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**Surface-modified phillipsite-rich tuff from the Campania region (southern Italy)**
as a promising drug carrier: An Ibuprofen sodium salt trial

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**ABSTRACT**

The encapsulation and delivery of drugs often involves the use of expensive microporous materials, and we have investigated the potential for natural zeolites from the widespread volcanic formations of southern Italy as alternatives to these carriers.

Surface-modified natural zeolites (SMNZs) with diverse micellar structures (patchy
and complete bilayers) were obtained by using different cationic surfactants (cetylpyridinium chloride (CP-Cl), benzalkonium chloride (BC-Cl), hexadecyltrimethylammonium chloride (HDTMA-Cl) and bromide (HDTMA-Br) with phillipsite-rich tuff from the Campania region (southern Italy). Loading and release kinetics tests of sodium Ibuprofen (IBU) were carried out with organo-phillipsite composites using Fourier-transform infrared spectroscopy (FTIR) and thermal analysis coupled with evolved gas analysis (EGA). Results from these tests were mathematically modeled to evaluate IBU adsorption and release mechanisms. The maximum loaded amount of IBU was attained for organo-phillipsite modified with HDTMA-Br (PHB), which showed a complete bilayer micellar structure. Whenever a patchy bilayer micellar structure formed, the lowest adsorptions of IBU were observed. Equilibrium adsorption results were fit using Langmuir, Sips and Toth models. Pseudo first-order and pseudo second-order fits to the loading kinetic data provided significant Goodness of Fit. Good fits to the release kinetic data were obtained using first-order and Weibull equations, shedding new light on the release mechanism of IBU from phillipsite. The active amount of IBU on the modified zeolite surface was almost totally available for pharmaceutical purposes.

Keywords: phillipsite; Neapolitan Yellow Tuff; Ibuprofen sodium salt; functionalization; SMNZ; carrier; drug delivery; SIPS model; TOTH model.

INTRODUCTION
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Recent research has demonstrated that natural and surface-modified zeolites containing cationic surfactants are selective towards some pharmacological molecules (i.e., diclofenac sodium, diclofenac diethylamine, and Ibuprofen). Available data suggest that zeolites represent a low cost and easily accessible natural excipient that can be used in biomedicine as carriers for drug delivery (Cerri et al. 2004, 2016, Krajšnik et al. 2013b, 2015, 2010a, 2010b, 2011, 2013a; Cappelletti et al. 2017; de Gennaro et al. 2015, 2016; Janićijević et al. 2015; Marković et al. 2016, 2017; Pasquino et al. 2016; Serri et al. 2016, 2017). Based on the premise that such natural carriers are non-toxic (Mercurio et al. 2012, 2016b; Krajšnik et al. 2013b; Cerri et al. 2016), several aspects of their performance should be clarified before modified zeolites can be used on an industrial scale. In order to evaluate their functional therapeutic performance, it is particularly important to expand the data for a breadth of different systems such as zeolite vs. surfactant vs. active substance. Careful evaluation of loading and release performances under controlled conditions is also required (Krajšnik et al. 2015, 2010a, 2010b, 2011, 2013a, 2013b, de Gennaro et al. 2015, 2016, 2017; Janićijević et al. 2015; Marković et al. 2016, 2017; Pasquino et al. 2016; Serri et al. 2016, 2017; Izzo et al. 2017). Several recent studies have documented the efficacy of zeolites as pharmacological carriers. Serri et al. (2017) demonstrated that granulate could be formed using a functionalized natural clinoptilolite, suitable for the release of sodium diclofenac. Krajšnik et al. (2016) demonstrated that non-steroidal anti-inflammatory drugs (NSAID), for example IBU, benefit particularly from use with therapeutic devices providing prolonged release, such as clinoptilolite-rich carriers. For loading purposes, Krajšnik et al. (2016) used clinoptilolite modified with two surfactants.
(cetylpyridinium chloride and benzalkonium chloride) at different concentrations, and their results showed that different adsorbed amounts of IBU depended on the type and/or the amount of surfactant used to functionalize the zeolite-rich carrier. In vitro release tests also demonstrated that IBU was released from the composite material for up to eight hours, as illustrated by mathematical models Bhaskar (Bhaskar et al. 1986) and Higuchi (Higuchi 1963). Krajšnik et al. (2016) hypothesized that the adsorption process involved hydrophobic-hydrophilic interactions between the drug molecules and the surfactants on the zeolite surface.

In order to meet the demand of the pharmaceutical industry searching for new and inexpensive carriers for the encapsulation and delivery of drugs (Tan et al. 2013), we investigated natural and widespread phillipsite-rich rock from southern Italy (Campania region) as alternatives to the usual expensive prepared mesoporous materials. This geomaterial, widely occurring in the Neapolitan Yellow Tuff (NYT) Formation and the Campanian Ignimbrite (CI) Formation, has been studied in detail (de Gennaro et al. 1992, 1995, 1999, 2000a; Colella et al. 1998, 2013, 2017; Langella et al. 2002, 2013; Cappelletti et al. 2003; Calcaterra et al. 2004; Buondonno et al. 2008; Morra et al. 2010), and existing data support applications in the areas of cation exchange (Pansini et al. 1996; Colella et al. 1998; Gatta et al. 2015), animal feeding (Mercurio et al. 2012, 2016b), oenotechnical (Mercurio et al. 2010, 2014, 2016a), soil remediation (Coppola et al. 2003), production of lightweight aggregates (de Gennaro et al. 2004, 2005, 2007, 2008; Dondi et al. 2016), and ceramic manufacturing (de Gennaro et al. 2003; Cappelletti et al. 2011).
Application of natural zeolites in the pharmaceutical field requires evaluation of the performance of functionalized zeolites as carriers for drug delivery. Modification of the zeolite surface was performed in our studies using four different surfactants (cetylpyridinium chloride, benzalkonium chloride, hexadecyltrimethylammonium chloride and bromide) at a concentration equal to 200% of the external cation exchange capacity (ECEC) of the zeolite. The amount of surfactant was chosen based on published results (Li and Bowman 1997; de Gennaro et al. 2016; Cappelletti et al. 2017) that demonstrated that this concentration guarantees the almost complete formation of a bilayer of the surfactants on the zeolite surface. In order to clarify the properties of this specific phillipsite-IBU composite material, equilibrium isotherms as well as IBU loading and release kinetics were measured. Basic characterization of the composite material was obtained using thermal analysis (STA coupled with EGA) and FT-IR spectroscopy.

**Materials**

A phillipsite-rich tuff from the Campania Region (southern Italy) and four cationic surfactants were selected for the preparation of surfactant modified natural zeolites (SMNZs) and were used for subsequent IBU sodium loading and release tests. Mineralogical and technological characterization of the natural zeolite-rich material has been reported by Cappelletti et al. (2017) and is only briefly summarized here. NYT phillipsite-rich rocks from Marano (Savanelli quarry, Naples, Italy; hereafter PHI_SAV) contain about 70 wt.% phillipsite with minor chabazite (~5 wt.%) and analcime (~3 wt.%) (de’ Gennaro et al. 2000b). This phillipsite from the PHI_SAV
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114 sample has a low Si/Al ratio (approximately 2.5) and it is characterized by a high K⁺
115 content, which reflects the typical composition of trachytic rocks from Campi Flegrei
116 (southern Italy) (Morra et al. 2010). It contains subordinate amounts of Ca²⁺ and Na⁺.
117 The experimental ECEC value (0.144 mEq/g) was evaluated using the method
118 suggested by de Gennaro et al. (2014), which involves contacting a zeolite sample (2.5
119 g) with 10 mL of 20-mM surfactant solution in a 50-mL polyallomer centrifuge tube,
120 shaking at 100 rpm for 24 h at 25 °C. The sample was then centrifuged and the
121 supernatant analyzed for the anion concentration by HPLC.
122 Leaching tests confirmed that the available contents of heavy metals such as Ni, As,
123 Cd and Pb were all below 20 mg/kg, confirming the correlation with the total amount
124 of these elements in the whole rock (Mercurio et al. 2012).
125 PHI_SAV was surface modified using cetylpyridinium chloride (CP-Cl),
126 benzalkonium chloride (BC-Cl), hexadecyltrimethylammonium chloride (HDTMA-Cl)
127 and bromide (HDTMA-Br). The resulting SMNZs were labeled as PCC, PBC, PHC
128 and PHB, respectively. Anion exchange capacity (AEC) values for these were ~0.09
129 mEq/g for PBC and PC, and ~0.110 mEq/g and 0.140 mEq/g for PHC and PHB. These
130 results are consistent with the different micellar structure (patchy and complete bilayer)
131 obtained using different surfactant molecules (Cappelletti et al., 2017).
132 These organo-philipsite composites were used for loading and release tests of sodium
133 IBU. Chemical characteristics of surfactants and IBU are presented in Figures 1 and 2.

135

METHODS

136 SMNZs preparation

6
In order to obtain SMNZs for the IBU loading tests, a suspension containing PHI_SAV and each of the selected surfactants, having an initial concentration equivalent to 200% of the ECEC, was prepared. The suspension was mixed at 3,000 rpm using a FALC AT-M 20 stirrer at ~ 50 °C for ~ six hours, with a solid to liquid (S/L) ratio of 1/40. The suspensions were then filtered and the obtained SMNZs were washed with ultrapure water to remove the unnecessary surfactant and were then dried at room temperature for 24 hours.

**Drug loading tests**

Maximum IBU adsorption capacities of SMNZs were determined by means of equilibrium and kinetics adsorption tests. The pH of each suspension was adjusted to 7.4 with a sodium tetraborate buffer solution (CAS No. [1303-96-4]) as this pH value allows the IBU sodic salt to remain in its ionic form (Krajišnik et al. 2015; Oh et al. 2016).

For the equilibrium adsorption measurements, 100 mg of each SMNZ were treated with 20 mL of IBU solution, having concentrations ranging between 50 and 1000 mg/L, and continuously stirred in 25 mL Nalgene centrifuge tubes at room temperature. After four hours (sufficient time to attain equilibrium based on the kinetic tests), samples were centrifuged to separate solid from liquid and the supernatant was analyzed using an AquaMate UV-VIS spectrophotometer. The IBU calibration curve ($R^2=0.999$) was obtained using the adsorption band at 224 nm, in accordance with (Sena et al. 2007; Gondalia et al. 2010; Joshi et al. 2011). Each measurement was made in triplicate.
Kinetic studies were carried out in batch experiments at room temperature and under continuous stirring, by shaking 100 mg of each sample with 20 mL of IBU solution (400 mg/L). To avoid variation of this solution/SMNZ ratio the mixture was placed into 25 mL high density polyethylene centrifuge tubes. A test tube was withdrawn (after 5’, 10’, 15’, 30’, 60’, 90’…240), centrifuged, and the non-adsorbed amount of IBU was determined in the supernatant.

**Drug release tests**

IBU in vitro release experiments were carried out using IBU-loaded SMNZs dispersed in simulated intestinal fluid (SIF), prepared as described in the United States Pharmacopoeia 25 Ed. and later editions (USP-NF 2002, 2003). 15 mg of IBU-loaded SMNZs were added to 10 mL of SIF and placed in a thermostatic bath at 37 °C under continuous stirring (100 rpm). Samples were kept in the thermostatic bath until the released amount of the drug reached a plateau. The IBU-loaded SMNZ/SIF ratio was chosen in order to ensure sink conditions. 5 mL aliquots of supernatant were withdrawn at fixed interval times (30 min), centrifuged at 9,000 rpm (room temperature, 5 min), and replaced by the same volume of fresh medium. IBU was quantified by spectrophotometric assay (Aquamate UNICAM) at 224 nm. Experiments were run in triplicate.

**Mathematical modeling**

To evaluate IBU adsorption and release mechanisms of SMNZs, adsorption isotherms and kinetic measurements were fit using several mathematical models proposed in the
Fit parameters were determined by non-linear regression using the Generalized Reduced Gradient algorithm (Gabriele and Ragsdell 1977), based on the assumption that non-linear regression provides the best fit results (Ho et al. 2005; Lin and Wang 2009; Chen 2013; Markandeya and Kisku 2015).

Model fit and applicability were evaluated by considering determination coefficients ($R^2$), as well as other statistical methods for non-linear regression (Costa et al. 2003; Spiess and Neumeyer 2010) such as the Akaike Information Criterion (AIC) (1) and the Bayesian Information Criterion (BIC) (2). These methods take into account the number of parameters of the mathematical model and the number of experimental data and can be expressed as follows:

$$AIC = 2p - 2\ln(L) \quad (1)$$

$$BIC = p\ln(n) - 2\ln(L), \quad (2)$$

where $p$ is the number of parameters and $n$ is the sample size. $\ln(L)$, the maximum log-likelihood of the estimated model (Spiess and Neumeyer 2010), was calculated as follows: $\ln(L) = 0.5 \times [-N \times (\ln 2\pi + 1 - \ln N + \ln \sum_{i=1}^{N} x_i^2)]$, where $x_i$ are the residuals from the nonlinear least squares fit and $N = \text{the number of residuals}$.

**Thermal analyses**
Thermal analysis (thermogravimetry and differential scanning calorimetry, TG/DSC) was performed on phillipsite-rich material, cationic surfactants, IBU, SMNZs and IBU-loaded SMNZs using a NETZSCH STA 449 F3 Jupiter instrument with alumina crucibles. Samples were heated from room temperature to 1050 °C at a heating rate of 10 °C/min in an ultra-pure air atmosphere (N₂/O₂ = 80/20; flow 60 mL/min). EGA were carried out by FTIR with a BRUKER Tensor 27 instrument, coupled to the STA 449 F3 instrument by a transfer line heated to 200 °C. Netzsch Proteus 6.1.0 (NETZSCH-Gerätebau GmbH) and Opus 7.2 (Bruker Optics GmbH) software packages were used for data analysis.

FTIR

The phillipsite-rich material, cationic surfactants, IBU, SMNZs and IBU-loaded SMNZs were analyzed using a Bruker Alpha FTIR spectrometer in attenuated total reflectance (ATR)-mode with 128 scans at a spectral resolution of 4 cm⁻¹ in the spectral range of 400-4000 cm⁻¹. Spectra were analyzed with Opus 7.2 software (Bruker Optics GmbH).

RESULTS AND DISCUSSION

Characterization of SMNZs

FTIR spectroscopy

The infrared spectrum of PHI_SAV shows the typical absorption bands of zeolite-rich tuffs (Cappelletti et al. 2017), including absorption bands associated with internal and external framework vibrations of primary building units (PBUs) and secondary
building units (SBUs) of zeolites (Karge 2001; Byrappa and Kumar 2007; Mozgawa et al. 2011). A strong band at ~1000 cm$^{-1}$ (Table 1 and Fig. 3) was assigned to asymmetric stretching Si-O vibrations. Bands at ~780 and ~719 cm$^{-1}$ were assigned to asymmetric and symmetric stretching T-O-T vibrations, respectively, and the remaining bands are generally referred to bending vibrations characteristic for silicates, also occurring in the sample, such as pyroxene (3.3 wt.%), K-feldspar (13.3 wt.%) and traces of mica. The weak, broad band at ~3419 cm$^{-1}$ and the band at ~1638 cm$^{-1}$ suggest the presence of hydrogen-bonded H$_2$O molecules. Moreover, a very weak broad band at ~1456 cm$^{-1}$ could indicate traces of carbonate minerals (C-O asymmetric stretching in the carbonate ion). IR vibrations associated with exchangeable cations usually occur in the far-IR region (200-50 cm$^{-1}$) (Karge 2001), and any structural modification caused by external cation substitution with cationic surfactants could not be detected by mid-IR spectroscopy. On the other hand, FTIR spectra of SMNZs and IBU-loaded SMNZs can be clearly distinguished from those of the starting materials by the presence of absorption bands in the spectral range 3000-2800 cm$^{-1}$ (Table 1; Fig. 3) (Barczyk et al. 2014), which correspond to the strong bands (C-H stretching vibrations) observed both in surfactants and IBU (Figures 1 and 2). These organic compounds also share two very weak bands at ~1487 cm$^{-1}$ and ~1468 cm$^{-1}$ (C-H bending vibrations). However, IBU-loaded SMNZs show increased intensity of C-H stretching vibrations (Krajišnik et al. 2010b, 2015), as well as the occurrence of additional bands at ~1578 cm$^{-1}$ and ~1380 cm$^{-1}$ (Table 1; Fig. 3) attributable to asymmetric and symmetric stretching vibrations in carboxylate ions (Ambrogi et al. 2001; Wray et al. 2011).
STA coupled with FT-IR/EGA

Thermal analysis has been widely used in the characterization of natural zeolites and their modified forms (Sullivan et al. 1997; Bish and Carey 2001; Langella et al. 2003; Krajšnik et al. 2011, 2013a, 2013b; de Gennaro et al. 2016; Marković et al. 2017). So-called “zeolitic water” is found in the open cavities (channels and cages) of zeolites (Coombs et al. 1997), where it can move more-or-less freely through the interconnected cavities (Bish and Carey 2001; Langella et al. 2003). The phillipsite-rich starting material shows the typical thermal behavior of a zeolite with a high kinetic pore diameter (Bish and Carey 2001; Langella et al. 2003), as much of the weight loss occurs below 250 °C with the maximum dehydration rate at ~ 176 °C (Fig. 4).

Dehydration continued gradually to ~ 550 °C, likely due to the presence of other natural zeolites with lower kinetic diameters such as chabazite and minor analcime as well as hydroxilated phases (micas). Cumulatively, the “zeolitic” H$_2$O evolving over the 40-550 °C range is ~10 wt.%. This H$_2$O content is consistent with the high K$^+$ content of the zeolites in the tuff. The presence of large monovalent cations, such as K$^+$, generally results in moderate or low H$_2$O contents (Bish 1984, 1988; Kranz et al. 1989; Carey and Bish 1996; Fialips et al. 2005; Esposito et al. 2015).

H$_2$O evolved during dehydration was detected via FTIR/EGA (Fig. 4), along with a weak emission of CO$_2$ attributable to the decomposition of calcite in the 550-800 °C thermal range.

The thermal behavior of SMNZs and IBU-loaded SMNZs is mainly characterized by the occurrence of two principal processes (Table 2). The first, occurring below 200 °C,
is related to dehydration of the zeolitic component, and decomposition of cationic surfactants was not significant in this temperature range (Fig. 4). The second process (>200 °C) is linked to decomposition and subsequent combustion of surfactants (SMNZs) and IBU (IBU-loaded SMNZs) (Table 2; Figs 1 and 2). Thus the total mass loss for IBU-loaded SMNZs is greater than the mass loss for the starting material and the SMNZs before drug adsorption (Table 2). These results could attest the effective functionalization of zeolite and subsequent drug loading although, it requires a further validation by technological performance.

**Technological performance of the phillipsite-IBU composite material**

*Equilibrium isotherms*

Table 3 and Figure 5 report the results of equilibrium adsorption measurements fit using three mathematical models, Langmuir (Fig. 5a) (Langmuir 1916), Sips (also called Langmuir-Freundlich, Fig. 5b), and Toth (Fig. 5c) equations. The shape of the curves shows that the plateau, i.e., the maximum drug adsorption, was reached for the initial IBU concentration of 400 mg/L, regardless of the type of surfactant. Moreover, the maximum loaded amount was attained for the PHB (~29 mg/g), in agreement with complete bilayer formation, whereas lower adsorption was achieved for PBC and PCC (21.2 mg/g) where the two surfactants formed only a patchy bilayer at the zeolitic surface. The latter are in agreement with Cappelletti et al. (2017), who emphasized the effects of the counterions on micellar structure formation. The same behavior was also recorded for PHC, although it achieved a higher IBU loaded amount. This may indicate that, for its benzene ring-free structure (different
from benzalkonium and cetylpyridinium), the HDTMA-Cl can form a more
homogeneous patchy bilayer than the other two chlorinated surfactants, as found in
previous research (Cappelletti et al., 2017).

The Langmuir adsorption isotherm model is commonly used to fit the performance of
different bio-mineral adsorbents such as SMNZs (Li et al. 1998, 1999; Krajišnik et al.
2010a; Wang and Peng 2010; Cappelletti et al. 2017; de Gennaro et al. 2016; Marković
et al. 2017) and other geomaterials (Campbell and Davies 1995; Li and Bowman 1997,
1998, 2001; Janićijević et al. 2015), although it was originally developed to describe
gas-solid-phase adsorption onto activated carbon (Langmuir 1916; Foo and Hameed
2010). On the other hand, the Sips (1948) and Toth (1971) models were developed to
improve fits based on Langmuir isotherms (Hinz 2001; Limousin et al. 2007; Foo and
Hameed 2010).

The Langmuir (equation 3), Sips (equation 4), and Toth (equation 5) equations can be
expressed as follows:

\[ S = S_m \frac{K C_e}{1 + K C_e}, \]  
(3)

\[ S = S_m \frac{(K C_e)^n}{1 + (K C_e)^n}, \]  
(4)

\[ S = S_m \frac{K C_e}{[1 + (K C_e)^n]^{\frac{1}{n}}}, \]  
(5)

where \( S \) is the amount of solute adsorbed by the solid at equilibrium conditions (mg/g);
\( C_e \) is the concentration of solute in solution after equilibrium (mg/L); \( S_m \) is the
maximum adsorption capacity at equilibrium (mg/g), $K$ (L/mg) is the adsorption intensity, a constant related to binding energy, and $n$ is a fitting parameter related to heterogeneity of the system. If $n = 1$, the Sips and Toth equations become a simple Langmuir equation.

The Sips and Toth models generally provided improved Goodness-Of-Fit (GOF) values observed as a reduction of AIC and BIC values, as well as an increase in the determination coefficient $R^2$ (Table 3). Maximum IBU adsorption capacities ($S_m$) of 22.0 mg/g, 20.4 mg/g, and 20.4 mg/g was calculated for sample PCC according to the Langmuir, Sips, and Toth isotherm equations, respectively (Table 3). Both the Sips (1948) and Toth (1971) provided best fits ($R^2 = 0.987$; AIC = 23.1; BIC = 22.9) for PCC, but no significant differences were found between these three models for IBU adsorption by PBC (Table 3).

Greater maximum adsorption capacities were obtained for PHC and PHB compared with PCC and PBC, and the Toth equation provided the best fit to the data (Table 3 and Fig. 5), particularly for PHB. The Toth fit parameters yield an amount of adsorbed IBU of 24.4 mg/g for PHC and 28.8 mg/g for PHB. The better performance of PHB can be explained by the tendency of this composite to form a more compact bilayer sheet micelle due to the presence of a Br counterion (Li and Bowman 1997; Cappelletti et al. 2017; de Gennaro et al. 2016). The general improvement of the GOF with the Sips and Toth equations instead of the Langmuir can be explained by taking into account the theoretical basis of the Langmuir isotherm model (Langmuir 1916; Limousin et al. 2007; Foo and Hameed 2010). The Langmuir model is strictly intended for materials where sorption mechanisms are fully...
associated with adsorption processes. The model is therefore inappropriate for SMNZs where sorption of NSAIDs is controlled by multiple mechanisms, including both external anionic exchange and partition into the hydrophobic portion of the micelle (Krajišnik et al. 2010a, 2010b, 2011, 2013a, 2013b, 2015; de Gennaro et al. 2015; Marković et al. 2016; Pasquino et al. 2016; Serri et al. 2017). In case of multiple sorption mechanism, although the adsorption mechanism always predominates (de Gennaro et al. 2015; Krajišnik et al. 2015), partition may influence the sorption of IBU by SMNZs, especially when IBU molecules can change their ionic form (e.g. by pH variations). Thus, from a mathematical point of view, the Sips or Toth equations fit the adsorption data better than the Langmuir model and they provide a well-defined equilibrium asymptotic plateau, useful for the identification of the real maximum adsorption capacity of SMNZs. In this way, equilibrium isotherm modeling can be used to optimize the appropriate initial concentration of IBU for kinetic experiments.

**In vitro IBU loading and release tests**

As mentioned above, the initial concentration of the IBU solution for the kinetic tests was 400 mg/L; at this concentration, complete saturation of the host composite material (SMNZ) is guaranteed, as suggested by the model equilibrium isotherms, and greater initial concentrations of the drug do not provide further IBU uptake. Figure 6 highlights the rapid rate of the loading process, and > 90% of IBU was loaded onto the SMNZs after 30 min, except for PBC which required ~120 min. Comparison of kinetic curves reveals that the maximum amount of loaded IBU was reached for PHC and PHB (26.8 and 28.1 mg/g, respectively). The latter case illustrates that a compact
bilayer is not an indication of the best loading, as it can create a "crowding" of anionic sites that are not all available for drug adsorption due to the larger size of IBU when compared with the Br ion. The maximum loaded amounts for PBC and PCC are still comparable (20.0 and 19.2 mg/g, respectively), confirming the similar behavior of SMNZs modified with these two surfactants. Lastly, the similarity of the values (Table 4, in mEq/g) of the maximum amounts of drug loaded onto SMNZs and their respective AECs (with the exception of PHB, as reported above) strongly suggests that anion exchange is the primary mechanism involved in the loading of IBU on SMNZs.

As often reported in the literature (Bowman 2003; de Gennaro et al. 2015; Serri et al. 2016), the drug adsorption kinetics of SMNZs generally follow pseudo-first order (PFO) (6) (Ho 2004) and pseudo-second order models (PSO) (7) (Ho 2006). These models can be written as follows:

\[ Q_t = Q_0 \left(1 - e^{-K_1 t}\right) \quad \text{and} \]

\[ Q_t = \frac{K_2 Q_0^2 t}{1 + K_2 Q_0 t}, \]

(6)

(7)

where \( Q_t \) is the amount of IBU loaded in SMNZ (mg/g) as a function of time \( t \) (min), \( Q_0 \) is the drug concentration at equilibrium, and \( K_1 \) (min\(^{-1}\)) and \( K_2 \) (g/mg\(^{-1}\) min\(^{-1}\)) are the pseudo-first and the pseudo-second order constants, respectively.

Non-linear regression validated both of these models (Table 4 and Fig. 6), although the best fit was obtained with the pseudo-second order model, consistent with previous...
Research on NSAIDs loaded on SMNZs (de Gennaro et al. 2015). Maximum adsorption capacities were 19.3 mg/g for PCC, 20.9 mg/g for PBC, 26.4 mg/g for PHC, and 27.9 mg/g for PHB (calculated using the PSO model). Once again, the highest IBU adsorption was achieved by PHB and PHC, whereas the amount of IBU adsorbed by PCC and PBC were lower, although quite similar.

IBU-release kinetics, rapid and practically complete (> 95%) for all the SMNZs, were fit using several mathematical models reported in the literature (Costa and Sousa Lobo 2001; Costa et al. 2003; Dash et al. 2010; Yadav et al. 2013), but the best fit was obtained using the first-order equation (8) and the Weibull equation (9), expressed as follows:

\[
M_t = M_0(1 - e^{-K_1 t}) \quad \text{and} \quad (8)
\]

\[
M_t = M_0 \left[ 1 - e^{-\left(\frac{t - T_i}{a}\right)^b} \right] \quad , \quad (9)
\]

where \(M_t\) is the amount of IBU released by SMNZ (mg/g) as a function of time \(t\) (min), \(M_0\) is the drug concentration at equilibrium (mg/g), \(K_1\) is the first-order constant (min\(^{-1}\)), \(T_i\) is the lag time (usually zero), \(a\) defines the time scale of the process (min), and \(b\) is a parameter describing the shape of the dissolution profile. In particular, the curve is exponential when \(b = 1\), the profile becomes sigmoidal with a turning point after an upward curvature if \(b > 1\), and the profile is parabolic with a steeper initial slope when \(b < 1\).
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Table 5 reports the parameters of these two models fitted by non-linear regression, and the dissolution profiles are shown in Figure 7, which shows that 50-60% of IBU was released by all samples in the first 30 min and 85-90% released within the first hour. Nevertheless, slower drug release from the SMNZs occurred up to 5 hours, with none of them achieving 100% release (Table 5).

Although the Weibull model is often useful for comparing dissolution profiles of matrix-type drug delivery (Costa and Sousa Lobo 2001), providing good fitting results (Costa et al. 2003), it represents an empirical model without any kinetic basis. The Weibull model can therefore not be used to adequately describe the dissolution rate of a drug or to establish effective correlations between in vitro and in vivo experiments (Costa and Sousa Lobo 2001).

Alternatively, a first-order kinetic equation may better describe dissolution profiles of IBU-loaded SMNZs, as the drug release appears to be proportional to the IBU remaining in the composites (Yadav et al. 2013). In particular, much of the released NSAID may be related to the amount of IBU adsorbed on the surface of SMNZs, whereas minor amounts of IBU located in the hydrophobic chains of micelles would be more slowly released due to diffusion processes (Pasquino et al. 2016).

**IMPLICATIONS**

One of the most important implications of this research is the possible use of low-cost and largely available natural zeolites in advanced technological sectors such as biomedicine. Our research has demonstrated that a phillipsite-rich rock is a good drug carrier, comparable to clinoptilolite-bearing rock carriers. Our results provide added
value to the southern Italian zeolite deposits, representing a by-product of the building stone industry that is currently disposed in landfills. However, due to the natural variability of this resource, careful characterization of production batches is mandatory.

Experimental results provide evidence that this material, properly surface modified by long-chain surfactants, is an excellent carrier of NSAIDs. Appropriate pharmaceutical preparations for oral use can be developed, possibly as granulates or as dispersions in order to increase the amount of the released drug. This application is supported by laboratory data that have shown the prompt release of a pain-killing drug within the first 30-50 min, thereby making these natural materials suitable for providing rapid palliative effects to the patient. It should be remarked however that the formulation of a composite system able to provide a sustained- in time drug release is required by pharmacologists. The IBU-phillipsite composite material investigated in the present research provided a slow release of a small amount of drug (5-10 %). Further investigation is required to understand if this low amount is significant of pharmacological point of view.

The functionalized phillipsite-rich rock may have other important applications in environmental fields (Hailu et al. 2017) such as the absorption/removal of pharmaceuticals from ground or surface waters, a rather growing problem which has yet to find a satisfactorily solution (Larsson 2014; Płuciennik-Koropczuk 2014).

ACKNOWLEDGMENTS
This work was carried out with the financial support of MIUR (Ministero dell’Istruzione, dell’Università e della Ricerca) Progetti di Ricerca di Interesse Nazionale (PRIN 2010). Authors wish to thank K. Putirka and two anonymous referees for their suggestions, which deeply improved the manuscript. The Authors are also in debt with L. Campbell and D.L. Bish for the invaluable contribution to the clarity of the manuscript.

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United States Pharmacopeial Convention Inc., Rockville, MD, USA.
United States Pharmacopeial Convention Inc., Rockville, MD, USA.
FIGURE CAPTIONS

Figure 1 - Physico-chemical and thermal properties of IBU
Figure 2 - Physico-chemical and thermal properties of surfactants
Figure 3 - FTIR spectra of starting materials (PHI_SAV), SMNZ (PCC), IBU-loaded SMNZ (PCC+IBU)
Figure 4 - Thermal properties of starting materials by TG/DSC coupled with FTIR-EGA
Figure 5 - Isotherms: A-Langmuir; B-Sips; C-Toth
Figure 6 - Kinetic loading curves: A- Pseudo-first order, B- Pseudo-second order
Figure 7 - Kinetic release curves: A- First-order, B- Weibull, C- First order (%), D-Weibull (%).
**Table 1 – FTIR data**

<table>
<thead>
<tr>
<th>PHI SAV</th>
<th>PCC</th>
<th>PBC</th>
<th>PHC</th>
<th>PHB</th>
<th>PCC+IBU</th>
<th>PBC+IBU</th>
<th>PHC+IBU</th>
<th>PHB+IBU</th>
<th>Tentative vibrational assignments</th>
<th>Chemical phase</th>
</tr>
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<tbody>
<tr>
<td>3419 w</td>
<td>3422 w</td>
<td>3436 w</td>
<td>3425 w</td>
<td>3427 w</td>
<td>3426 w</td>
<td>3434 w</td>
<td>3422 w</td>
<td>3425 w</td>
<td>O-H stretching</td>
<td>water</td>
</tr>
<tr>
<td>2958 sh</td>
<td>2959 sh</td>
<td>2958 sh</td>
<td>2959 sh</td>
<td>2955 vw</td>
<td>2960 sh</td>
<td>2954 sh</td>
<td>2954 sh</td>
<td>C-H stretching</td>
<td>Surfactant/IBU</td>
<td></td>
</tr>
<tr>
<td>2917 w</td>
<td>2923 vw</td>
<td>2923 vw</td>
<td>2923 vw</td>
<td>2921 w</td>
<td>2924 vw</td>
<td>2920 w</td>
<td>2922 w</td>
<td>C-H stretching</td>
<td>Surfactant/IBU</td>
<td></td>
</tr>
<tr>
<td>2850 w</td>
<td>2853 vw</td>
<td>2852 vw</td>
<td>2852 vw</td>
<td>2851 w</td>
<td>2853 vw</td>
<td>2851 w</td>
<td>2852 w</td>
<td>C-H stretching</td>
<td>Surfactant/IBU</td>
<td></td>
</tr>
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<td>1638 w</td>
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<td>1639 w</td>
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<td>1639 w</td>
<td>1635 w</td>
<td>1638 w</td>
<td>1638 w</td>
<td>1638 w</td>
<td>O-H bending</td>
<td>water</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Asymmetric stretching in carboxylate ion</td>
<td>Surfactant/IBU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-H bending</td>
<td>Surfactant/IBU</td>
</tr>
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<td>1489 vw</td>
<td>1481 vw</td>
<td>1489 sh</td>
<td>1489 sh</td>
<td>1489 vw</td>
<td>1489 sh</td>
<td>1489 sh</td>
<td>1489 sh</td>
<td>C-H bending</td>
<td>Surfactant/IBU</td>
<td></td>
</tr>
<tr>
<td>1469 vw</td>
<td>1466 vw</td>
<td>1470 vw</td>
<td>1470 vw</td>
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<td>1466 vw</td>
<td>1469 vw</td>
<td>1467 vw</td>
<td>C-H bending</td>
<td>Surfactant/IBU</td>
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<tr>
<td>1456 vw</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-O asymmetric stretching</td>
<td>Calcite</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>Symmetric stretching in carboxylate ion</td>
<td>Surfactant/IBU</td>
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<tr>
<td>1000 vs</td>
<td>995 vs</td>
<td>992 vs</td>
<td>995 vs</td>
<td>992 vs</td>
<td>989 vs</td>
<td>992 vs</td>
<td>991 vs</td>
<td>989 vs</td>
<td>T-O asymmetric stretching</td>
<td>Silicates</td>
</tr>
<tr>
<td>780 w</td>
<td>774 w</td>
<td>781 w</td>
<td>779 w</td>
<td>777 w</td>
<td>781 w</td>
<td>776 w</td>
<td>778 w</td>
<td>778 w</td>
<td>T-O-T asymmetric stretching</td>
<td>Silicates</td>
</tr>
<tr>
<td>719 w</td>
<td>717 w</td>
<td>723 w</td>
<td>720 w</td>
<td>719 w</td>
<td>724 w</td>
<td>720 w</td>
<td>719 w</td>
<td>719 w</td>
<td>T-O-T symmetric stretching</td>
<td>Silicates</td>
</tr>
<tr>
<td>597 w</td>
<td>596 w</td>
<td>597 w</td>
<td>597 w</td>
<td>599 w</td>
<td>595 w</td>
<td>596 w</td>
<td>598 w</td>
<td>598 w</td>
<td>T-O-T bending</td>
<td>Silicates</td>
</tr>
<tr>
<td>516 vw</td>
<td>515 vw</td>
<td>519 vw</td>
<td>517 vw</td>
<td>516 vw</td>
<td>514 vw</td>
<td>517 vw</td>
<td>519 vw</td>
<td>516 vw</td>
<td>T-O-T bending</td>
<td>Silicates</td>
</tr>
<tr>
<td>426 w</td>
<td>427 w</td>
<td>427 w</td>
<td>424 w</td>
<td>429 w</td>
<td>423 w</td>
<td>428 w</td>
<td>427 w</td>
<td>421 w</td>
<td>T-O-T bending</td>
<td>Silicates</td>
</tr>
</tbody>
</table>

Legend: w, weak; vw, very weak; sh, shoulder; s, strong; vs, very strong; T, tetrahedral cation (Si or Al).
## Table 2 – Thermal Analysis (TG-DTG-DSC and FTIR-EGA) data

<table>
<thead>
<tr>
<th>Samples</th>
<th>T &lt; 200 °C</th>
<th>200 °C &lt; T &lt; 1050 °C</th>
<th>L.O.I (%)</th>
<th>R.M. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔW(%)</td>
<td>DTG (°C)</td>
<td>DSC(°C)</td>
<td>EGA</td>
</tr>
<tr>
<td>PCC</td>
<td>6.3</td>
<td>157</td>
<td>131</td>
<td>H₂O</td>
</tr>
<tr>
<td>PCC+IBU</td>
<td>6.6</td>
<td>162</td>
<td>118</td>
<td>H₂O</td>
</tr>
<tr>
<td>PBC</td>
<td>6.1</td>
<td>153</td>
<td>164</td>
<td>H₂O</td>
</tr>
<tr>
<td>PBC+IBU</td>
<td>6.8</td>
<td>150</td>
<td>167</td>
<td>H₂O</td>
</tr>
<tr>
<td>PHC</td>
<td>6.7</td>
<td>144</td>
<td>157</td>
<td>H₂O</td>
</tr>
<tr>
<td>PHC+IBU</td>
<td>7.6</td>
<td>154</td>
<td>151</td>
<td>H₂O</td>
</tr>
<tr>
<td>PHB</td>
<td>6.9</td>
<td>146</td>
<td>144</td>
<td>H₂O</td>
</tr>
<tr>
<td>PHB+IBU</td>
<td>6.8</td>
<td>146</td>
<td>153</td>
<td>H₂O</td>
</tr>
</tbody>
</table>

**LEGEND:**

\(^{(a)}\)= Endothermic
\(^{(b)}\)= Exothermic

L.O.I. = loss on ignition
R.M. = residual mass
ΔW = residual mass
ΔW = weight loss (by TG)

\(^{(a)}\)= traces
Table 3 - Isotherm parameters

<table>
<thead>
<tr>
<th>Samples</th>
<th>Mathematical model</th>
<th>Parameters</th>
<th>Goodness-of-fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>K (L/mg) n</td>
<td>S_m (mg/g) S_m (mEq/g)</td>
</tr>
<tr>
<td>PCC</td>
<td>Langmuir</td>
<td>0.032</td>
<td>22.0 ± 0.6 0.096</td>
</tr>
<tr>
<td></td>
<td>Sips</td>
<td>0.026</td>
<td>20.4 ± 0.25 0.089</td>
</tr>
<tr>
<td></td>
<td>Toth</td>
<td>0.014</td>
<td>20.4 ± 0.2 0.089</td>
</tr>
<tr>
<td>PBC</td>
<td>Langmuir</td>
<td>0.039</td>
<td>21.9 ± 0.5 0.096</td>
</tr>
<tr>
<td></td>
<td>Sips</td>
<td>0.040</td>
<td>21.7 ± 0.4 0.095</td>
</tr>
<tr>
<td></td>
<td>Toth</td>
<td>0.033</td>
<td>21.4 ± 0.4 0.094</td>
</tr>
<tr>
<td>PHC</td>
<td>Langmuir</td>
<td>0.018</td>
<td>26.1 ± 0.5 0.114</td>
</tr>
<tr>
<td></td>
<td>Sips</td>
<td>0.018</td>
<td>24.6 ± 0.3 0.108</td>
</tr>
<tr>
<td></td>
<td>Toth</td>
<td>0.011</td>
<td>24.4 ± 0.2 0.107</td>
</tr>
<tr>
<td>PHB</td>
<td>Langmuir</td>
<td>0.006</td>
<td>36.2 ± 1.6 0.158</td>
</tr>
<tr>
<td></td>
<td>Sips</td>
<td>0.008</td>
<td>31.0 ± 0.9 0.136</td>
</tr>
<tr>
<td></td>
<td>Toth</td>
<td>0.004</td>
<td>28.8 ± 0.3 0.126</td>
</tr>
</tbody>
</table>

Table 4 - IBU Loading kinetic runs parameters

<table>
<thead>
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<th>Samples</th>
<th>Mathematical model</th>
<th>Parameters</th>
<th>Goodness-of-fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>K_1 (min^-1) K_2 (g·mg^-1·min^-1) Q_0 (mg/g) Q_0 (mEq/g)</td>
<td>R^2</td>
</tr>
<tr>
<td>PCC</td>
<td>Pseudo-first order</td>
<td>0.333</td>
<td>18.9 ± 1.1 0.083</td>
</tr>
<tr>
<td></td>
<td>Pseudo-second order</td>
<td>0.041</td>
<td>19.3 ± 0.5 0.085</td>
</tr>
<tr>
<td>PBC</td>
<td>Pseudo-first order</td>
<td>0.073</td>
<td>19.2 ± 0.7 0.084</td>
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<tr>
<td></td>
<td>Pseudo-second order</td>
<td>0.005</td>
<td>20.9 ± 0.5 0.091</td>
</tr>
<tr>
<td>PHC</td>
<td>Pseudo-first order</td>
<td>0.620</td>
<td>26.3 ± 0.4 0.115</td>
</tr>
<tr>
<td></td>
<td>Pseudo-second order</td>
<td>0.155</td>
<td>26.4 ± 0.4 0.116</td>
</tr>
<tr>
<td>PHB</td>
<td>Pseudo-first order</td>
<td>0.005</td>
<td>27.0 ± 1.7 0.118</td>
</tr>
<tr>
<td></td>
<td>Pseudo-second order</td>
<td>0.021</td>
<td>27.9 ± 0.9 0.122</td>
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</tbody>
</table>

Table 5 - IBU Release kinetic runs parameters

<table>
<thead>
<tr>
<th>Samples</th>
<th>Mathematical model</th>
<th>Parameters</th>
<th>Goodness-of-fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>K_1 (min^-1) a (min) b M_0 (mg/g) M_0 (%)</td>
<td>R^2</td>
</tr>
<tr>
<td>PCC</td>
<td>First-order</td>
<td>0.033</td>
<td>18.4 ± 0.9 95.45</td>
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<td>Weibull</td>
<td>31.61 1.31</td>
<td>18.3 ± 0.6 94.71</td>
</tr>
<tr>
<td>PBC</td>
<td>First-order</td>
<td>0.036</td>
<td>19.0 ± 0.7 98.44</td>
</tr>
<tr>
<td></td>
<td>Weibull</td>
<td>30.53 1.89</td>
<td>18.8 ± 0.2 97.26</td>
</tr>
<tr>
<td>PHC</td>
<td>First-order</td>
<td>0.036</td>
<td>25.5 ± 1.0 96.54</td>
</tr>
<tr>
<td></td>
<td>Weibull</td>
<td>30.08 1.51</td>
<td>25.3 ± 0.5 95.71</td>
</tr>
<tr>
<td>PHB</td>
<td>First-order</td>
<td>0.033</td>
<td>25.9 ± 1.2 92.83</td>
</tr>
<tr>
<td></td>
<td>Weibull</td>
<td>33.19 1.68</td>
<td>25.6 ± 0.6 91.58</td>
</tr>
</tbody>
</table>
Figure 1

Name: Ibuprofen sodium salt
CAS number: 31121-53-4
Molecular Weight, MW: 228.26 g/mol
Solubility in water: soluble 100 mg/mL

Structural formula:

Thermal properties:

FTIR spectrum:

Evolved Gas Analysis:
Figure 3
Figure 4
Figure 5

A)

B)

C)

LEGEND:  
PBC  PCC  PHC  PHB
Figure 6
Figure 7