8th Serbian-Croatian-Slovenian Symposium on Zeolites

Proceedings

Editors

Vesna Rakić
Jasna Hrenović
Alenka Ristić

Belgrade, 2019

Proceedings of the 8th Serbian-Croatian-Slovenian Symposium on Zeolites
Proceedings of the 8th Croatian-Slovenian-Serbian Symposium on Zeolites
Proceedings of the 8th Slovenian-Serbian-Croatian Symposium on Zeolites

ISBN:
978-86-916637-2-8

Publisher

Serbian Zeolite Association (SZA)

Editors

Vesna Rakić
Jasna Hrenović
Alenka Ristić

Print

Development and Research Centre of Graphical Engineering
Faculty of Technology and Metallurgy
Belgrade
SERBIA

Copies 80

Belgrade, 2019

PROCEEDINGS OF THE 8th SERBIAN-CROATIAN-SLOVENIAN SYMPOSIUM ON ZEOLITES

3 - 5 October 2019.

Belgrade, Serbia

Organizers

SERBIAN ZEOLITE ASSOCIATION

CROATIAN ZEOLITE ASSOCIATION

SLOVENIAN ZEOLITE ASSOCIATION

Co-organizers

CHAMBER OF COMMERCE AND INDUSTRY OF SERBIA

FACULTY OF PHYSICAL CHEMISTRY, UNIVERSITY OF BELGRADE

Under the auspices of

Federation of European Zeolite Associations (FEZA)

The Proceedings is printed under auspices of the

Ministry of Education,

Science and Technological Development, Republic of Serbia

All articles in the Proceedings were reviewed.

Organizing committee

Prof. **Vesna Rakić**, University of Belgrade, Faculty of Agriculture, Serbia.

Prof. **Nevenka Rajić**, University of Belgrade, Faculty of Technology and Metallurgy, Serbia.

Prof. **Vladimir Simić**, University of Belgrade, Faculty of Mining and Geology, Serbia.

Dr. **Aleksandra Daković**, Institute for Technology of Nuclear and Other Mineral Raw Materials, Serbia.

Prof. **Ljiljana Damjanović-Vasilić**, University of Belgrade, Faculty of Physical Chemisty, Serbia.

Dragan Stevanović, Chamber of Commerce and Industry of Serbia

Prof. **Nataša Zabukovec Logar**, National Institute of Chemistry, Ljubljana, and University of Nova Gorica, Slovenia.

Prof. **Nataša Novak Tušar**, National Institute of Chemistry, Ljubljana, and University of Nova Gorica, Slovenia.

Dr. **Josip Bronić**, Ruđer Bošković Institute, Zagreb, Croatia.

Dr. **Tatjana Antonić-Jelić**, Ruđer Bošković Institute, Zagreb, Croatia.

Scientific Committee

Prof. **Đorđe Stojaković**, University of Belgrade, Faculty of Technology and Metallurgy, Serbia.

Prof. **Vera Dondur**, University of Belgrade, Faculty of Physical Chemisty, Serbia.

Prof. **Dragana Životić**, University of Belgrade, Faculty of Mining and Geology, Serbia.

Dr. **Ana Radosavljević-Mihajlović**, Institute for Technology of Nuclear and Other Mineral Raw Materials, Serbia.

Prof. **Aleksandar Simić**, University of Belgrade, Faculty of Agriculture, Serbia.

Dr. **Sanja Jevtić**, University of Belgrade, Faculty of Technology and Metallurgy, Serbia.

Dr. **Vladislav Rac**, University of Belgrade, Faculty of Agriculture, Serbia.

Prof. **Gregor Mali**, National Institute of Chemistry, Ljubljana, Slovenia.

Dr. **Matjaž Mazaj**, National Institute of Chemistry, Ljubljana, Slovenia.

Dr. **Alenka Ristić**, National Institute of Chemistry, Ljubljana, Slovenia.

Dr. **Tomislav Ivanković**, University of Zagreb, Faculty of Science, Croatia.

Prof. **Vesna Tomašić**, University of Zagreb, Faculty of Chemical Engineering and Technology, Croatia.

Dr. **Marin Ugrina**, University of Split, Faculty of Chemistry and Technology, Croatia.

Dr. **Ana Palčić**, Ruđer Bošković Institute, Zagreb, Croatia.

CIP- Каталогизација у публикацији

Народна библиотека Србије

549.67(082)

SERBIAN-Croatian-Slovenian Symposium on Zeolites (8 ; 2019 ; Beograd)
Proceedings of the 8th Serbian-Croatian-Slovenian Symposium on Zeolites, 3 - 5 October 2019, Belgrade, Serbia / organizers Serbian Zeolite Association ... [et al.] ; [editors Vesna Rakić, Jasna Hrenović, Alenka Ristić]. - Belgrade : Serbian Zeolite Association, 2019 (Belgrade : Development and Research Centre of Graphical Engineering, Faculty of Technology and Metallurgy). - VIII, 158 str. : ilustr. ; 30 cm

Tiraž 80. - Bibliografija uz svaki rad. - Registar.

ISBN 978-86-916637-2-8 (SZA)

a) Зеолити -- Зборници

COBISS.SR-ID 279616268

AN INVESTIGATION OF IBUPROFEN RELEASE FROM A CLINOPTILOLITIC ZEOLITIC TUFF MODIFIED WITH CATIONIC SURFACTANT

Danina Krajišnik[1], Bojan Čalija[1], Ljiljana Djekić[1], Vladimir Dobričić[2], Aleksandra Daković[3]
[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade-Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia
[2]Department of Pharmaceutical Chemistry, University of Belgrade-Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia
[3]Institute for Technology of Nuclear and Other Mineral Raw Materials, Franche d'Epere 86, 110000 Belgrade, Serbia
E-mail: danina@pharmacy.bg.ac.rs

ABSTRACT

The biopharmaceutical performance of ibuprofen – surfactant modified zeolitic tuff composites prepared in a one-step preparation procedure was evaluated by *in vitro* drug release experiments. Furthermore, to reveal stability upon desorption, the release of surfactant was also investigated. Results showed that the prolonged ibuprofen release from the tested composites was achieved over a period of 8 h. The analysis of the drug release profiles indicated to a combination of drug diffusion and ion-exchange as predominant release mechanisms. A negligible surfactant desorption demonstrated during release testing alongside with non-toxic nature of these materials may encourages further researches of these functionalized mineral materials as prospective excipients for pharmaceutical application.

Keywords: clinoptilolitic zeolitic tuff, cationic surfactant, ibuprofen, release, mathematical modelling.

INTRODUCTION

The potential use of natural or surface-modified zeolites in biomedical applications, namely as active ingredients in medical devices, drug carriers (for i.e. antibiotics or nonsteroidal anti-inflammatory drugs (NSAIDs)), wound healing accelerators, and several other applications, has emerged as a promising field during the last few years [1-3]. The adsorption of cationic surfactants at the solid–liquid interface may modify the properties of the solid (zeolitic) surface and favors the uptake of molecules from solution. Interactions of cationic surfactants with natural zeolites have been extensively studied since surfactant-modified zeolites (SMZs) proved to be excellent adsorbents for various drug molecules contributing the possibility of their application in drug delivery[4].

Usually, investigation of a drug molecule adsorption includes a two-step preparation procedure of drug-SMZs composites. According to this procedure, in the first step SMZs were prepared (in accordance with external cation-exchange capacity (ECEC) of a starting mineral) and then in the second step drug-SMZs were obtained by a drug adsorption on SMZs at an appropriate solid to liquid ratio [1,5]. In our previous contribution, a study of direct method of drug-SMZs composites preparation using ibuprofen (as representative of NSAIDs; practically insoluble in water) was performed [6]. The influence of cationic surfactant:drug molar ratio on adsorption properties of clinoptilolitic zeolitic tuff was investigated by photon correlation spectroscopy, zeta potential and FT-IR analysis.

In the present study, ibuprofen release testing from drug-SMZs composites was performed with the aim of determining the possibility of their application as prospective drug carriers for NSAIDs. Additionally, the surfactant release from drug-SMZs composites was

also investigated in order to elucidate stability and safety of these composites under physiological conditions.

EXPERIMENTAL

Hexadecyltrimethylammonium bromide (HB)(Sigma-Aldrich, St. Louis, MO, USA) and ibuprofen (IBU) (Ph. Eur. quality) were used for preparation of composites by the direct method. During the preparation procedure, initial clinoptilolitic zeolitic tuff from Zlatokop deposit (Serbia) was treated with solutions comprising HB in amounts equivalent to 100, 200 and 300 % of its ECEC. In the surfactant solutions IBU was solubilized at the same drug:surfactant molar ratio. The conditions for preparation of the composites are given elsewhere [6]. The amounts of HB and IBU adsorbed after the preparation procedure were calculated from the difference between initial and final concentrations in the supernatants after equilibrium, assayed by HPLC analysis. The obtained drug/modified zeolites composites were denoted as ZHB-10 IBU/DM, ZHB-20 IBU/DM and ZHB-30 IBU/DM.

The biopharmaceutical performance of drug-SMZs composites was evaluated by *in vitro* dissolution experiments. The flat-faced punches with a diameter of 11 mm were used to compress the prepared composites into 300 mg comprimates using an eccentric compressing machine (EKO Korsch, Berlin, Germany). The release of both IBU and HB from the comprimates was carried out in a rotating paddle apparatus (Erweka DT 600, Heusenstamm, Germany) in 600 ml of phosphate buffer solution pH 7.2(USP) during 8 hours. The rotating paddle was 50 rpm and the temperature was maintained at 37 ± 0.5 °C. All data-points (after 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min) were determined as the average value for three independent measurements. The amounts of IBU and HB released were determined by HPLC analysis and expressed as the percentage of drug and surfactant contents in the tested composites.

Concentration of IBU was determined on Dionex Ultimate 3000 system (Thermo Fisher Scientific, Dreieich, Germany) equipped with Dionex Ultimate 3000 quaternary pump, autosampler and DAD detector. The column chosen was ZorbaxExtend-C18 (150 mm × 4.6 mm, 5 μm particle size). The mobile phase consisted of methanol and water (80:20, V/V) and pH was adjusted to 2.5 with phosphoric acid. The column temperature was 30 ºC, the flow rate was 1 ml/min and the UV detection was performed at 210 nm. HB concentration was determined using LC-MS/MS method. The analysis was performed on UHPLC chromatograph ACELLA (Thermo Fisher Scientific Inc., Madison, WI, USA), coupled to a triple quadrupole mass spectrometer TSQ Quantum Access MAX (Thermo Fisher Scientific Inc., Madison, WI, USA) with heated electrospray ionization (HESI) interface. The column wasAcclaim HILIC-10 (150 mm x 4.6 mm, 3μm particle size) from Thermo Fisher Scientific Inc(Sunnyvale, CA, USA). Mobile phase was acetonitrile/20 mM ammonium acetate = 50:50 (V/V), flow rate was 0.5 ml min^{-1}, column temperature was set to 30 ºC and injection volume was 5 μl.

To evaluate the mechanism of IBU release, the release data were fitted by mathematical models describing various kinetic [7,8]. The model applicability was based on a comparison of the coefficient of determination (r^2). The amount of HB released was determined after 30, 60, 120, 240 and 480 min.

RESULTS AND DISCUSSION

Dissolution profiles of ZHB 10-30 IBU/DM composites are shown in Figure 1. Prolonged release of IBU from all the three composites over 8 h was achieved. For ZHB-10 IBU/DM and ZHB-30 IBU/DM composites up to ~ 40 % of the drug was released, while a lower amount (~ 30%) of IBU was released from ZHB-20 IBU/DM composite. The adsorbed

amounts of IBU on the prepared composites were lower for ZHB-10 IBU/DM (19.6 mg/g) compared to approximately the same amounts for ZHB-20 IBU/DM and ZHB-30 IBU/DM (39.06 mg/g and 40.32 mg/g, respectively), as previously reported [6].

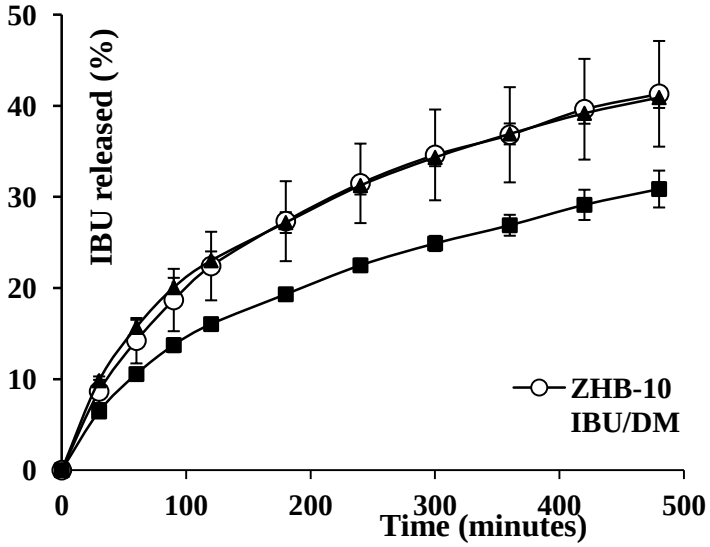

Figure 1. *In vitro* release profiles of IBU from the ZHB 10-30 IBU/DM composites.

The observed alterations in the drug release could be attributed to a different surfactant coverage and organization at the mineral surface. The investigated composites demonstrated much slower IBU release compared with drug-SMZs, prepared by modification of phillipsite-rich tuff with HB in amount (equivalent to 200 % of ECEC) to obtain the complete bilayer formation of surfactant and subsequent IBU adsorption [5].The maximum loaded drug amount in these phillipsite-IBU composites was ~ 29 mg/g and 85-90 % of IBU was released within the first 60 min. The values of the fitted parameters by different mathematical models used to describe IBU dissolution curves are listed in Table 1.

Table 1. Values of fitted parameters by different mathematical models for IBU release from the ZHB10-30 IBU/DM composites.

Model	**Fitted parameters**	**Sample**		
		ZHB-10 IBU/DM	ZHB-20 IBU/DM	ZHB-30 IBU/DM
Zero order	r^2	0.9340	0.9536	0.9367
	k_0	0.0686	0.0509	0.0645
First order	r^2	0.9603	0.9696	0.9620
	k_1	0.0009	0.0006	0.0009
Higuchi	r^2	0.9897	0.9962	0.9906
	k_h	1.9805	1.4587	1.8593
Korsmayer-Peppas	r^2	0.9855	0.9908	0.9875
	k	3.5640	3.5220	3.1500
	n	0.5520	0.5468	0.4985
Bhaskar	r^2	0.9856	0.9906	0.9862
	k_b	0.0039	0.0026	0.0036
Hixon-Crowell	r^2	0.9522	0.9646	0.9543
	k_c	0.0013	0.0009	0.0012

For all the three composites the better fitting r^2 were obtained by the Higuchi model, followed by Korsmeyer-Peppas and the Bhaskar models, which indicates to a combination of drug

diffusion and ion exchange as predominant drug release mechanisms. The surfactant release (Table 2) from the drug-SMZs composites was less than 5 %, demonstrating good stability in physiological conditions.

Table 2. HB released (%) from the ZHB10-30 IBU/DM composites during testing period.

Time	***HB released (%)***		
(minutes)	ZHB-10 IBU/DM	ZHB-20 IBU/DM	ZHB-30 IBU/DM
30	0.09	0.08	0.09
60	0.11	0.21	0.20
120	0.20	2.17	0.60
240	0.59	2.95	1.28
480	3.38	3.92	1.99

CONCLUSION

The study demonstrated prolonged ibuprofen release over 8 h from the clinoptilolitic zeolitic tuff modified with hexadecyltrimethylammonium bromide.The investigated drug release profiles indicated that the passive drug diffusion is not the sole mechanism of drug release. Previously demonstrated non-toxic nature of these zeolitic materials, accompanied by the results of this study for drug and surfactant release, encourages further research of these functionalized mineral materials as prospective drug carriers.

ACKNOWLEDGEMENT

This work was realized within the frameworks of the projects TR 34031, OI 172018 and III 46010 supported by The Ministry of Education and Science of the Republic of Serbia.

REFERENCES

[1] D. Krajišnik, A. Daković, J. Milić and M. Marković, Chapter 2 *"Zeolites as potential drug carriers"*, in: *"Modified Clay and Zeolite Nanocomposite Materials: Environmental and Pharmaceutical Applications"*, M. Mercurio, B. Sarkar and A. Langella (Eds.),Elsevier, Amsterdam, 2019, 27-56.

[2] G.P. Barbosa, H.S. Debone, P. Severino, E.B. Souto and C.F. da Silva, Mater. *Sci. Eng. C*, 2016, **60**, 246-254.

[3] J. Cervini-Silva, A. Nieto-Camacho, S. Kaufhold, K. Ufer, E. Palacios, A. Montoya and W. Dathe, *Micropor. Mesopor. Mater.*, 2016, **228**, 207-214.

[4] J. Milić, A. Daković, D. Krajišnik and G.E. Rottinghaus, Chapter 10 *"Modified natural zeolites-functional characterization and biopharmaceutical application"*in: *"Advanced Heathcare Materials"*, A. Tiwari (Ed.), John Wiley & Sons, Inc. Hoboken, New Jersey, and Scrivener Publishing LLC, Salem, Massachusetts, 2014, 361-403.

[5] M. Mercurio, F. Izzo, A. Langella, C. Grifa, C. Germinario, A. Daković, P. Aprea, R. Pasquino, P. Cappelletti, F.S. Graziano and B. de Gennaro, *Am. Mineral.*, 2018, **103,**700-710.

[6] D. Krajišnik, B. Čalija, Lj. Djekić, V. Dobričić, A. Daković, M. Marković and J. Milić, Proceedings of the 10th International Conference on the Occurrence, Properties and Utilization of Natural Zeolites, Cracow, Poland, 2018, 191-192.

[7] P. Costa and J.M.S. Lobo, *Eur. J. Pharm. Sci*., 2001, **13,** 123-133.

[8] L. Perioli, T. Posati, M. Nocchetti, F. Bellezza, U. Costantino and A. Cipiciani, *Appl. Clay Sci.*, 2011, **53,** 374-378.