REVIEW

by Prof. Tatyana Todorova Tabakova, PhD, Institute of Catalysis – BAS

of the dissertation for awarding the degree "Doctor of Science"
in the Field of higher education 4.0. "Natural Sciences",
Professional field 4.2. Chemical Sciences,
scientific specialty "Organic Chemistry"

Author: Prof. Margarita Dimitrova Popova, PhD, Institute of Organic Chemistry with Centre of Phytochemistry – BAS

Topic: Novel approaches in the preparation of nanoporous materials with application as catalysts or drug carriers

1. Subject of review

The set of documents presented by Prof. Dr. Margarita Dimitrova Popova is in accordance with the Rules for development of academic staff of Institute of Organic Chemistry with Centre of Phytochemistry – BAS (IOCCP – BAS) and meets the criteria of IOCCP – BAS for acquiring the scientific degree "Doctor of Sciences".

The materials are prepared very carefully and contain the necessary information. The report on the minimum requirements shows that for all groups of indicators the points fulfilled by Prof. Popova exceed many times the required ones, namely, on indicator D reflecting the publishing activity are declared 700 in comparison with the required 150, and in group E referring to the citations in scientific journals indexed by Web of Science and Scopus are fulfilled 1356 points at a limit of 200 points.

In the dissertation thesis are summarized 28 scientific publications from the last 14 years. The results included in the thesis were obtained during the implementation of 5 research projects funded by the Bulgarian National Science Fund, a project for establishment of a Center of Excellence „National Centre for Mechatronics and Clean Technologies", National Scientific Program „Low-carbon energy for transport and domestic use" (E+) and 3 projects for Inter-academic exchange between Bulgarian Academy of Sciences and Hungarian Academy of Sciences. In total 37 oral or poster contributions are presented at scientific conferences in Bulgaria and abroad. A detailed list (authors, title, link) is attached with 678 citations of the papers included in the dissertation.

2. Brief biographical data

Prof. Margarita Popova graduated from the Higher Institute of Chemical Technology – Sofia (currently University of Chemical Technology and Metallurgy) in 1989 with distinction and qualification „chemical engineer" in the specialty "Technology for organic synthesis and fuels". She has been working at IOCCP – BAS since 1991. In 1998 she defended her dissertation entitled „Conversion of methanol to light alkenes on isomorphically substituted aluminophosphate molecular sieves with different acidity" and was awarded PhD degree. She has successively worked as Assistant (2000 – 2004) and Assistant Professor (2004 – 2011). She acquired the academic position "Associate Professor" in 2011. After winning a competition in 2017, she occupied the academic position of "Professor". The results of Prof. Popova's research have been published in

110 scientific publications in reputable scientific journals with impact factor and have been cited more than 1400 times, according to the Scopus database. She has participated in the implementation of more than 20 competitive projects funded by the Bulgarian National Science Fund (coordinator of 5 of them) and 8 projects in the frame of Inter-academic exchange (coordinator of 4 of them). Results of the investigations, carried out with the participation of Prof. Popova, have been presented at 67 international events, incl. 35 lectures at conferences and invited lectures by scientific institutions. Prof. Popova is scientific secretary of IOCCF since 2012. In 2021 she was elected scientific secretary of BAS in the field of „Nanosciences, new materials and technologies". She is Bulgarian representative in the Management committee of 3 COST Actions and European Federation of catalytic societies.

3. Relevance of the topic and expediency of the objectives and tasks

The doctoral thesis of Prof. Popova is devoted to the application of advanced approaches in the development of new efficient and economically profitable materials with defined properties and application in processes that are related to improvement of quality of life, such as environmental protection by abatement of volatile organic compounds in the atmosphere and protection of human health by development of new drug delivery systems.

The aim of the study and the tasks planned for its achievement define this thesis as very topical and of high scientific and applied significance.

4. Knowledge of the problem

The introduction of the dissertation showed excellent knowledge of the current state of the studied problems. After assessment of the potential of nanotechnologies and nanomaterials for the development of various areas of human life, Prof. Popova revealed their importance in heterogeneous catalysis and nanomedicine. The unique properties of the modified mesoporous silicas and mesoporous metal oxides, which determine their high activity and selectivity in a number of catalytic processes, are subject of increasing research interest. The ever-increasing requirements for limiting the concentration of volatile organic compounds (VOCs) in gaseous emissions due to real threats to the environment and human health determine the relevance of the development of heterogeneous nanoscale catalysts with predetermined structural and compositional characteristics.

A relatively new and rapidly developing direction is the application of mesoporous silicates in the development of systems for controlled delivery and release of medicinal substances. In-depth knowledge of the specific structural and physicochemical properties of this type of silicas allowed Prof. Popova to prove his high competence as one of the Bulgarian researchers who started the first research in this attractive and innovative topic for the country, which is currently developed only in IOCCF – BAS.

5. Research methodology

The research methodology includes the application of new approaches for the synthesis of nanomaterials with desired morphology, particle size and texture characteristics, and is a targeted strategy for successful application of these materials in various catalytic processes and as carriers in drug delivery systems for treatment and diagnosis. Suitable synthetic techniques for modification of mesoporous silicates with metal/metal oxides or organic functional groups are developed and optimized in the dissertation. A successful solution to a key challenge in heterogeneous catalysis

has been found, such as the control of the distribution of multicomponent active sites on the mesoporous surface, which is directly related to the efficiency of catalytic materials.

New approaches have been applied to obtain drug delivery systems with modified release based on mesoporous materials. New procedures have been used for surface functionalization and control of the morphology and particle size of mesoporous silicates. An attractive strategy is the modification of the surface of the particles with ligands for the purpose of active targeted drug delivery and release. Very original approach is the incorporation of magnetic nanocrystals into mesoporous silicate structures, which allows the drug to be selectively delivered to a desired organ or tissue in the body.

An in-depth study of the relationship between the preparation method or modification routes and predetermined properties and functionalities was performed to obtain the desired structures with controllable catalytic and drug delivery properties, using a large number of physicochemical methods. It can definitely be said that the chosen methodology is realistic and addresses well objectives and tasks set in the dissertation.

6. Characterization and evaluation of dissertation

The dissertation is written in English on 215 pages and includes 173 figures, 53 tables, 18 diagrams. 287 literature sources are cited. In Introduction are pointed out the advantages of using modified mesoporous silicates or mesoporous metal oxides as catalysts for VOC elimination. Different mechanisms for obtaining mesoporous silicates are discussed. Special attention is paid to the influence of the synthesis and modification procedure on the textural, structural and catalytic properties. A critical review of the catalysts for complete oxidation of VOCs studied so far is presented. The factors determining the successful application of mesoporous silicates in the development of systems for controlled delivery and release of drugs are described. Approaches for obtaining drug delivery systems with modified-release based on mesoporous materials are analyzed. The possibility for surface functionalization and control of the morphology and particle size of mesoporous silicate materials is considered to solve the problems related to the low load efficiency and the rapid initial release of the included drug substance from the starting silicates.

Based on the excellent knowledge of the state of research on the problems and the conclusions about the unresolved issues and challenges, Prof. Popova clearly formulated the goal of the dissertation, the main objectives and the specific tasks for its achievement.

In Part 3 “Materials and methods” are described in detail the experimental conditions for new nanoporous materials synthesis, functionalization or modification by various procedures. A set of proper-selected modern physicochemical methods was used to characterize the obtained samples. Toluene was chosen as the test molecule to evaluate the catalytic activity for complete oxidation of VOCs. The measurement of the adsorption capacity with respect to CO_2 was used to evaluate the adsorption properties of some materials. The loading capacity of the drug substance was assessed through textural measurements and thermogravimetric analysis. By UV-Vis spectroscopy was monitored the release rate.

In the largest part “Results” are presented studies in two main areas: the development of catalysts for processes related to environmental protection and nanoporous materials for the preparation of new drug delivery systems. The description and analysis of the results related to the heterogeneous catalysts for complete VOCs oxidation include monocomponent and twocomponent

metal oxide-modified mesoporous silicates and zeolites. Transition metals such as Co, Cu, Fe, Cr, etc. were selected as a cost-efficient alternative of precious metals.

Experimental evidence is found for the influence of the method and conditions of synthesis, the amount and type of transition metal, on the interaction between metal oxide nanoparticles and mesoporous silicates and zeolites, which plays a decisive role in controlling the dispersion, reducibility and nature of formed metal oxide structures and active sites. The investigation of bicomponent catalytic systems is aimed at studying the influence of the structural features of carriers with different porous structures (SiO_2, SBA-15, SBA-16, KIL-2, MCM-41) on the state of supported nanoparticles. The effect of different methods for deposition and the ratio between two metal components on the surface, reductive and catalytic properties is analyzed. The results of the research of zeolites obtained from fly coal ash, a waste product generated by combustion of lignite coal in thermal power plants, are also described in detail. Due to their good adsorption and catalytic properties, these zeolites are used as carriers for copper or cobalt-containing catalysts with high efficiency for VOCs oxidation. The catalytic activity data of the catalysts developed in the present dissertation for complete oxidation of toluene are compared in a table. Based on this comparison the best-performing and most cost-effective catalyst is proposed.

A significant part of the dissertation is dedicated to the rational design of mesoporous silicates with appropriate pore topology, particle size, and morphology in order to use them as effective drug delivery systems. The effect of functionalization with amino and COOH groups or modification with Zn or Ag of nanoporous silicate materials with diverse structures on the controlled release of drug species with various applications was studied. The results of the successfully developed drug delivery systems based on hybrid mesoporous silicate-polymer carriers by post-synthetic modification with amino and amino/carboxyl groups and the application of a polymer coating are described in detail. The contributions of the candidate to the development of a bicomponent drug system based on new nanocomposites composed of magnetic and silicate nanoparticles are also summarized. It has been found that these nanocomposites are very promising in the development of delivery systems for antitumor drugs. The incorporation of magnetic nanocrystals into the structure of mesoporous silicas has been shown to be an effective approach for obtaining original drug delivery systems, allowing selective delivery and release of the drug substance into the target organ or tissue when an external magnetic field is applied.

After the cited references, the conclusions are summarized. They fully reflect the obtained results. The report on the contributions contains the scientific and scientific-applied achievements of the dissertation.

The following information is provided in the Appendix: (i) a list with a complete bibliographic description, incl. impact factor, rank, and citations of the publications included in the dissertation; (ii) a list containing authors, title and type of scientific forum in Bulgaria and abroad, where oral and poster reports have been presented; (iii) a list of projects in which implementation have been obtained the results included in the dissertation.

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

The contributions of the dissertation of Prof. Popova, containing new and original scientific information, as well as the extension of existing knowledge, are related to pioneering approaches in the application of procedures for synthesis of nanomaterials with desired morphological, structural, and textural properties, and the use of suitable methods for modification of mesoporous silicas with

metal/metal oxides or organic functional groups, which predetermines their successful application in two attractive fields – catalytic processes for environmental protection and carriers of drug delivery systems for treatment and diagnosis.

The development of effective (active, selective and stable) catalysts for complete VOCs oxidation has been achieved through:

- finding new data on the role of the modification procedure and the carrier peculiarities in the synthesis of monocomponent Co-, Fe-, Ti-, Ag-, Cr-, Cu- and twocomponent Cr/Cu, Cu/Fe, Co/Fe and Co/Ti mesoporous KIL-2, MSM-41, SBA-16 and SBA-15 silicas;
- establishment of the optimal ratio for modification with different metal oxides (Cu-Cr, CuFe, Co-Fe, Fe-Ti, Co-Ti) in the bicomponent catalytic systems;
- optimization of the catalytic properties as a result of an appropriate pretreatment procedure (temperature and gaseous medium);
- for the first time, silver nanoparticles located in the nanopores and on the outer surface of SBA-15were obtained and stabilized by ultra-short pulsed laser ablation. The activity for complete oxidation of toluene was demonstrated.

The contribution with a clear potential for practical application address a dual adsorption/catalytic system for VOC oxidation and CO_2 adsorption based on cheap zeolites synthesized from fly ash due to the economic benefit and the double ecological effect of waste ash from thermal power plants utilization.

Contributions related to drug delivery systems are as follows:

- development of novel routes for modification of mesoporous silicas with amino and carboxyl groups; For the first time, a reaction with ninhydrin is proposed for the quantitative determination of primary amines in a heterogeneous phase. This concept allows to optimize the degree of modification of mesoporous silicates with amino groups;
- carriers containing mesoporous silicas and external stimuli-responsive polymers are used as a base for the development of drug delivery systems for controlled and targeted delivery of anti-inflammatory drugs;
- for the first time is demonstrated that Ag sulfadiazine can be effectively replaced by sulfadiazine-loaded Ag-MCM-41, Ag-SBA-15, and AgY materials, thus significantly improving its water solubility and antimicrobial properties;
- verapamil delivery systems based on bimodal mesoporous ZSM-5/SBA-15 and ZSM-5/KIT-6 nanocomposites modified with -SO3H and -COOH groups is designed;
- A novelty is a procedure for obtaining magnetic nanoporous silica nanoparticles with spherical morphology, small particle sizes (around 100 nm) and high surface area (> 800 m_2/g), functionalized by sulfonic groups, which are effective carriers in delivery systems containing anti-tumor and an anti-inflammatory drug.

8. Evaluation of publications and personal contribution of the author

The results included in the thesis are reported in 28 articles published in reputable international journals. Confirmation of the high scientific level of the obtained results are the following issues: all the journals are ranked in quartile Q1, incl. one paper in Applied Catalysis B: Environmental (IF =16.68), which is top-ranking; total IF is 125.63, and average - 4.5. The interdisciplinary character of the research requires the participation of 4-5 co-authors, but the

leading role and contribution of Prof. Popova are indisputable, as she is the corresponding author of 18 of the publications.

The high number of citations, namely 678 (excluding self-citations of all coauthors), as well as the contributions presented at a large number of important international forums are a clear confirmation of the significance of the results obtained.

9. Abstract

The abstract is very well prepared and reflects fully and correctly the research results. It complies with the requirements of the Regulations for the conditions and order for acquiring academic degrees and for occupying academic positions at IOCCF-BAS. After a short introduction, the objectives and main tasks are formulated. The main experimental results are described and discussed. The general conclusions and contributions correspond to the conclusions made for the new approaches developed in the dissertation for the synthesis of nanomaterials with defined properties for use in various catalytic processes and as carriers of drugs for treatment and diagnosis.

10. Critical remarks and recommendations

I have no critical remarks about the research. All results have been published in renowned journals and have passed the critical evaluation of experts in the relevant fields.

11. Personal impressions

I know Prof. Popova personally and I have excellent impressions of her qualities as a scientist and colleague. Her hard-working ability, passion, and complete dedication to achieving the scientific goals are remarkable. High competence and expertise, wide scope of scientific interests and creativity are the basis of her original and innovative research and achieved results.

CONCLUSION

The doctoral thesis of Prof. Dr. Margarita Popova contains scientific and applied research results, which represent an original contribution to the science and meet all the requirements of the Law for the development of the academic staff in the Republic of Bulgaria, the Regulations for the implementation of the Law for the development of the academic staff, and the Regulations for the implementation of this law of the Bulgarian Academy of Sciences. The presented materials and the dissertation results are in full compliance with the specific requirements of the Regulation for the application of the Law for the development of the academic staff, adopted of the IOCCP-BAS.

The doctoral thesis shows that Prof. Dr. Margarita Popova has in-depth theoretical knowledge and professional skills in the scientific specialty “Organic Chemistry”, demonstrating qualities and abilities for conducting research with obtaining original and significant scientific contributions.

Based on the above and my excellent personal impressions, I convincingly give my positive assessment of the conducted research presented by the dissertation, abstract, achieved results and contributions, and propose to the Honorable Scientific Jury to award the degree “Doctor of Sciences” of Prof. Dr. Margarita Popova in a field of higher education „Natural Sciences“, professional field „Chemical Sciences“, scientific specialty „Organic Chemistry”.

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/Prof. Tatyana Tabakova/