ABSTRACT

The Habilitation Thesis entitled "BIOMEDICAL APPLICATIONS OF POLYMERS. INTELLIGENT POLYMERS FOR DRUG DELIVERY SYSTEMS" includes the most representative results of my research activity carried out after defending the PhD thesis (September 28, 1999). The thesis comprises three main parts: **Section I** – Professional and academic career, **Section II** – Scientific achievements and **Section III** – Scientific and professional development plan.

SECTION I – *PROFESSIONAL AND ACADEMIC CAREER*

This section refers to the scientific and professional activity that I have carried out after defending the doctoral thesis which focused mainly on the design and development of intelligent systems for controlled release of drugs or other biologically active substances. This section presents the main research directions and significant achievements in these areas. It also mentions the prestigious specialty journals in which the results of the research were published, the national and international projects obtained through the competition, as well as the prizes and scholarships obtained during this period.

SECTION II – *SCIENTIFIC ACHIEVEMENTS*

This section contains and describes the most significant scientific results obtained in this period in the field of controlled release of bioactive substances.

"Intelligent" drug delivery systems have been designed to eliminate the drawbacks of classical systems that release active principles at constant rate. These progressive devices have the ability to perceive some changes in normal physiological parameters (pH, temperature, presence of biomolecules) and release a certain dose of medicine in response to these changes. Furthermore, these systems may contain a sensor capable of detecting these changes and transmitting a signal to a delivery element (actuator) that is usually obtained from a hydrogel. These devices were constructed from intelligent polymers or polymers sensitive to external stimuli.

Among polymers sensitive to external stimuli, those sensitive to pH and temperature have been used in these studies because they use human body pH and temperature changes as "triggering agents" in controlled drug delivery.

As a result, scientific activity (**Section I**) was concentrated in four chapters:

Chapter I: *Drug Delivery Systems Sensitive to pH*

Chapter II: *Drug Delivery Systems Sensitive to Temperature*

Chapter III: *Drug Delivery Systems Sensitive to pH/Temperature*

Chapter IV: *Thermosensitive Drug Delivery Systems based on β-Cyclodextrin*

Drug Delivery Systems Sensitive to pH (**Chapter I**) have been designed to "exploit" the pH variation in different compartments of the human body. These systems control the timing and release rate of drugs in response to changing the pH from 1.2 in gastric juice to pH 7.4 in the colon. The polymers used contain carboxyl groups having a pK_a value of 4.5-5 and are therefore protonated in the gastric juice (pH = 1.2) and ionized in the intestinal fluid (pH = 7.4). These polymers have been transformed into thermosensitive microgels that do not swell in the gastric juice, stopping the diffusion of the drug and protecting it from its degrading action, but it swells greatly in the intestinal juice where it releases the drug in a controlled manner.

Drug Delivery Systems Sensitive to Temperature (**Chapter II**) have the property of releasing the drug whenever human body temperature deviates from normal values and therefore has self-regulation capability. These systems are based on poly (N-isopropylacrylamide) (poly(NIPAAm)) because this polymer has a lower critical solution temperature (LCST) at about 32 ^{o}C. To bring the transition temperature to the temperature of the human body, NIPAAm was copolymerized with hydrophilic monomers such as acrylamide (AAm) and hydroxyethyl acrylate (HEA).

These copolymers have been transformed by original methods into thermosensitive porous microspheres which have very high swelling/collapse rates and release the drug through a pulsating mechanism. To obtain drug delivery systems that are biodegradable and release the drug through an ON-OFF mechanism, linear thermosensitive polymers were grafted on pullulan microspheres. The release of the drug in this case was controlled by extension/contraction of the pendant thermosensitive polymeric chain, acting as a valve. The correlation of the thermosensitive chain length with the biologically active substance molecule size in order to

regulate the release mechanism of the active principle was done by the inverse size exclusion chromatography method.

Drug Delivery Systems Sensitive to pH/Temperature (**Chapter III**) have the property of responding simultaneously to pH and temperature, modifying their solubility or swelling according to the two parameters. Poly(N-isopropylacrylamide-co-methacrylic acid-co-methyl methacrylate), in its linear form, was designed and developed to be insoluble in gastric fluid at pH = 1.2 and T = 36 ^{o}C but with different solubilities at pH = 6.8 and 7.4. It was used as an enteric-soluble adjuvant in combination with cellulose acetate butyrate to release DNA into the intestinal fluid after oral administration.

In the form of microgels, NIPAAm copolymerized with pH-sensitive monomers such as maleic acid, methacrylic acid or aminoethyl acrylamide was used to obtain controlled self-regulating delivery systems. These hydrogels, at certain molar ratios of co-monomers, and under physiological conditions, lose their sensitivity to temperature due to the ionization of pH-sensitive units.

Remarkably, after the electrostatic interaction of these groups with some biologically active substances (biomolecules), the hydrogel regains its thermosensitivity and collapses, releasing a certain dose of medicine. Hydrogels designed and built in this study are the starting point for obtaining a new generation of controlled release systems based on a sensor and an actuator. The pH-sensitive groups play the role of the sensor because they give thermosensitivity to the system only after electrostatic interaction with certain biomolecules, and the NIPAAm-based hydrogel plays the role of actuator because it shrinks only after this interaction.

Thermosensitive Drug Delivery Systems based on β-Cyclodextrin (**Chapter IV**) have been designed to cumulate the thermosensitive properties of N-isopropylacrylamide with the ability for selective retention of bioactive compounds and biodegradability of β-cyclodextrin. Cyclodextrins are known as cyclic oligosaccharides having a hydrophobic cavity in which they can retain drugs or other hydrophobic compounds. In addition, as starch derivatives, cyclodextrins can be degraded by starch-specific enzymes. In order to be used as a monomer and as a crosslinker, β-cyclodextrin was functionalized with more than one double bond on the molecule. The microgels obtained were characterized by high swelling/collapsing ratios and high drug retention capacity (diclofenac). These systems were able to release diclofenac

through a pulsatile mechanism. Also, "in vitro" degradation studies have shown that degradation of microgels occurs on the surface and only in the presence of α-amylase.

SECTION III – *SCIENTIFIC AND PROFESSIONAL DEVELOPMENT PLAN*

Scientific development will aim to continue the topics already addressed on polymers sensitive to external stimuli used in the controlled release of active principles and other types of biomedical applications. The development of polymeric systems sensitive to other types of stimuli such as ionic strength, the presence of glucose and other biomolecules as well as the increase in their selectivity will be considered.

Given the experience in the use of polymers for biomedical applications, biomimetic biomaterials for tissue engineering and regenerative medicine will be designed and developed. Last but not least, hybrid materials will be created that will cumulate the biocompatibility and biodegradability properties of natural polymers with those of mechanical resistence of synthetic polymers.