Review

of prof. Denitsa Yancheva Pantaleeva, PhD,
Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences,
Laboratory of Structural Organic Analysis, member of the scientific jury

regarding**:** The quality of Doctoral Thesis in the field of higher education: 4. "Natural Sciences, Mathematics and Informatics"; Professional Field: 4.2. Chemical Sciences, Scientific Specialty: Organic Chemistry, Author: Prof. Dr. Margarita Dimitrova Popova, Institute of Organic Chemistry with Centre for Phytochemistry – Bulgarian academy of sciences. Topic: "Novel approaches in the preparation of nanoporous materials with application as catalysts or drug carriers"

1. Subject of review

The set of documents submitted by the candidate, Prof. Dr. Margarita Popova, includes: CV (European standard), DSc thesis, thesis abstract (in Bulgarian and English), reference for compliance with the criteria for the scientific degree "Doctor of Sciences", copy of PhD diploma, 28 publications in scientific journals, 37 abstracts from conference presentations, list of citations, and information about participation in research projects related to the thesis topic. The documents are prepared according to the requirements of the Regulations for the Development of Academic Staff of the Institute of Organic Chemistry with the Centre of Phytochemistry (IOCCP) – BAS.
The materials not only fulfill all criteria specified in the Law for the Development of Academic Staff in the Republic of Bulgaria, the National regulations for the application of the law as well as the corresponding Regulations of the Institute of Organic Chemistry with the Centre of Phytochemistry (IOCCP) - BAS, for the scientific degree "Doctor of Sciences", but strongly exceed the minimum requirements: by 550 points in category D (publications) and by 1286 in category E (citations by other authors). The DSc thesis is supported by 28 scientific publications in journals from quartile Q1, cited more than 600 times by other authors.

2. Brief Biographical data

Prof. Dr. Margarita Popova has graduated the University of Chemical Technology and Metallurgy – Sofia in 1989 as A Master in Organic Synthesis and Fuels and after a short period of working in industrial environment, she continued her education as a phD student (1991-1998) at the IOCCP, Bulgarian Academy of Sciences. She has defended her PhD thesis in 1998 and

developed further her scientific career at IOCCP until present consecutively occupying all academic positions from a chemist (1998-2000), assistant professor (2000-2004), senior assistant professor (2004 г. – 2011), associate professor (2011-2017) and professor (2017 – until present).

3. Topicality of the thesis and relevance of the research aims and tasks

The presented research is focused on the development of novel approaches for preparation of nanoporous materials, characterization of the new materials and tailoring of their properties for application as catalysts or drug carriers. The research merges several hot topic scientific areas such as the nanotechnology, green chemistry and medicinal chemistry. Moreover, it relies on an extensive material characterization by a broad spectrum of analytical techniques able to provide in-depth knowledge of their properties and function. Therefore, the topic of the research is of great scientific importance and the methodology selected to achieve the goals seems appropriate and reliable. A good evidence for the topically of the research is the large number of citations of the publications supporting the thesis results.

4. Familiarity of the author with the scientific problem

The literature review provided in the first section of the DSc thesis demonstrate an excellent knowledge of the candidate on the current state-of-art in the flied of the preparation and applications of nanomaterials, and particularly the nanoporous materials, as well as complete oxidation of volatile organic compounds and strategies for preparation of novel drug delivery systems. The candidate has analyzed and summarized the most important publications on the topic, including the recent ones and crucial European regulations in a condensed and concise manner. The summery provided at the end of the Section is very helpful to my opinion and contributes significantly to define accurately the research aims and the tasks for their completion.

5. Methodology of the study

The chosen research methodology has granted completion of the tasks defined in the DSc thesis and achievement of the research aims. It has comprised briefly in the following steps:

1. *Preparation of nanoporous materials*

1.1. Various approaches for preparation of a large number of versatile nanoporous catalytic systems were applied, including: modification of mesoporous silicas and zeolites by the preparation method (direct synthesis, impregnation, reaction in solid phase), by variation of the

amount of metal oxides, type of modifying metal salts, modification media, use of one or more metals (Cu, Co, Ti, Fe, Cu-Cr, Ti-Fe, Cu-Fe, Co-Fe etc). The various approaches used allowed preparation of two groups of catalytic systems: monocomponent and bicomponent catalytic systems.

1.2. Various approaches for preparation of DDS based on mesoporous silicas with different structure and surface functionality were applied, namely amine functionalization of spherical MCM-41 and SBA-15, carboxylic functionalization of MCM-41 and SBA-15 materials, mesoporous pure silica (spherical MCM-41 and KIL-2) and nanosized zeolite BEA, functionalization of MCM-41, SBA-15 and SBA-16 mesoporous silicas by Zn, incorporation of Ag in mesoporous silica SBA-15 and MCM-41 carriers, zeolites, two-layer polymer coating of SBA-15, SBA-16 and MCM-41, functionalization of KIT-6 and KIL-2 mesoporous silica/polymer composites by amino groups, functionalization of mesoporous ZSM-5/KIT-6 and ZSM-5/SBA15 polymer nanocomposites with sulfonic and carboxylic groups, and functionalization of bicomponent drug system based on magnetic nanoporous silicate nanoparticles with sulfonic groups

2. Methods and Instrumental Techniques

The prepared materials were extensively characterized by combined experimental spectral and analytical techniques. Atomic absorption spectroscopy (AAS) was used for determination of the chemical compositions of the template-free samples, while powder X-ray diffraction and solid-state NMR spectroscopy – for characterization of the crystalline structure of the materials and TEM and AFM imaging – for the morphology of the materials. The local environment of the incorporated metals is obtained through FTIR, UV/Vis, Mossbauer, EPR and temperature-programmed reduction (TPR) experiments. Nitrogen physisorption measurements were applied for determination of the pore size. The surface active centers were investigated by means of FT-IR spectroscopy.

3. Catalytic and adsorption experiments

The catalytic activity of the newly prepared materials was monitored by model reaction of toluene oxidation (VOC oxidation), CO_2 adsorption in static conditions and dynamic conditions. The conducted studies on the catalytic activity has demonstrated high activity and stability of the prepared mono- and bicomponent catalysts resulting in improved toluene conversion. The catalytic study has also provided important structure-activity relationships for the modified materials, their catalytic activity and mechanism of oxidation related to the presence of different active centers in the catalyst. Based on the results from the catalytic study it was possible to

outline the synthetic approaches and modifications leading to the strongest enhancement of the catalytic properties.

4. Drug loading and in-vitro investigations of the technological, biopharmaceutical and pharmacological properties of the obtained drug-delivery systems

The adsorption capacity and modified release rate of the newly synthesized DDS, based on mesoporous silicas with different structure and surface functionality, were studied by loading with several model drugs – ibuprofen, sulfadiazine, resveratrol, mesalazine, quercetin, propolis, verapamil, mitoxantrone and prednisolone. As important step toward application in the medicinal practice, the cytotoxicity of the new DDS systems was also studied.

6. Characterization and evaluation of the thesis

The dissertation is written on 215 pages, of which 204 pages are text with 53 tables, 173 figures and 18 schemes, references, conclusions and contributions. The thesis is structured as follows: Introduction, Aim and tasks of the thesis, Materials and methods, Results, References, Conclusions and contributions of the thesis and Appendix. The references cited in the thesis are more than 250 (ordered by author names).

The *Introduction* section presents an overview of the current literature on the preparation and applications of nanomaterials with emphasis on nanoporous materials, catalysts for complete oxidation of volatile organic compounds and strategies for preparation of novel drug delivery systems.

In the *Aims and tasks of the thesis* along with presenting the aim of the study – development of novel approaches for preparation of new nanosized materials with tailored properties as catalysts for processes related to the protection of clean air and drug carriers ensuring the controlled delivery of drugs in oral, dermal or parenteral systems; two groups of research tasks relevant to the research aims are defined: (i) development of catalysts for total oxidation of volatile organic compounds (VOCs) based on mono- and dicomponent metal oxide modified mesoporous silicas and zeolites as an ecological process for the protection of clean air; and (ii) development of new procedures for synthesis and modification of mesoporous silicas and zeolites with predetermined structural and surface properties, hybrid mesoporous silica-polymer carriers and nanoscale magnetic iron oxide/silica composites and their application for the preparation of drug delivery systems (DDS).

The *Materials and Methods* section presents all above-described methods of preparation and modification of the nanoporous materials, the methods used for characterization of the structure, properties, catalytic activity, drug loading and in-vitro drug release experiments.

The *Results* section (consisting in 164 pages) presents in details the preparation and study of Co-containing MCM-41, SBA-15 and KIL-2 catalysts, Fe-functionalized silica nanoparticles with textural mesoporosity, Ti-modified MCM-41 catalysts, Ag-nanoparticles confined in nanoporous silica catalysts as monocomponent catalytic systems; Cr- and Cu-modified SiO and SBA-15 catalysts, Cu- and Fe-containing SBA-15 and SBA-16 materials, CuO nanocrystals and Cu-oxo-Fe clusters on silica support, ferrite-containing MCM-41 and SBA-15 catalysts, Ti- and Fe-modified MCM-41 catalysts, Co- and Fe-containing Ti-MCM-41 catalysts, Cu- and Co-modified coal ash zeolites as bicomponent catalytic systems. In the group of monocomponent catalysts, the nature and dispersion of the formed metal oxide particles were controlled through interaction between the metal oxide nanoparticles and the mesoporous silicas or zeolites. In the group of bicomponent catalysts - mixed metal oxides with new physicochemical properties influencing their catalytic activity were formed by incorporation of additional metal oxide species. The catalytic studies demonstrated significant advances in the catalytic properties of the new materials.

The section also covers the development of DDS based on mesoporous silicas with different structure and surface functionality. In this part, the study was focused on the effect of amine functionalization of spherical MCM-41 and SBA-15 on controlled Ibuprofen release and, the preparation of carboxylic modified spherical mesoporous silicas as drug delivery carriers, preparation of resveratrol loaded nanoporous silica materials with different structures, preparation of efficient quercetin delivery system on Zn-modified mesoporous MCM41, SBA-16 and SBA-15 silica carriers, nanostructured Ag-silica materials as potential propolis carriers, Ag and sulfadiazine loaded nanostructured silica materials as potential replacement of silver sulfadiazine, and solid-state encapsulation of Ag and sulfadiazine on zeolite Y carrier.

A second approach for development of DDS was applied based on hybridization of mesoporous silica carriers with stimuli responsive polymers. Within this strategy, a new method for preparation of delivery systems of poorly soluble drugs on the basis of functionalized mesoporous MCM-41 was established. The drug loading and delivery of several new materials (polymer coated SBA-16 systems, polymer-coated mesoporous silica nanoparticles, amino-modified KIT-6 and KIL-2 mesoporous silica/polymer composites, and mesoporous ZSM-5/KIT-6 and ZSM5/SBA-15 polymer nanocomposites) was studied and allowed pH-dependent delivery of mesalazine, controlled and targeted delivery of mesalazine, sulfasalazine, and quercetine.

Furthermore, new magnetic nanoporous silica nanoparticles were developed and proved to be efficient carriers in dual delivery systems containing anti-tumor and anti-inflammatory drugs frequently used in antitumor therapy. Each subsection in the *Results* concludes with a summary and a conclusion emphasizing the most important achievements in the relevant group of results.

The experimental data and original research results are systematically presented in the thesis supported by a detailed discussion at a high scientific level.

7. Contributions and significance of the development for science and practice

The DSc thesis of Prof. Dr. Popova presents a broad study covering all step from the preparation of nanoporous materials by novel approaches to the possibilities for their application in environmental protection and medicinal chemistry. Therefore, the results obtained in the study have interdisciplinary nature and high potential for practical application. The most significant contributions of the DSc thesis can be summarized in the following groups:

- Clarification of the role of the modification procedure and the support peculiarities, optimal ratio for the modification with different metal oxides in bicomponent catalytic systems, and pretreatment procedure for the preparation of different monocomponent and bicomponent catalysts with high catalytic activity, selectivity and stability in the process of total oxidation of VOC and VOC mixture;
- Development of dual adsorption/catalytic system for VOC oxidation and CO_2 adsorption on the basis of cheap fly ash zeolites for maximum environmental effect;
- Implementation of the ninhydrin reaction for the quantitative determination of primary amines in heterogeneous phase, which allows optimization of the extent of modification of mesoporous silicas with amino groups;
- Development of a novel route to modify the mesoporous MCM-41 and SBA-15 materials with carboxylic, applying mild conditions combined with less toxic reagents;
- Demonstration of the efficiency of solid-state procedure for loading of the medical compounds with low solubility and for stabilization of their bioactive form;
- Development of various drug delivery systems based on mesoporous silicas with different structure and surface functionality, able to carry and deliver drugs of different chemical classes.

8. Assessment of the publications related with the thesis.

The total number of publications related with the thesis is 28. All of them are published in journals indexed in Scopus and Web of Science, with high impact factors and ranked in the highest category – Q1 of the relevant scientific areas. According to the list of citations provided by the author, the papers are cited 678 times by other authors.

9. Personal participation of the author

The leading role of Prof. Dr. Popova in the design of the study, gathering of the experimental data, analysis and interpretation of the results are well demonstrated by her leading position and correspondence in the majority of the publications related to her DSc thesis.

10. Thesis abstract

The abstract in Bulgarian and English accurately and completely reflects the materials of the dissertation. It contains all main results, conclusions and contributions and the relevant publication, citation and project participation lists supporting the DSc thesis. The abstracts are prepared according to the requirements of the IOCCP-BAS.

11. Critical remarks and recommendations

I have no critical remarks or recommendations.

12. Personal impressions

As a colleague of Prof. Dr. Popova, I have excellent personal impressions of her as a scientist with profound knowledge, high academic achievements, and advanced training and organizational skills.

13. Recommendations for future use of dissertation results and achievements

As mentioned above, I believe that at present prof. Dr. Popova has acquired a high-level competence within a scientific area of great interest and advanced skills in training of young researchers. Therefore, I cordially recommend her to continue in future her work in the field of the new nanoporous materials with tailored properties and successfully expand this field of research in Bulgaria by attracting new young colleagues within her research group.

CONCLUSION

The dissertation is based on robust scientific results and written at high scientific level complying with all requirements specified in the Law for the Development of Academic Staff in the Republic of Bulgaria, the National regulations for the application of the law as well as the corresponding Regulations of the Institute of Organic Chemistry with the Centre of Phytochemistry (IOCCP) - BAS, for the scientific degree "Doctor of Sciences". This dissertation has an original contribution to the organic chemistry, material science, environmental science and medicinal chemistry and offers good prospects for practical application of the obtained scientific results. In view of the

above, I give my positive assessment of the research presented by the dissertation, abstracts, results and contributions described above, and recommend to the Scientific Jury to award the degree of Doctor of Science to Prof. Dr. Margarita Popova in the field of higher education: 4. "Natural Sciences, Mathematics and Informatics"; Professional Field: 4.2. Chemical Sciences, Scientific Specialty: Organic Chemistry.

20.09.2021.
Sofia

Reviewer: .....
(Prof. Dr. Denitsa Pantaleeva)