R E V I E W

on a dissertation entitled:

„Novel approaches in the preparation of nanoporous materials with application as catalysts or drug carriers",

submitted for the scientific degree „Doctor of Sciences" (DSc)
in Professional field 4.2 „Chemical Sciences" (Organic Chemistry),
candidate: Prof. Margarita Dimitrova Popova, PhD

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Biographical data

Margarita Dimitrova Popova graduated in 1989 from the University of Chemical Technology and Metallurgy, Sofia, with a Master degree in Organic Synthesis and Fuels (chemical engineer). She received a Ph.D. degree in 1998 and was appointed as a chemist at the Institute of Organic Chemistry with Centre of Phytochemistry at the Bulgarian Academy of Sciences (IOCCP-BAS), where she held the positions of Assistant Professor (2000-2004), Chief Assistant Professor (2004-2011), Associate Professor (2011-2017) and Full Professor (2017-2021). Since 2012, M. Popova became a scientific secretary of the institute (IOCCP-BAS) and later, since 2021, she became a scientific secretary of BAS in the field "Nanosciences, New Materials and Technologies". Prof. M. Popova authored over 100 scientific publications, which have over 1400 citations (Scopus). She was a participant in more than 20 scientific projects of the National Science Fund, and a project leader of 5 of these projects.

Aim of the dissertation and actuality of the scientific topic

The research and results presented in the dissertation are dedicated to the preparation of nanoporous materials with application in two main areas: as catalysts and as carriers of

medicinal substances. On the one hand, heterogeneous catalysis is a classic and at the same time modern research field, which is the subject of great attention due to the diverse possibilities for application in industry, as well as for the elimination of volatile organic compounds in environmental protection. In this respect, some nanoporous materials as catalysts with high activity and selectivity, as well as with the possibility of reusability, offer many new possibilities. On the other hand, nanoporous materials have a place in a new, but extremely fast-growing and modern scientific field - nanomedicine, which combines chemistry, medicine, pharmacy and nanotechnology. The use of nanoporous materials as drug carriers could lead to increased drug bioavailability, provide targeted drug delivery and controlled release. The dissertation describes new approaches in the production and application of some modified nanoporous materials in these two modern and promising areas of research. After a literature review and analysis of the state of research in the respective fields, the author clearly formulated the aim and tasks of the dissertation. The presented results are from the research work of the candidate for a 12-year period (2008-2020).

Review of the dissertation and results

The dissertation is written in English and contains 215 pages, which include 173 figures, 18 diagrams, 53 tables and 273 references. The abstract is presented in both Bulgarian and English, on 107 pages and summarizes the main results and contributions of the dissertation. The dissertation is based on research published in 28 scientific publications (all in Q1, Scopus / WoS), which have received more than 670 independent citations in the scientific literature. In 24 of the 28 scientific publications the candidate is on the first or second place among the author's team, and in 18 articles she is also an author for correspondence, which testifies to her leading and responsible role in the presented scientific papers. The scientific results are presented at 37 reports at scientific forums and conferences in Bulgaria and abroad.

The dissertation is structured in the following sections: title pages with a table of contents and acknowledgements (5 pages), introduction (12 pages), aim and tasks (1 page), materials and methods (14 pages), main results (164 pages), references (6 pages), conclusions and contributions (5 pages), appendix with lists of publications, participation in conferences and projects (6 pages).

Initially, the author describes results on the development of catalysts for complete oxidation of volatile organic compounds. In most cases mesoporous silicate carriers (MSM-41, SBA-15, etc.) are used, which are obtained in their pure form (unmodified) by methods known from the literature, based generally on sol-gel synthesis in micellar solutions of amphiphilic substances with subsequent purification and calcination. The new results and contributions of the dissertation are mainly in the preparation and application of the modified silicate carriers. The methods used for modification are of two main types – post-synthetic (modification of previously prepared mesoporous material) and methods, in which a modifier is added during the synthesis of the mesoporous material. These methods allow variations within certain limits of some experimental conditions (ratio of reagents, concentration of modifiers, etc.), through which a material with optimal target (catalytic) properties can be obtained. In the study of catalytic activity, toluene was in most cases used as a model volatile compound subjected to complete oxidation. The following results should be noted as more significant in this area of research:

1) When modifying mesoporous silicates (KIL-2, MSM-41 and SBA-15) with different cobalt salts by wet impregnation, cobalt oxide particles with different reducibility (Co_3O_4, Co^{2+} and Co-silicate) and catalytic activity were obtained. The formation of easily reducible Co_3O_4 nanoparticles lead to increased catalytic activity.

2) Fe-containing KIL-2, MCM-41 and SBA-15 were obtained and the optimal Fe/Si ratio for the highest catalytic activity was found.

3) In the modification of MCM-41 by direct synthesis with the inclusion of titanium ions in the silica, a material with higher catalytic activity was obtained in comparison with similar catalysts obtained by impregnation.

4) For the first time, homogeneously dispersed silver nanoparticles in SBA-15 were obtained by pulsed laser ablation.

5) Modification with chromium and copper by impregnation of SBA-15 gave more active catalysts compared to their SiO_2 analogues. The optimal content of the respective metal oxides was determined.

6) SBA-15 and SBA-16 were found to be suitable carriers for the preparation of highly active catalysts containing copper and iron, in which finely dispersed particles of CuO and copper

ferrite were formed in the pores of SBA-15. It was found that the addition of iron results in more stable catalytic activity due to the formation of bimetallic oxide phases (copper ferrite).

7) It was found that the catalytic activity of CuFe-KIL-2 catalysts depends on the load of Fe in the silicate matrix - at low concentrations of iron, nanocrystals of CuO and Cu-oxo-Fe clusters were formed and the catalytic activity was significantly increased compared to Cu-KIL-2.

8) MCM-41 and SBA-15 were found to be suitable carriers for the preparation of highly active catalysts containing cobalt ferrite.

9) An active catalyst was prepared by introducing titanium into Fe-modified MCM-41 by impregnation, forming TiO_2 nanoparticles.

10) Highly active catalysts were obtained and characterized by modifying Ti-MCM-41 with cobalt and iron.

11) Zeolites were obtained by processing from coal ash and were modified with cobalt or copper to obtain a cheap adsorption/catalyst system.

The following important results stand out in the field of mesoporous materials for drug delivery applications:

1. Spherical amino-modified MCM-41 particles with a size of 100 nm and SBA-15 particles with a size of 5 μm were synthesized, which were shown as carriers of ibuprofen with a high degree of loading and a modified release rate. A correlation was found between the content of amino groups in the modified materials and their ability to adsorb ibuprofen.

2. A new procedure for modification of MCM-41 and SBA-15 with carboxylic groups was developed, which was realized under mild conditions and with less toxic reagents.

3. MCM-41, KIL-2 silicates and nanosized BEA zeolite were loaded with resveratrol by two different methods (reaction in solid phase and deposition from ethanol solution), where the loading by interaction in solid phase was more efficient.

4. Systems for delivery of mesalazine were developed by means of modified with amino or carboxyl groups SBA-16 and MSM-41 carriers, which reduced drug cytotoxicity in epithelial cells.

5. For the first time, the formation of stable Zn-quercetin complexes loaded on MCM-41, SBA-15 and SBA-16 was demonstrated, where quercetin loaded on a Zn-modified SBA-15

carrier showed a higher antineoplastic potential against HUT-29 cells, compared to the free drug.

6. Silver-modified MCM-41 and SBA-15 were shown to be suitable carriers for propolis. Studies of antibacterial and antifungal activity demonstrated a synergistic effect of silver and propolis.

7. It was shown for the first time that silver sulfadiazine can be replaced by sulfadiazine-loaded Ag-MCM-41, Ag-SBA-15 and AgY.

8. Sulfasalazine prodrug was loaded into the channels of spherical MCM-41 (100 nm) and SBA-15 (400 nm) materials modified with amino groups. A multilayer coating of a polyelectrolyte complex of Eudragit S and Eudragit RL was deposited on the particles to achieve a controlled release that depends on the pH.

8. Quercetin was loaded by reaction in solid phase, and also from solution, on nanoparticles of amino-modified KIL-2 and KIT-6 with sizes about 40 and 60 nm, respectively. Controlled release was achieved by polyelectrolyte coating.

9. Verapamil delivery systems were developed based on mesoporous nanocomposites ZSM-5/SBA-15 and ZSM-5/KIT-6, modified with -SO_3H and -COOH groups and futher coated with polyelectrolyte layers for achieving controlled release of verapamil.

10. The cytostatic mitoxantrone and the anti-inflammatory substance prednisolone were co-loaded into silicate nanoparticles (100 nm) containing also magnetic nanoparticles, while maintaining the cytotoxicity of the loaded mitoxantrone.

Contributions

Contributions of the dissertation are related to the modification and application of nanoporous silicates in two main directions: I) as efficient catalysts for complete oxidation of volatile organic compounds, and II) as drug delivery systems. Briefly, the contributions can be summarized in these areas as follows:

1. The role of the synthesis procedure and the modification with metal (Co-, Fe-, Ti-, Ag-, Cr-, Cu-, Cr / Cu-, Cu / Fe-, Co / Fe-, Co / Ti-) oxides of mesoporous silicates (KIL-2, MSM-41, SBA-16 and SBA-15) and zeolites from coal ash on their catalytic activity, selectivity and stability in the process of complete oxidation of volatile organic compounds was found. The optimal ratios for modification with metal oxides for catalytic oxidation of

toluene were found. A two-component adsorption-catalytic system for oxidation of volatile organic compounds and adsorption of CO_2 on the basis of cheap zeolites obtained by processing from coal ash was developed.

2. A procedure was developed for the preparation of amino-modified spherical particles of MCM-41 with a size of 100 nm and spherical particles of SBA-15 with a size of about 5 μm with high loading efficiency and modified release of ibuprofen. A new procedure was developed to modify MCM-41 and SBA-15 materials with carboxyl groups under "soft" conditions and with less toxic reagents. Delivery systems for mesalazine, sulfasalazine and quartcetin, based on mesoporous silicates and polymers, were developed. It was shown for the first time that silver sulfadiazine can be effectively replaced by sulfadiazine-loaded onto silver-modified materials (Ag-MCM-41, Ag-SBA-15 and AgY). A system for delivery of verapamil based on nanocomposites (ZSM-5/ SBA-15 and ZSM-5/KIT-6) modified with -SO_3H and -COOH groups was developed. Also, a procedure for the production of spherical silicate nanoparticles (100 nm) with built-in magnetic nanoparticles was developed.

The main achievements presented in the dissertation were published in prestigious scientific journals with high impact factor, such as: Applied Catalysis B, Journal of Hazardous Materials, Catalysis Today, International Journal of Pharmaceutics, Journal of Materials Chemistry B, ChemCatChem, etc., and in most of these articles the leading role of the candidate, Prof. M. Popova, is clearly visible (first or second author and/or author for correspondence). The achieved results were obtained through funding received from the implementation of research project grants form the Bulgarian Science Fund, few national programs and inter-academic exchange programs. The high level of research is due to the proper selection and use of various instrumental methods for analysis, such as X-ray diffraction (XRD), TEM, infrared spectroscopy (FT-IR), Mössbauer spectroscopy, solid-state NMR spectroscopy, dynamic light scattering and others. The collaborations of Prof. M. Popova with Bulgarian and foreign scientists have also contributed to the successful development of the interdisciplinary topics presented in the dissertation.

Remarks and recommendations

The almost complete absence of spelling mistakes in the text makes a good impression. Some technical gaps in the texts below some of the figures (the so-called "figure captions") can be

noted. For example, in the description of Fig. 5 on page 37 of the dissertation, description is given only for Fig. 5a and 5b, but it is missing for the other two graphs - 5c and 5d (which are described only in the text). These gaps concern only the technical layout and have no bearing on the scientific value of the research. Regarding the use of ninhydrin for the quantification of primary amino groups of modified surfaces (in heterogeneous systems), I would mention some similar methods, described previously in: Taylor & Howard, Analytica Chimica Acta, 271 (1993) 77; Pryce & Hench, J . Mater. Chem., 14 (2004) 2303; Chen et al., Am. Ceram. Soc., 92 (2009) 2074.

Conclusion

The dissertation presents Prof. Dr. Margarita Popova as a great scientist with her own and in-depth approach to research problems and approaches to solving them. The contribution of the candidate in the presented research and published results is indisputable. My personal impressions of Prof. Dr. Margarita Popova are excellent. Last but not least, her excellent organizational and administrative skills for managing many scientific projects and programs, as well as her responsible position of scientific secretary of BAS, should be noted. The interdisciplinary orientation of the research, covering structural analysis of inorganic and organic materials, catalysis, polymer and medicinal chemistry, makes a great impression.

The presented dissertation, the abstract, the scientific publications in prestigious international journals, as well as the number of citations, fully satisfy the requirements of the law and the recommendations of IOCCP-BAS for the scientific degree "Doctor of Sciences".

Based on the above, I give a positive assessment of the dissertation of Prof. Dr. Margarita Popova and with a great pleasure I recommend the Scientific Jury to award her the degree of "Doctor of Science" in the Professional field 4.2. "Chemical Sciences" (Organic Chemistry).

09 Sept., 2021 Reviewer: .....

Sofia /Assoc. Prof. G. Yordanov, DSc/