**R E V I E W**

by

Prof. Dr. Elena Vassileva

Member of the Academic Jury set to render a decision on a procedure for the acquisition of Academic Degree "Doctor of Philosophy" (PhD) in the Professional Field **4.2.** Chemical Sciences according to the Classifier of the Areas of Higher Education and the Professional Fields (Scientific Specialty "Polymers and Polymer Materials")

This Peer Review is prepared following the decision made by the Academic Jury in response to Order № РД-09-54 from 07.04.2026 г. issued by the Director of the Institute of Polymers, Bulgarian Academy of Sciences. The Review is in compliance with *Development of Academic Staff in the Republic of Bulgaria Act (DASRB)*, *the Rules for the Application of the Development of Academic Staff in the Republic of Bulgaria Act*, the *Rules of BAS* and with the *Rules set at the Institute of Polymers, Bulgarian Academy of Sciences, for applying the Act aforementioned*.

*PhD candidate*: Erik Dimitrov

*Title of dissertation*: Macromolecular Design and Synthetic Strategies for the Preparation of Polymers for Delivery of Biologically Active Substances and Oligonucleotides

*Scientific Supervisors*: Prof. Dr. Stanislav Rangelov
Assos. Prof. Dr. Natalia Toncheva-Moncheva

The dissertation presented by PhD student Erik Dimitrov is a great example of how the vast possibilities of organic synthesis and polymer chemistry enable the realization of desired and targeted structures, architectures, molecules, and their combinations, with the goal in this case being the exploitation of these materials for biomedical applications. Undoubtedly, the dissertation is at the forefront of the advanced polymer science, and on a broader scale, of materials science. The choice of topic and the synthetic approaches employed in the dissertation demonstrate the breadth of knowledge and perspectives of both the doctoral student and their supervisors, as it is precisely them who make the realization of their concept possible.

The dissertation has an ambitious and scientifically significant goal for contemporary science: namely, by employing modern methods for the synthesis and functionalization of monomers, oligomers, and their conjugates/hybrid structures with biological or biomimetic motifs, to create macromolecules that can "transport" diverse cargo within the body (biological molecules, nucleic acids, etc.). More importantly, the dissertation unequivocally demonstrates the beauty and power of organic chemistry in achieving materials with diverse composition, structure, architecture, and functions, which furthermore possess demonstrated applied potential.

The literature review covers 125 references and spans 44 pages. It begins with an overview of methods for polymer synthesis, the main characteristics of chain-growth polymerization and

polycondensation, and then proceeds to describe methods for the controlled synthesis of copolymers with different architectures. Special attention is given to approaches for obtaining block copolymers, with the main and most commonly used methods presented, namely: (1) living polymerization; (2) the macroinitiator technique; and (3) direct coupling of two functionalized polymer chains. Some of the properties that make polymers highly valuable and suitable for medical applications are also presented, such as biodegradability, smart behavior, and biocompatibility. The main components (polymers) of the new materials synthesized and characterized within the dissertation are then briefly described. The review is written clearly, demonstrates a solid understanding of the topic, and critically presents the synthesis methods and polymers used in the dissertation, along with their advantages and disadvantages. It reflects the candidate's own perspective on the subject matter and a good command of the described methods, which also enables the critical assessment of the work, demonstrated in this part of the dissertation.

In my opinion, however, the amount of information included in the review is excessive; too many synthesis methods are presented, and not all of them are used later in the dissertation. Some inaccuracies in terminology and nomenclature are also noticeable, for example, the naming of copolymers is not always consistent with the correct nomenclature.

The stated aim of the dissertation is clear and is based on a wide range of polymer materials that differ in composition, structure, and architecture, with their main intended application being in medicine. The tasks are ambitious and require a complex route of synthesis and functionalization, as well as a detailed characterization of the behavior of these new carriers. At the same time, this demonstrates the candidate's and the supervisors' determination and capability to carry out such an ambitious project.

The experimental part is presented on 36 pages, and the description of the experiments performed is clear, precise, and detailed. The large number of monomer and polymer syntheses carried out, the functionalization of some of them, and the diversity of synthetic methods used are particularly noteworthy. This part of the work demonstrates the exceptionally broad range of tools mastered by the candidate, by which I mean not only the planning, design, and execution of monomer and polymer syntheses, but also the performance of specific functionalization reactions that, in practice, extend beyond the scope of polymer science and enter the realm of organic synthesis. It is also striking how easily the candidate overcomes challenges arising during the course of the work by applying an approach that allows him to achieve what was originally intended in the experimental design. The use of such a broad set of synthetic approaches is rarely encountered nowadays in dissertation theses in the field of polymer science.

The Results and Discussion part of the dissertation spans 59 pages. The presentation of the newly obtained molecules, oligomers, and their conjugates/supramolecular assemblies is detailed, and their characterization is convincing, being supported in each case by at least two methods for confirming the proposed structures. The dissertation places its main emphasis on the chemistry underlying the newly created molecules/conjugates/materials and on their physicochemical characterization. Although the publications contain sufficient data also on their behavior in the intended biological and medical applications, these aspects are not discussed in detail in the dissertation. Thus, on the one hand, the dissertation clearly highlights

the interests, focus, and, the most important aspect according to the candidate's view, namely chemistry and its vast possibilities; in this way, it strongly emphasizes the candidate's own contribution while minimizing the contribution of the other co-authors of the scientific publications. On the other hand, however, there is a lack of clarity regarding the behavior of the synthesized new systems in the intended applications, i.e., it is not sufficiently clear to what extent the synthetic procedures carried out lead to the desired properties and behavior of the newly created systems. This diminishes part of the value of the polymer materials presented in the dissertation, mainly because the structure–property relationship for the newly developed materials is not clearly defined. As a result, unfortunately, the subtle connecting thread that links all the new molecules/conjugates/materials presented in the dissertation is also not clearly seen. For example, it remains unclear why, in addition to spherical nucleic acids based on DHP-functionalized oligonucleotides, analogous systems based on a rigid polymer core were also obtained by synthesizing linear polystyrenes grafted with nucleic acids. What advantages do they offer, and what drawbacks of the former systems do they compensate for? Similarly, it is not sufficiently clear why exactly polyglycerol (PG) and poly(ε-caprolactone) (PCL) were chosen as the building blocks of the obtained linear and star-shaped copolymers.

The positive aspect of this way of presenting the results, however, is that it is crystal clear that the described results are the work of the doctoral candidate, and thus the candidate's contribution to the development of the sequence of synthesis and functionalization steps for these new polymer carriers becomes very evident. And this contribution is significant. The writing style also demonstrates the candidate's commitment and deep involvement in the topic and in planning the synthetic approaches through which it was realized, i.e., it truly reflects the candidate's own merits in the presented work.

The dissertation fully meets the specific requirements of the Institute of Polymers, Bulgarian Academy of Sciences, namely:

- It contains scientific and applied-scientific results that represent an original contribution to the field of polymer science.
- Its content and volume not only correspond to, but exceed, the current requirements in the field of polymer research.
- It brings together results included in five! scientific publications, all published in Q1 journals, with 15 citations received so far. The doctoral candidate has participated in, and is still involved in, 8 national and 2 international research projects (with Poland).
- The abstract corresponds to the content of the dissertation and accurately reflects its contributions.

I have the following questions for the doctoral candidate:

1. Do you believe that the molecular masses determined and presented in Table 1 (p. 105) and Table 2 (p. 116) are sufficient grounds for considering the obtained molecules to be polymeric? Is there any reason why the synthesis was stopped at these molecular masses, i.e., why were larger ones, for example twice as high, not attempted?
2. In Table 3 (p. 117), for sample DHP-PETEGA, the results for the diffusion coefficients obtained after mono- and biexponential fitting are presented. The biexponential fitting gives two values. What does this mean? Is it related to a possible second particle population?

3. Figure 3.42 (p. 118): the transition in DHP-PAA (b) is sharper than in DHP-PG (a). The dissertation notes that “the nature and width of this transition depend on the nature, length, and architecture of the polymer chain attached to the lipid-mimetic fragment.” In this specific case, what do you think are the reasons for this difference?

All these questions arise from the interesting topic and the significance of the obtained results, both for polymer science and for modern materials science.

The presented dissertation and the accompanying materials give me full confidence to recommend to the scientific jury, and to vote “in favor” of awarding Eric Dimitrov the educational and scientific degree of “Doctor” in the field of higher education 4. Natural Sciences, Mathematics and Informatics, professional direction 4.2. Chemical Sciences, scientific specialty “Polymers and Polymer Materials.”

Reviewer: …….……..…….
Prof. Dr. E. Vassileva
Member of the Academic Jury

Sofia, 22.06.2026