micelle Concentration, CMC: 0.9 mmol/L

Structural formula (3D model):

Name: Benzalkonium chloride
CAS number: 63449-41-2
Molecular Weight, MW: 354 g/mol
Critical Micelle Concentration, CMC: 5 mmol/L

Structural formula (3D model):

Name:Hexadecyltrimethylammonium chloride
CAS number: 112-02-7
Molecular Weight, MW: 320 g/mol
Critical Micelle Concentration, CMC: 1.3 mmol/L

Structural formula (3D model):

Name: Hexadecyltrimethylammonium bromide
CAS number: 57-09-0
Molecular Weight, MW: 364.46 g/mol
Critical Micelle Concentration, CMC: 0.9 mmol/L
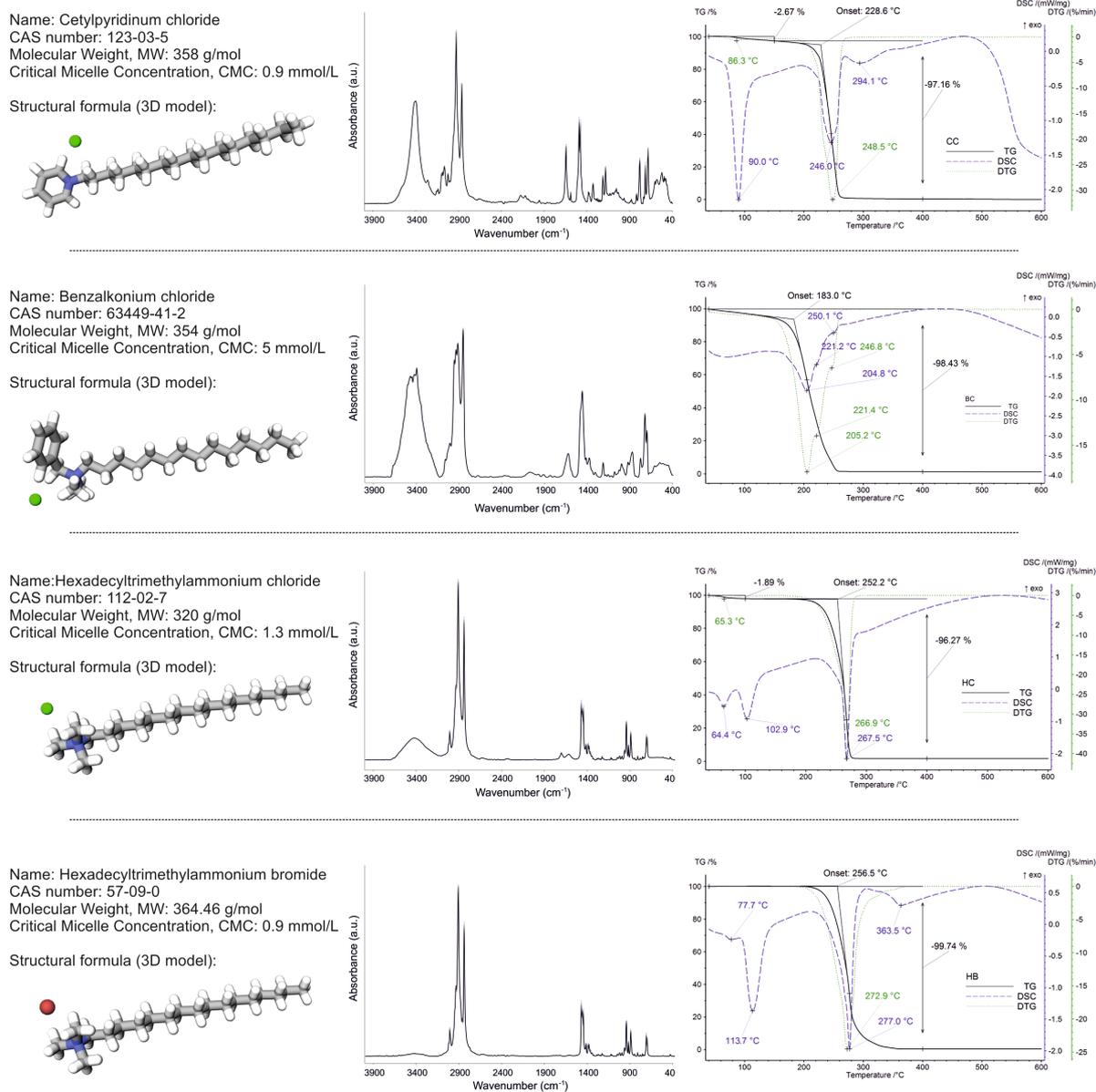
Structural formula (3D model):

Fig. 1 - Physico-chemical property, structural formula (3D models), infrared spectral features and thermal behavior of surfactants (modified from Mercurio *et al.*, 2018).

Name: Ibuprofen sodium salt
CAS number: 31121-93-4
Molecular Weight, MW: 228.26 g/mol
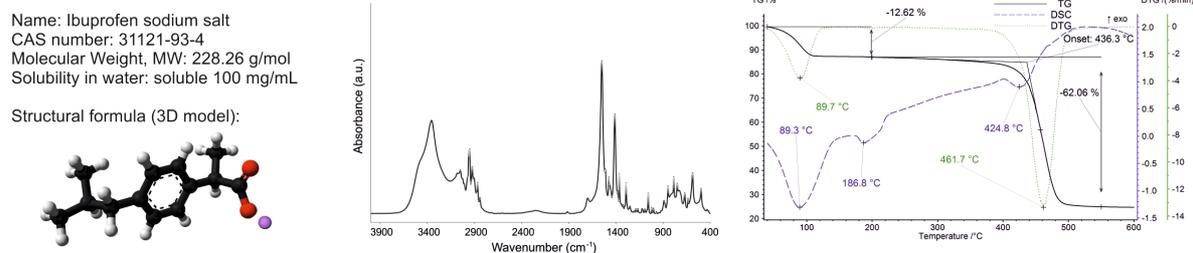Solubility in water: soluble 100 mg/mL

Structural formula (3D model):

Fig. 2 - Physico-chemical property, structural formula (3D models), infrared spectral features and thermal behavior of ibuprofen (modified from Mercurio *et al.*, 2018).

In order to improve the knowledge of ibuprofen-SMNZ composite materials, loading and release performances were determined by means of equilibrium isotherms as well as loading and release kinetic runs. Experimental data were fitted using a non-linear regression and the applicability of the mathematical models was evaluated considering determination coefficients (R^2), Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

RESULTS AND DISCUSSION

Functionalization of zeolite-rich rocks

Surface modification of natural zeolite-rich rocks by cationic surfactant (SMNZs) involves both cation exchange and hydrophobic bonding (Li & Bowman, 1997). Firstly, the electrostatic attraction between the positively charged head groups in surfactants and negatively charged framework of zeolites (cation-exchange) leads to the formation of a monolayer. The amount of surfactant necessary for the production of a monolayer is directly proportional to the ECEC of zeolite (Fig. 3).

In this step, exchangeable cations on the external sites of zeolite are released in the solution for a concentration equal to the experimental ECEC, as observable via ICP-OES, whereas surfactants release an amount of anions (determinate by means of LC) equal to the concentration of surfactant used (generally between 150-200% of ECEC). Then, surfactant molecules exceeding the ECEC value form a second layer (bilayer) by means of tail-to-tail hydrophobic interactions (London-van der Waals type). Finally, head-group of surfactant molecules in the second layer are electrostatically balanced by a negatively charged counterion (Cl^- or Br^-) contained in the solution, which amount gradually decreases.

Other interactions in SMNZs are the electrostatic repulsions between the head groups of surfactant of the first and second layers, as well as the electrostatic repulsions between anionic field strength of zeolite framework and anions released in solution by surfactant molecules, mainly of the first layer.

The tendency to form a complete or a patchy bilayer is mainly related to counterion effects and subordinately by the type of surfactant employed (Cappelletti *et al.*, 2017; de Gennaro *et al.*, 2014; Li & Bowman, 1997). Generally, bromide surfactant provides onto the zeolite surface a more stable bilayer than chloride surfactant, that usually forms a patchy bilayer. As a matter of fact, counterion can affect the size of micelle as a function of the aggregation number. The latter generally follow the lyotropic series (de Gennaro *et al.*, 2014; Li & Bowman, 1997): $IO^{3-} < HCO^{3-} < BrO^- < F^- < Cl^- < NO^{3-} < Br^- < ClO^{3-} < SCN^-$. In particular, since hydrated Br^- is smaller than Cl^-, it is able to neutralize the positively charged micelle head group. As a consequence, when Cl^- is the counterion, aggregation number decreases and the average head group separation is higher in order to minimize electrostatic repulsion. Additionally, cationic surfactant balanced by chloride anion has a higher critical micelle concentration (CMC) than bromide surfactant (Fig. 1), resulting in a higher ratio between the monomers and the micelle at a given solution concentration.

Results demonstrated that functionalization of Italian and Slovakian zeolite-rich rocks occurred after 70 minutes of solid/liquid interaction with a total yield equal to 150% of the ECEC, thus indicating the formation of a patchy bilayer. By contrast, Californian one behaves completely differently since the formation of micelle was achieved only at much higher speed (18000 rpm) and not earlier than 90 minutes of mixing. This fast functionalization provides an optimization of the charging process that turns into an economic saving at industrial scale. This is the effect of the significant decrease of solid/liquid interaction times (de Gennaro *et al.*, 2016).

Technological performance of SMNZs

The optimal initial ibuprofen concentration for the loading kinetics was estimated around 400 mg/L, since higher initial concentration of the drug does not provide further NSAID uptake by SMNZs.

Mathematical modelling of experimental curves reflected the complexity of equilibrium NSAIDs sorption mechanisms occurring in SMNZs since the use of a three-parameters mathematical model (*i.e.*, Sips or Toth

equations) could be required. This complexity is due to the simultaneous occurrence of external anionic exchange process (predominant) and subordinately partition into the hydrophobic portion of micelle (Fig. 3).
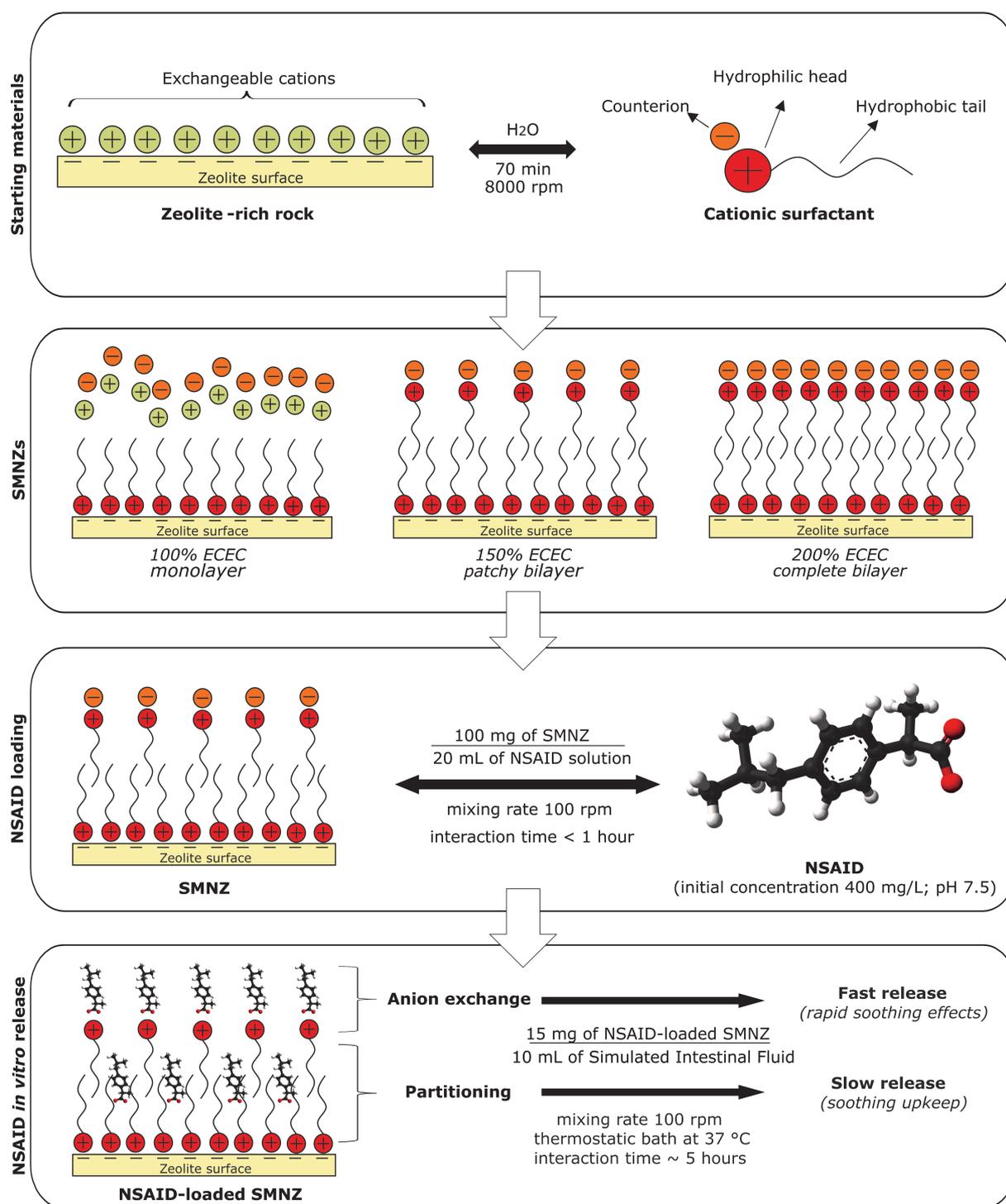

Fig. 3 - Synoptic scheme of the surface modification of zeolite by interaction with different amounts of cation surfactant and the technological performance of SMNZs for the uptake and *in vitro* release of NSAIDs (modified from Izzo *et al.*, 2019).

A fast ibuprofen loading was recorded for the SMNZs achieving its maximum according to the type of zeolite (and zeolite contents) and the type of surfactant. In particular, maximum ibuprofen sorption generally ranges from ~13 mg/g for chabazite-rich sample surface modified with BC to ~28 mg/g for phillipsite-rich

sample modified with HB, following the trends PHI_SAV > CLI_SK > CHA_SM and HB > HC > CC ≥ BC according to anion exchange capacities (AECs) of examined SMNZs. Hydrophobicity and molecular conformation of the two NSAIDs can also play a significant role in the drug loading processes on SMNZs (Pasquino *et al.*, 2016; de Gennaro *et al.*, 2017). For example, the amount of diclofenac trapped into the hydrophobic portion of micelle is significantly higher (at least twice) than ibuprofen (de Gennaro *et al.*, 2016). Pasquino *et al.* (2016) interpreted this result as a consequence of the different molecular structure of diclofenac and ibuprofen. Firstly, the presence of two aromatic groups and the higher hydrophobicity of the diclofenac compared to ibuprofen brings the diclofenac far away from an unfavourable environment, namely on the zeolite surface in bigger quantities than ibuprofen. Secondly, molecular structure is more compact (minor steric hindrance) and the aromatic anions can more easily reach the hydrophobic portion of micelle.

Lastly, the results evidenced a prompt ibuprofen release within the first 30-50 minutes, making these natural materials suitable to provide rapid soothing effects. The tail drug released up to 5 hours allows to guarantee a soothing upkeep until the following drug administration, usually occurring within 4-6 hours. For a more sustained drug release, pharmaceutical form and experimental conditions must be properly considered as inferable by recent studies (Krajišnik *et al.*, 2013; de Gennaro *et al.*, 2015; Marković *et al.*, 2016; Serri *et al.*, 2016, 2017).

CONCLUSIONS

The results of this research emphasized the possibility to use natural zeolites for high-value technological applications as efficient carrier for the delivery of nonsteroidal anti-inflammatory drugs (*i.e.*, ibuprofen sodium salt), preferably in the place of synthetic zeolites. In facts, synthetic zeolites lattices are generally manufactured in energy-intensive (and more expensive) chemical processes. If on one hand, synthetic zeolites meet ion-specific exchange requirements in highly discriminating applications, on the other hand natural zeolites are characterized by the higher Si/Al ratio making them more versatile in a broad array of applications and more durable in mildly acidic environments (Cerri *et al.*, 2016). Furthermore, this kind of applications involving natural zeolite-rich rocks give more added-value to some geological formations that are usually used for low-value, high-volume construction applications, such as dimension stone (Langella *et al.*, 2013), lightweight aggregate (Dondi *et al.*, 2016) and pozzolanic cement, especially in ancient structures (Izzo *et al.*, 2016; Jackson *et al.*, 2017). However, an estimation of the real amounts of suitable georesource for high-value technological applications requires a thorough characterization of geological deposits from each potential exploitation site, including performance of analytical techniques widely used in mineralogical and petrographic fields. Furthermore, in-depth investigation of each single batch is strictly required especially for environmental and biomedical applications.

This research demonstrated that a fast functionalization of zeolite-rich carriers can be achieved with a high speed disperser with an optimization of the charging process, turning into an economic saving at industrial scale. Furthermore, the present research aimed to evaluate the technological performance of SMNZs in loading and in vitro release of NSAIDs demonstrating that the examined natural zeolite-rich rocks turned out to be promising drug carriers, fully comparable to other adsorbent carriers. Lastly, SMNZs could be also used to solve the problem related to the pollution of wastewaters, surface waters, and drinking waters due to drug manufacturing (Płuciennik-Koropczuk, 2014; Larsson, 2014).

REFERENCES

Bowman, R.S. (2003): Applications of surfactant-modified zeolites to environmental remediation. *Micropor. Mesopor. Mat.*, **61**, 43-56.

Buondonno, A., Grilli, E., Capra, G.F., Glorioso, C., Langella, A., Leone, A.P., Leone, N., Odierna, P., Vacca, S., Vigliotti, R.C. (2013): Zeolitized tuffs in pedotechnique for the reclamation of abandoned quarries. A case study in the Campania region (Italy). *J. Environ. Manage.*, **122**, 25-30.

Cappelletti, P., Rapisardo, G., De Gennaro, B., Colella, A., Langella, A., Graziano, S.F., Bish, D.L., de Gennaro, M. (2011): Immobilization of Cs and Sr in aluminosilicate matrices derived from natural zeolites. *J. Nucl. Mater.*, **414**, 451-457.

Cappelletti, P., Colella, A., Langella, A., Mercurio, M., Catalanotti, L., Monetti, V., de Gennaro, B. (2017): Use of surface modified natural zeolite (SMNZ) in pharmaceutical preparations Part 1. Mineralogical and technological characterization of some industrial zeolite-rich rocks. *Micropor. Mesopor. Mat.*, **250**, 232-244.

Cerri, G., Farina, M., Brundu, A., Dakovi , A., Giunchedi, P., Gavini, E., Rassu, G. (2016): Natural zeolites for pharmaceutical formulations: Preparation and evaluation of a clinoptilolite-based material. *Micropor. Mesopor. Mat.*, **223**, 58-67.

de Gennaro, B., Catalanotti, L., Bowman, R.S., Mercurio, M. (2014): Anion exchange selectivity of surfactant modified clinoptilolite-rich tuff for environmental remediation. *J. Colloid Interf. Sci.*, **430**, 178-183.

de Gennaro, B., Catalanotti, L., Cappelletti, P., Langella, A., Mercurio, M., Serri, C., Biondi, M., Mayol, L. (2015): Surface modified natural zeolite as a carrier for sustained diclofenac release: A preliminary feasibility study. *Colloid. Surface B*, **130**, 101-109.

de Gennaro B., Izzo F., Catalanotti L., Langella A., Mercurio M. (2016): Surface modified phillipsite as a potential carrier for NSAIDs release. *Adv. Sci. Lett.*, **23**, 5941-5943.

de Gennaro, B., Mercurio, M., Cappelletti, P., Catalanotti, L., Daković, A., De Bonis, A., Grifa, C., Izzo, F., Kraković, M., Monetti, V., Langella, A. (2016): Use of surface modified natural zeolite (SMNZ) in pharmaceutical preparations. Part 2. A new approach for a fast functionalization of zeolite-rich carriers. *Micropor. Mesopor. Mat.*, **235**, 42-49.

Dondi, M., Cappelletti, P., D'Amore, M., de Gennaro, R., Graziano, S.F., Langella, A., Raimondo, M., Zanelli, C. (2016): Lightweight aggregates from waste materials: Reappraisal of expansion behavior and prediction schemes for bloating. *Constr. Build. Mater.*, **127**, 394-409.

Jackson, M.D., Mulcahy, S.R, Chen, H., Li, Y., Li, Q., Cappelletti, P., Wenk, H.R. (2017): Phillipsite and Al-tobermorite mineral cements produced through low-temperature water-rock reactions in Roman marine concrete. *Am. Mineral*, **102**, 1435-1450.

Izzo, F., Arizzi, A., Cappelletti, P., Cultrone, G., De Bonis, A., Germinario, C., Graziano, S.F., Grifa, C., Guarino, V., Mercurio, M., Morra, V., Langella, A. (2016): The art of building in the Roman period (89 B.C. - 79 A.D.): Mortars, plasters and mosaic floors from ancient Stabiae (Naples, Italy). *Constr. Build. Mater.*, **117**, 129-143.

Izzo F., Mercurio M., Aprea P., Cappelletti P., de Gennaro B., Germinario C., Grifa C., Pasquino R., Langella A. (2017): Technological performance of surface modified natural zeolite (SMNZ) for in vitro loading/release of ibuprofen sodium salt: new insights on chabazite-rich tuff. SIMP-SGI-SOGEI-AIV 2017 Geosciences: a tool in a changing world, 3-6 September 2017, 221.

Izzo F., Mercurio M., Cappelletti P., de Gennaro B., Dakovi A., Germinario C., Grifa C., Smiljani D., Langella A. (2018): New insights on surface modified natural clinoptilolite-rich carrier for sorption and in vitro release of ibuprofen sodium salt. ZEOLITE 2018, 24-29 June 2018, Krakow, Poland, 191-192.

Izzo F., Mercurio M., de Gennaro B., Aprea P., Cappelletti P., Daković A., Germinario C., Grifa C., Smiljanić D., Langella A. (2019): Surface modified natural zeolites (SMNZs) as nanocomposite versatile materials for health and environment. *Colloid. surface B*, **182,** 110380

Krajišnik, D., Daković, A., Malenović, A., Djekić, L., Kragović, M., Dobričić, V., Milić, J. (2013): An investigation of diclofenac sodium release from cetylpyridinium chloride-modified natural zeolite as a pharmaceutical excipient. *Micropor. Mesopor. Mat.*, **167**, 94-101.

Langella, A., Pansini, M., Cappelletti, P., De Gennaro, B., de Gennaro, M., Colella, C. (2000): NH_4^+, Cu^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} exchange for Na^+ in a sedimentary clinoptilolite, North Sardinia, Italy. *Micropor. Mesopor. Mat.*, **37**, 337-343.

Langella, A., Bish, D.L., Cappelletti, P., Cerri, G., Colella, A., de Gennaro, R., Graziano, S.F., Perrotta, A., Scarpati, C., de Gennaro, M. (2013): New insights into the mineralogical facies distribution of Campanian Ignimbrite, a relevant Italian industrial material. *Appl. Clay Sci.*, **72**, 55-73.

Larsson, D.G.J. (2014): Pollution from drug manufacturing: review and perspectives. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **369 (1656),** 20130571.

Li, Z., & Bowman, R.S. (1997): Counterion effects on the sorption of cationic surfactant and chromate on natural clinoptilolite. *Envir. Sci. Technol.*, **31**, 2407-2412.

Marković, M., Daković, A., Krajišnik, D., Kragović, M., Milić, J., Langella, A., de Gennaro, B., Cappelletti, P., Mercurio, M. (2016): Evaluation of the surfactant/phillipsite composites as carriers for diclofenac sodium. *J. Mol. Liq.*, **222**, 711-716.

Mercurio, M., Mercurio, V., de Gennaro, B., de Gennaro, M., Grifa, C., Langella, A., Morra, V. (2010): Natural zeolites and white wines from Campania region (Southern Italy): a new contribution for solving some oenological problems. *Period. Mineral.*, **79**, 95-112.

Mercurio, M., Langella, A., Cappelletti, P., de Gennaro, B., Monetti, V., de Gennaro, M. (2012): May the use of Italian volcanic zeolite-rich tuffs as additives in animal diet represent a risk for the human health. *Period. Mineral.*, **81**, 393-407.

Mercurio, M., Cappelletti, P., De Gennaro, B., De Gennaro, M., Bovera, F., Iannaccone, F., Grifa, C., Langella, A., Monetti, V., Esposito, L. (2016a): The effect of digestive activity of pig gastro-intestinal tract on zeolite-rich rocks: An in vitro study. *Micropor. Mesopor. Mat.*, **225**, 133-136.

Mercurio, M., Bish, D.L., Cappelletti, P., Gennaro, B. de, Gennaro, M. de, Grifa, C., Izzo, F., Mercurio, V., Morra, V., Langella, A. (2016b): The combined use of steam-treated bentonites and natural zeolites in the oenological refining process. *Mineral. Mag.*, **80**, 347-362.

Mercurio, M., Izzo, F., Langella, A., Grifa, C., Germinario, C., Daković, A., Aprea, P., Pasquino, R., Cappelletti, P., Graziano, F.S., de Gennaro, B. (2018): Surface modified phillipsite-rich tuff from Campania region (southern Italy) as promising drug carrier: An Ibuprofen sodium salt trial. *Am. Mineral*, **103**, 700-710.

Misaelides, P. (2011): Application of natural zeolites in environmental remediation: A short review. *Micropor. Mesopor. Mat.*, **144**, 15-18.

Pasquino, R., Di Domenico, M., Izzo, F., Gaudino, D., Vanzanella, V., Grizzuti, N., de Gennaro, B. (2016): Rheology-sensitive response of zeolite-supported anti-inflammatory drug systems. *Colloid. Surface B*, **146**, 938-944.

P uciennik-Koropczuk, E. (2014): Non-Steroid Anti-Infflamatory Drugs in Municipal Wastewater and Surface Waters. *Civ. Environ. Eng. Rep.*, **14**.

Serri, C., De Gennaro, B., Catalanotti, L., Cappelletti, P., Langella, A., Mercurio, M., Mayol, L., Biondi, M. (2016): Surfactant-modified phillipsite and chabazite as novel excipients for pharmaceutical applications? *Micropor. Mesopor. Mat.*, **224**, 143-148.

Serri, C., de Gennaro, B., Quagliariello, V., Iaffaioli, R.V., De Rosa, G., Catalanotti, L., Biondi, M., Mayol, L. (2017): Surface modified zeolite-based granulates for the sustained release of diclofenac sodium. *Eur. J. Pharm. Sci.*, **99**, 202-208.