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HABILITATION THESIS

POLYMERIC SYSTEMS FOR BIO-APPLICATIONS: FUNCTIONAL COMPOUNDS AND (NANO)STRUCTURED INTERPENETRATED NETWORKS

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ABSTRACT

The habilitation thesis entitled "**Polymeric systems for bio-applications: functional compounds and (nano)structured interpenetrated networks**" presents the results of the research carried out after the defend of the PhD thesis (September 2007). This thesis consists in three main parts: Section I-Overview of professional and scientific career; Section II- Scientific achievements from the postdoctoral period; Section III- Future research directions.

SECTION I – ***Overview of professional and scientific career***

This section presents a brief overview of the scientific and professional activity that I have carried out after I defended my doctoral thesis. This activity has been done both in a fundamental and applicative way, using a multidisciplinary approach, allowing me to develop the following research directions: - obtaining of pH and thermo-sensitive hydrogels by adjusting the chemical functionality of the copolymers structure, and by including into a double interpenetrated network of specific macromolecular chains and/or specific molecules into the preformed matrix, - obtaining hydrogels with multi-membrane organization through multi-stages gelation processes; - obtaining and testing the systems that have encapsulated bioactive compounds, starting from advanced functional macromolecular structures made by self - assembling processes; - testing the possibility of using the hydrogels as controlled drug delivery systems. This section presents the main research directions and the most significant achievements in these areas. There are also mentioned achievements in the scientific publications field, prizes and scholarship obtained during this period and the national or international projects in which I was involved as leader or member of the team.

Thus, I was honoured to receive in 2013 the "Nicolae Teclu" Award of the Romanian Academy for ***„scientific contributions in the field of biodegradable/biocompatible polymer materials sensitive to external stimuli for biomedical applications***", which is an encouragement for writing this habilitation thesis.

The main results obtained during this period were included in **more than 100 scientific papers published as a coauthor in journals indexed by Web of Science, 11 chapters in books, 2 books,** and more than **100 participations** at national and international scientific meetings. The innovative activity was included in **10 OSIM patents**, 9 distinctions (7 gold and two silver medals) awarded at the "Inventica", "Ecoinvent" and "ARCA" Salons of Inventions.

SECTION II – ***Scientific achievements from the postdoctoral period***

This section contains and describes the most significant scientific results obtained in the field of polymeric systems for bio-applications.

The application of synthetic macromolecular compounds in medicine and therapeutics must solve the complex problems arising from the temporary or long-term contact of the polymeric materials with tissues and biological substances. For bio-applications, only polymers or polymeric composites which are attested as biocompatible may be used. Among these, the polymers sensitive to temperature and/or pH are the most investigated. In various studies, temperature sensitivity was combined with pH sensitivity, which was obtained by copolymerization of various monomers with required specificity, or by preparing interpenetrated polymer networks (IPN). Fully/semi interpenetrated structures, or other gelling materials based on natural or synthetic polymers, belong to a privileged class of polymer systems studied extensively due to their multiple technological applications. The research theme

pursued the development of a systematic study to understand and improve the processes related on the obtaining biomaterials based on advanced functional macromolecular structures. Thus, new complex polymeric materials (interpenetrated structures - IPN - or interpolymeric complexes - IPC -) with biodegradable and biocompatible properties, pH / thermo-sensitive character, with biomedical applications, based on natural and synthetic polymers, have been synthesized.
As a result, the scientific activity (**Section II**) was merged in three chapters:
Chapter I: *Macromolecular structure: synthesis and functionalization*
Chapter II: *Polymeric networks*
Chapter III: *Interpolymeric complexes - further directions for obtaining bioactive compounds*

Chapter I "Macromolecular structure: synthesis and functionalization" presents synthesised macromolecular structures that can be divided into: (i) biocompatible and biodegradable compounds (such as poly(aspartic acid)); (ii) biocompatible and partially or non-biodegradable macromolecular compounds (copolymers with a comonomer with spiroacetal moiety and different monomers such us 2-hydroxyethyl methacrylate, N,N-dimethylacrylamide, itaconic anhydride); (iii) macromolecular structures obtained through reactive processing (in this categories was included process-controlled structure formation and imprinted polymer structure). All structures have been tested for biomedical application: magnetic carriers, drug delivery platforms or stimuli sensitive systems (polymeric matrix with pH and temperature response). The compounds were further examined by *in vivo* studies, which demonstrated good biochemical response and attested good biocompatibility for the new studied compounds. Thus, these preliminary *in vivo* studies further supported the nontoxic character of the bioconjugates.

Chapter II "Polymeric networks" presents the results obtained in the preparation of gels with medical applications: (i) multilayered structures prepared in multiphase gelation processes; (ii) multifunctional nanogels with dual temperature and pH responsiveness; (iii) hybrid gels. The prepared polymeric networks have dual thermal and pH sensitivity and were loaded with drugs and other bioactive substances to be tested as potential drug delivery systems. Near infrared chemical imaging - NIR-CI technique highlighted the degree of homogeneity of the bioactive substance dispersion in the polymeric matrix as well as the quantitative assessment of the drug loading. The *in vivo* studies (biocompatibility tests, somatic nociceptive experimental model (tail flick test) and visceral nociceptive experimental model (Writhing test)) attested the potential for the use of these compounds for biomedical purpose.

Chapter III "Interpolymeric complexes - further directions for obtaining of the bioactive compounds network"
The preparation of interpolymeric complexes based on poly(aspartic acid) and various synthetic or natural polymers (such us: Pluronic acid, collagen, albumin) ensures the obtainment of new biodegradable and biocompatible amphiphiles with balanced hydrophilic - hydrophobic properties, in the form of nanoparticles, films and gels. The presence of various functional groups will provide covalent and/or physical bonds with new sensitive and/or bioactive structures. The amphiphilic nature will also provide conditions for the immobilization of bioactive or liposoluble products, this being one of the requirements for "carrier" polymer matrix. An important aspect that has been emphasized was the evaluation of the specific interactions between the complex structures that determine the particular behaviour and performance of the new networks. Interpolymeric complexes have

been achieved by combining solutions, by harnessing the compatibility characteristics on pre-set pH and temperature ranges.

SECTION III. Future research directions: challenges and actual possibilities

Due to their ability to mimic the characteristics of the extracellular matrix (porous structure, adequate rigidity, and controlled mechanical properties) that allow the *in vitro* study of cell growth and proliferation, hydrogels have increasingly attracted particular interest in the biomedical field. However, in order to further improve their properties, the hydrogel design should also address other requirements, including: (i) *in situ* gelation at the defect site (i.e. injectability), (ii) self-healing, and (iii) improved mechanical properties. Nature offers a wide range of biocompatible, inexpensive natural polymers (e.g., alginate, gelatin, hyaluronic acid), which can easily form hydrogels with good self-healing properties. Although natural polymers have been extensively studied as basis for the construction of hydrogels, they have the disadvantage that they cannot be adjusted to different biological environments, exhibit low compressive strengths, and are irreproducible, which limits their potential. In order to overcome these limitations, interpolymeric networks can be designed. IPNs are formed by the intercalation of two hydrogel networks (e.g., a natural hydrogel compound and a synthetic one) during gelation. In this way, gel-like structures having the advantages of both the natural (healing and stretching) and the synthetic compound (i.e., adjustable stiffness, reproducibility and robust compressive strength), which are ideal features of an extracelullar matrix, are achieved. More importantly, many traditional hydrogels do not exhibit biological activities, hierarchical organization, and structural integrity that are necessary to facilitate cell infiltration and neovascularization.

The following directions will be taken into account:

(a) **New theoretical and experimental studies in the field of gels**:

(a_1) Supramolecular self-assembly of low molecular weight gelators, which are based on small molecular building blocks

- Understanding and explaining the transformation of small-molecule gelators into three-dimensional networks.
- Development of low-molecular-weight gelators and polymer-based gelators. The driving forces of gelation.

(a_2) Multicomponent systems: increasing the functionality of gels by employing a multi-component approach.

- Combining the beneficial properties of responsive supramolecular gels formed by self-assembling LMWGs with robust polymer gels formed from assembly, entanglement or crosslinking of polymer gelators.

(b) **Application platforms for the synthesized gels**

(b_1) Self-healing gels for biomedical applications

- Bioactive complex preparation based on new self-healing gels and specific compounds (for example by inclusion and complexation of specific antibacterial compounds in order to obtain biomaterials for bacterial infections minimization)
- New generation of injectable carriers for targeting drug-delivery

(b_2) inks for 3D or 4D printing, 3D cell culture media or tissue engineering.

CONTENT