

REPORT

on the PhD thesis
for acquiring of the educational and scientific degree *Doctor*

Title: INTELLIGENT POLYMER MATERIALS FOR MODIFIED RELEASE OF
TIMOLOL MALEATE IN EYES

Author: Denitsa Valerieva Nikolova

Supervisors: Assoc. Prof. Elena Vasileva, PhD
Assoc. Prof. Lachezar Christov, PhD

Field: Natural Sciences, Mathematics and Informatics

Professional field: 4.2 Chemical Sciences

PhD programme: Polymers

Member of Commission: Prof. Stanislav Rangelov, DSc
Institute of Polymers, Bulgarian Academy of Sciences, Acad. G. Bonchev St., Bl. 103-A,
Sofia

General overview of the thesis

The thesis is on a topic that fully corresponds to the professional field *Chemical Sciences* and the PhD programme *Polymers*. The thesis is written on 118 pages, contains 24 figures, 20 schemes and 24 tables; 163 references are used. The structure of the thesis is compatible with the requirements of the RULES FOR IMPLEMENTATION OF THE ACADEMIC STAFF DEVELOPMENT LAW IN SOFIA UNIVERSITY for acquiring of the educational and scientific degree *Doctor*. It is composed of 10 chapters: Introduction, Literature overview, Aim and tasks, Experimental, Results and Discussion, Conclusions, References as well as additional materials such as lists of papers and participations in scientific forums, specializations abroad and participations in scientific projects.

In the *Literature overview* chapter, the PhD student demonstrates in-depth theoretical knowledge of the material. The chapter is composed of several sections. In the first one, the structure, synthesis, and properties of polyzwitterions are considered. In the second, third, and fourth sections, various drug delivery systems such as polymer nano- and microparticles, polymer gels, and polysulphobetaines are overviewed, whereas the last two sections – ophthalmic pathways for drug delivery as well as basic characteristics and carriers of timolol maleate (a drug prescribed to patients suffering from increased intraocular pressure and glaucoma) – are related to the biological problem to which the thesis is dedicated. The former is clearly formulated already in the introduction – development of appropriate drug carriers of timolol maleate. The literature overview is very well focused and prepares the reader for the aim and tasks of the dissertation work. Although particular conclusions were not drawn in this

section, the attention of the reader is accurately directed to specific studies and/or systems and ways of delivering timolol maleate that are missing in the scientific literature, thereby outlining the scientific problems investigated in the dissertation.

The materials and methods in the *Experimental* chapter are described in details and allow reproduction of the experiments and investigations. Chapter *Results and Discussion* is structured around the two publications on the dissertation topic. This chapter is very well written, focused and concentrated. All results are summarized and discussed, and ways are found to refer to and support the discussion with current literature. The conclusions drawn are adequate and represent a fair reflection of the results and discussion. Overall, the thesis is written in a good scholarly style and is read without efforts. The expanded summary objectively reflects the main idea, purpose, content and conclusions of the dissertation.

Analysis of results, characterization and assessment of contributions

The dominant scientific problem is related to the development of timolol maleate carriers, which are (i) nano- and microparticles and (ii) hydrogels as drug-delivery contact lenses for eyes. Both forms are based on the zwitterionic polymer poly(sulfobetaine methacrylate) (PSBM), selected due to a complex of attractive characteristics – biomimetic properties and intelligent behavior. Two types of PSBM particles have been successfully synthesized – from linear and chemically cross-linked PSBM, as well as several polymer hydrogels poly(sulfobetaine methacrylate-co-vinylpyrrolidone) of different monomer ratios. A number of characterizing parameters of the timolol maleate carriers such as loading efficiency, drug loading capacity, release profiles are also determined. By analyzing the results obtained, the PhD student demonstrates the potential of the two forms (particulate and hydrogel) as carriers of timolol maleate, which help to prolong the contact between the drug and the ocular surface, thereby increasing the required dose and bioavailability. Factors, such as PSBM cross-linking in the nanoparticles and copolymer composition in the hydrogels, which can improve a number of characteristics as well as the potential of the systems, are outlined and investigated.

The thesis contains scientific and applied results, representing original contributions that can be defined as *complementing and enriching an existing scientific field*.

Opinion on the publications of the PhD student

The dissertation is based on two articles published in 2022 and 2023 in specialized and peer-reviewed scientific journals – *Polymer International* (IF 3.213) and *Gels* (IF 4.432), falling into quartiles Q2 and Q1, respectively, in *Polymer Science* (Web of Science). Results of the thesis have been presented as 3 oral and 2 poster presentations at various scientific forums. Denitsa Nikolova is a co-author of 2 more publications. She has participated in 5 scientific forums outside the topic of the dissertation and is a participant in 7 scientific projects.

I believe that the set of quantitative criteria for acquiring of the educational and scientific degree *Doctor*, defined in RULES FOR IMPLEMENTATION OF THE ACADEMIC STAFF DEVELOPMENT LAW IN SOFIA UNIVERSITY is fully satisfied.

Critical notes and comments

The dissertation contains an acceptable number of typographical/grammatical errors that are not annoying but noticeable. Some incorrectly/inaccurately used terms such as [**in Bulgarian:** *главна* вместо *основна* верига, *големина* вместо *размер*, *моларна* вместо *молна* маса, използване на скоби, например, *поли(сулфобетани)* вместо *полисулфобетани*, *бърст ефект* вместо *залпово освобождаване*, *сонифициране* вместо *озвучаване*, *светоразсейване* вместо *светлоразсейване*, *линейни наночастици* вместо *наночастици*, *получени от линеен полимер*] should be mentioned as well. I could not find information either in the thesis or in the publications about the molar mass of the PEGDA crosslinker. The results of Figures 7 and 9 could be presented more clearly in semi-logarithmic coordinates, that is, log(hydrodynamic diameter) vs. temperature. The He-Ne laser is red, whereas a 488 nm laser means a blue laser – perhaps, a typographical error in one of the publications, which, however, has been transferred in the thesis. The size of the particles in the temperature interval 33 – 36 °C (hydrodynamic diameter of 7 nm, Figure 7, page 62) is unrealistically small for a polymer with molar mass of about 140 kDa (Table 2, page 61). Toxicological studies of the two types of newly developed polymeric carriers are missing, although the need for such studies is unequivocally postulated on page 26: “... *toxicological studies for any new nanosystems for controlled and targeted release must be carried out, even though they are developed from already proven biocompatible and non-toxic materials.*”

The critical notes and comments made above do not contradict my overall good impression for the thesis of Denitsa Nikolova. They would be perhaps used as a basis for discussion.

Conclusion

The dissertation of Denitsa Valerieva Nikolova represents a scientific study conducted at a high experimental level, the results of which have been discussed critically and in depth with the undoubted participation of the PhD student. The thesis shows that she has in-depth theoretical and practical knowledge and abilities for independent scientific research. I give a *positive assessment*.

Sofia, 17.05.2023

Prof. Stanislav Rangelov, DSc