State of the art of smart polymers: from fundamentals to final applications

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This chapter discusses the state of the art of smart polymers with potential biomedical applications and focuses on the synthesis and characterization of such materials. In a more specific way the smart polymers were reviewed from their preparation and properties to their potential applications, such as drug delivery systems. The combination of smart polymers and drug delivery systems provides specific features for the development of intelligent materials and is capable of bringing to light enormous possibilities concerning biomedical applications. Advances in the fields of implants and controlled drug delivery systems have promoted the need for new properties such as temperature- and/or pH-responsive polymers with the capability to adsorb and release bioactive substances in a controlled way. By means of characterization, infrared spectroscopy, thermogravimetric analysis, differential scanning calorimetry, and scanning electron microscopy techniques have been usually employed in order to evaluate the properties of this kind of materials. In addition, stimuli-responsive behaviour has been studied by swelling and contact angle characterization techniques.

Keywords: Stimuli-sensitive polymers; LCST and pH responsive; Polymer characterization; State of the art of smart polymers; Biomedical applications

1. Introduction

Polymers stand as a wide group of materials present in our daily life, in which by definition, comprise molecules or macromolecules built up by subunits [1,2]. The sequence, orientation, disposition and nature of the subunits along the polymer chain assures distinct properties to this huge class of materials, including a wide range of molecular weights and properties [1-4]. As an example, while polypropylene, a synthetic polymer composed by repeated propylene units, is currently applied for the synthesis of materials such as desk or tables with high mechanical properties and toughness, elastomers do not show such properties, but on the other hand, they feature elasticity and plasticity suitable for the development of tyres and other materials.

Although polymers synthesis may be achieved by distinct routes and technologies, polymerization stands as the so-called process in which such subunits, also called monomers, are chemically attached to each other [1,2]. A great deal of techniques is currently available and emerges as technology advances. In practical terms, as polymer chemistry evolved novel materials with unique properties such as elasticity, mechanical resistance, crystallinity and other properties that were never seen before were generated.

Apart from the structure, polymers may also be characterized according to their nature. For instance, polystyrene, polyethylene or polypropylene are good examples of synthetic polymers, considering the synthetic nature of its monomers [5-8]. Consequently, natural polymers correspond to those materials composed by the polymerization of biological molecules such as proteins, amino acids and DNA among others [5, 9-10]. Concerning materials development, the nature of such materials impose several restrictions and require distinct properties when it comes to initial stages of production, such as polymerization process conditions to final applications, like biomedical or biotechnological applications [11,12].

The constant seek for advanced materials and technologies in distinct fields, e.g. polymer chemistry, materials science, engineering, technology, among others, converged in terms of supporting and providing the necessary tools to advance and optimize the use of this group of materials. By means of tools, such advances were expressive not only for the synthesis or fabrication, or the possibility to control or functionalize such materials, but for characterization techniques, with a highlights role, as it allowed the identification and monitoring, under specific or diverse conditions, of features and properties that were never assayed before [13].

The upsurge of the so called smart polymers changed this field changed considerably [13]. In essence, the term was given to polymers that were capable of responding to stimuli, and thus presented a smart or intelligent behavior, such as light, pH or temperature changes [14,15]. The impact of the so-called smart materials for biomedical applications was evidenced as novel technologies emerged, considering the broad range of novel possibilities and the huge potential involved, whether resultant from the fabrication and development of novel materials, or from the possibility to improve conventional ones [16-17]. In a sense, all areas benefitted from the advancement of the technology. Considering the relevance of this group of materials, the impact in the society was remarkable. Enormous advantages may be enlisted...
and of course, vary from case to case, but to some extent, apart from the functionality itself, such materials share one feature in common, the possibility to respond only under stimulus, or in practical terms, in a predictable manner, which was not achieved otherwise [17,18]. For instance, the applications of such materials concerning biomedical applications comprise, but are not limited to, drug delivery, tissue engineering, as novel technologies emerge [19,20].

Within this context, this chapter reviews the concept of “smart polymer”, comprising a detailed and up-to-date approach over fundamental aspects such as synthesis and characterization techniques with emphasis on the evaluation of the responsive properties, combined with an overview of the state-of-the-art, recent developments and potential biomedical applications.

2. Smart polymers

Stimuli-responsive”, “smart”, or “intelligent” polymers are those able to modify their physical-chemical properties in response to the variation of environmental factors. Stimuli-responsive systems can be designed to respond to a wide range of external variables, such as changes in temperature, ionic strength, pH, electric and magnetic fields, or light [21, 22]. These polymers can respond to stimuli in several ways by altering shape, solubility, wettability, color, conductivity, light transmitting abilities, and surface characteristics when a stimulus or stimuli are applied. The degree of response of such polymers can be trigged and controlled by the intensity of the applied stimuli. Typically, the changes are limited to the formation or removal of secondary forces, such as hydrogen bonding, hydrophobic effects, osmotic pressure, electrostatic interactions, etc.; [23]

Based on the structure-property relationship, synthetic and modified natural polymers have been obtained with well-controlled composition and architecture. Due to their well-controlled properties, stimuli-responsive polymers can be potentially utilized in many fields such as water treatment [24,25], enhanced oil recovery [26], catalysis [27], separation processes [28], etc.

Smart polymers have also been useful as drug delivery systems [29-31] and in the biotechnological field for enzyme immobilization [32,33]. Although more recently, coating medical devices with stimuli-responsive polymers may significantly widen their range of applications. Devices able to attract/repel certain cells of the body (e.g., for prevention of inflammatory responses or behaving as tissue scaffolds), or devices that should perform as membranes or artificial muscles take advantage of these smart materials [34-37]. A surface grafted with stimuli-responsive polymers has been highlighted for its interfacial and wetting applications. For example, a smart surface with switchable wettability could be potentially used in tissue engineering and antimicrobial coatings [38-40]. In addition, a polymer material responsive to temperature or light could also be potentially utilized as sensor and actuator. Currently, stimuli-responsive polymers have been mainly emphasized for their potential applications in nanotechnology, nanoscience, and nanomedicine [41-43].

2.1 Types

The classification of the smart systems could be carried out according to the stimulus they respond to. For example, they can be classified as pH-responsive, temperature-responsive, or light-responsive materials. Also, they can be divided as reversible or irreversible. Based on the material state, they can be divided into soluble or solids such as gels or films. In addition, they can be divided based on the number of stimuli they respond to as single, dual or multiple-stimuli responsive polymers. Finally, stimuli-responsive materials can be prepared in various architectures, such as micelles [44,45], hydrogels [46,47], interpenetrating networks (IPNs) [48,49], graft copolymers [50,51], and comb-type [52,53].

2.2 Functionalities/Stimuli responsive properties

2.2.1 Temperature-responsive polymers

Among all the existing physical stimuli, temperature has attracted a great deal of attention because this stimulus can be easily applied and monitored externally. Temperature-responsive polymers change their properties due to a variation in the environmental temperature. Temperature-responsive polymers undergo an abrupt decrease in physicochemical properties above a certain temperature which is named as the lower critical solution temperature (LCST) [54]. Polymer chains behave hydrophilic and remain swollen (in water) below LCST, while above this temperature, the polymer chains become increasingly hydrophobic and collapse. On the other hand, polymers that are hydrophobic below a critical temperature and hydrophilic above it present an upper critical solution temperature (UCST) [55]. Based on the end group chemistry, several temperature-responsive polymer systems have been reported: (a) poly(N-alkyl substituted acrylamides) [56,57], (b) poly(N-vinylalkylamides) [58,59] and (c) poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO) copolymers [60,61].

2.2.2 pH-responsive polymers

Polymer chains change their properties due to a variation in the environmental pH. pH-responsive polymers can be divided into three types: (a) weak polyacidic or basic polymers, (b) or (c) macromolecular ion exchanger. Weak polyacidic or basic polymers undergo a conformational change at a fixed pH, the change is due to protonation or deprotonation in the polymer backbone. Macromolecular ion exchangers are used as ion-specific binders, polyelectrolytes, etc.
2.2.2 pH-responsive polymers

pH-responsive polymers are those able to respond to perturbations in the environmental pH. The pH-responsiveness is due to the presence of ionizable pendant groups in the polymer backbone. When exposed to an aqueous solution of an appropriate pH, these pendant groups ionize giving as result the formation of a fixed charge along the polymer [62,63]. These smart polymers are of particular interest for biomedical applications due to several locations in the body exhibit substantial pH changes during either normal function or as part of a disease state. There are two type of pH-responsive polymers: anionic (polyacids) and cationic (polybases). The first one contain pendant groups that are ionized in solutions with high pH values and they swell at higher pH values than their acid dissociation constant (pKa). On the other hand, polybases are ionized and swell at pH values smaller than their pKa. Among the most common monomers used to obtain pH-responsive polymers, we can find acrylic acid (AA) [64,65], methacrylic acid (MAA) [66,67], and dimethylaminoethyl methacrylate (DMAEMA) [68,69]. Also, we can find natural pH-responsive polymers such as gelatin, chitosan, and alginate [70-72]. The advantage of natural pH-responsive polymers, as compared to their synthetic counterparts is their ability to degrade within the body over time, which is ideal for implanted materials or circulating drug delivery systems.

2.2.3 Electric/magnetic-responsive polymers

Electric and magnetic-responsive systems have attracted considerable attention because of their easy controllability and industrial needs. Electric-responsive polymers are typically conducting polymers that can transform their shape (shrink or swell) when subjected to an electric field [73]. Electrical stimulus can precisely control the response of polymers via the magnitude of the current, duration of an electrical pulse and intervals between the pulses. Usually explored electrically responsive polymers include polythiophene [74], polyaniline [75], and polypirrole [76]. On the other hand, polymers that respond to changes in magnetic fields are called magnetic-responsive polymer. These polymer systems are usually made of elastomers or gels with small magnetic particles [77]. These magnetic particles are usually iron (III) oxide particles, ferromagnetic particles, and nickel powders. Some polymers that have been explored for developing the magnetic-responsive materials are: poly(N-isopropylacrylamide) (PNIPAAm) [78], poly(dimethylsiloxane) (PDMS) [79], and poly(N,N'-dimethylacrylamide) (PDMAAam) [80]. The interesting smart electro/magneto-responsive characteristics of quick response and fine tuning make the appropriate candidates in broad engineering areas, such as medical therapies, artificial muscle stimulators, actuators, micro-fluidic control, and viscosity reduction of crude oil.

2.2.4 Light-responsive polymers

The use of light as external stimulus has received less attention by comparing with other stimuli such as temperature or pH. However, recently light responsiveness is gaining increasing attention in the biomedical field because of the opportunity of developing materials sensitive to innocuous electromagnetic radiation (e.g. ultraviolet (UV), visible and near-infrared), which can be applied on demand at well delimited sites of the body [81,82]. Light as a stimulus offers numerous advantages such as high accuracy with tunable exposure wavelength control and instantaneous application. Light can potentially trigger the phase transition of polymers applied on the skin or external surfaces of human body. Also, light can be applied directly on the polymer surface to trigger a response. In light-responsive polymers, the impact created by exposure to light induces photoisomerization and/or photochromism, which renders light as a highly versatile stimulus. The most common light-responsive polymers include azobenzene (trans–cis isomerization) [83], triphenylmethane [84], spiropyran [85], polymers containing cinnamates groups [86] which, in response to a specific radiation wavelength, undergo conformational changes or modifications in their hydrophilicity that are transmitted to the whole polymer. These materials can be used as smart coatings, soft actuators, catalysis, etc. [87-89].

2.3 Methods of Synthesis

By far, the most common stimuli-responsive polymers have been obtained as hydrogels of graft copolymer. This chapter focuses on this one.

2.3.1 Smart polymer hydrogels

Hydrogels are three-dimensional high-molecular weight networks that swell in water or in biological fluids without dissolving. They are organized as 3D networks of polymeric chains, physically and chemically bounded, and partially solvated by water molecules [90]. Hydrogels swell considerably in an aqueous medium which contributes to their good blood compatibility and maintains a certain degree of their structural integrity and elasticity. The 3D structural-integrity and properties of hydrogels are mainly dependent on their method of preparation. These materials have great interest in particular in biomedical applications, thanks to their three-dimensional structure, high water content, good biocompatibility, and mechanical properties [91].
Hydrogels can be synthesized with required properties depending on the chemical structure, composition and conformation of starting materials, density of linking of polymer chains, hydrophobicity and hydrophilicity for a particular application. Also, hydrogels can be prepared from either chemical or physical crosslinking. Hydrogels made from chemical crosslinking form permanent junction-type networks. On the other hand, hydrogels can be prepared from physical crosslinking allowing the formation of transient junction type networks, such as polymer chain entanglements or physical interactions such as, hydrogen bonds, ionic or hydrophobic interactions.

Smart hydrogels exhibit dramatic changes in their swelling behavior, network structure, permeability and mechanical strength in response to external stimuli, including pH, ionic strength, temperature and electrical or magnetic fields. Stimuli-responsive polymers play an important role in the development of novel smart hydrogels. The most important systems from a biomedical point of view are those sensitive to temperature and/or pH. Poly(N-isopropylacrylamide) (PNIPAAm) is one of the most extensively studied temperature-responsive polymer for the preparation of smart hydrogels [92,93]. However, other kind of smart polymers have been used for the preparation of smart hydrogels such as, poly(N-vinylcaprolactam) (PVCL) [94,95], poly(dimethylaminoethylmethacrylate) [96,97], poly(acrylic acid) (PAAc) [98,99], and poly(methacrylic acid) [100,101].

Smart hydrogels can be prepared from natural or synthetic polymers. The first ones have many advantages over the synthetic ones due to their low toxicity and good biocompatibility. However, they may not provide sufficient mechanical strength and may contain pathogens or evoke immune/inflammatory responses. A typical example of a smart hydrogel is the pH-responsive chitosan [102,103]. On the other hand, synthetic polymers usually have well-defined structures that can be modified to yield tailored degradability and functionality. They are prepared by chemical polymerization methods by using various types of monomers, for examples, acrylates, methacrylates, acrylamides, carboxylic acid, etc. [104,105]. Smart gels also can be prepared by frontal polymerization (FP), a technique that allows the conversion of a monomer into a polymer by formation and consequent propagation of a reaction front [106,107].

Finally, hydrogels can be prepared at nano and micro scale. Micro- and nanogels are crosslinked hydrogel particles with three-dimensional networks composed of water soluble and swellable polymers [108]. These materials present the same features of the hydrogels above mentioned and have great potential in the areas of bioimaging, anti fouling, DNA delivery, tissue engineering, drug delivery etc. [109,110] There are some strategies to prepare these materials such as inverse miniemulsion, microfluidics, and inverse nanoprecipitation [111,112].

2.3.2 Smart graft polymers

Graft polymers are segmented copolymers with a linear backbone of one polymeric matrix and randomly distributed branches of another polymer(s). Although the side chains are structurally distinct from the main chain, the individual grafted chains may be homopolymers or copolymers. Growing attention has been paid to the synthesis of well-defined graft copolymers with desired functional groups, chemical compositions, lengths of side chains and backbone, and grafting densities due to their special molecular structures and wide-ranging applications from biology to nanoscience [113]. According to the features of synthetic approaches different strategies could be employed to synthesize the graft copolymers: grafting-onto, grafting-from, and grafting-through method.

The grafting-onto strategy is based on attaching certain side chains onto a linear backbone by a coupling reaction. Since the linear backbone and side chains are prepared independently, they can be obtained by appropriate pathways and their chain lengths can be easily tuned. However, a highly efficient coupling method and the removal of unreacted side chains are required for preparing the graft copolymers with high grafting densities and narrow molecular weight distributions. The key in preparation of graft copolymers via the grafting-onto strategy is to employ an efficient and suitable coupling reaction of functionalized backbones with side chains [114]. The grafting-through strategy employs a preformed side chain that has a polymerizable group at one end of the chain (macromonomer or macromer). Grafting occurs when a regular monomer is polymerized in the presence of this macromonomer. The advantage of this approach is that the length of side chains and the grafting density can be controlled by adjusting the degree of polymerization of side chains and backbone, respectively [113]. The grafting-from approach begins the grafting event with only the main chain pre-polymerized. The main chain next serves as the multi-initiation site from which the side chains are then grown. This strategy is considered as a particularly attractive procedure to synthesize well-defined graft copolymers. The advantage of this method is that the reactive sites along the main chain are formed by chemical treatment or irradiation followed by addition of one monomer to generate graft copolymer. Also, in this approach there is no unreacted macroradical, which is often inevitable in another two strategies [114].

Also, smart graft polymers can be obtained by using gamma radiation. This method involves the formation of active sites on the polymer backbone by the use of high energy radiation. Monomers react with the active sites and then propagate to form side chain grafts [115-117]. Grafting using gamma radiation can be carried out following different approaches: direct method and pre-irradiation oxidative. In the first case, a polymeric material is irradiated in contact with a monomer. Irradiation produces active sites in the polymer matrix, mainly macroradicals, which initiate the graft polymerization. The second case consists in pre-irradiate the polymeric matrix in presence of air. During this process peroxydes and/or hydroperoxides species are formed in the polymeric backbone. Then, the irradiated polymer is heated in the presence of monomer (in the absence of air) in order to decompose the peroxides and hydroperoxides to give macroradicals, that are the active sites for graft polymerization. An advantage of the pre-irradiation oxidative method is...
the possibility of storing the irradiated polymer some time before grafting. Some disadvantages are that the hydroxyl radical induces homopolymerization and that the pre-irradiation method requires a higher dose of radiation than the direct method [118].

Graft copolymers can be obtained in one or two steps applying the pre-irradiation or the direct method; the way for obtaining the grafted materials depends of the chemical structure of polymer that serve as a substrate and/or the monomers that are going to be grafted. When the grafting is carried out in one step with two monomers, random copolymer branches are formed. By contrast, the two steps method leads to branches containing only one kind of monomers. Most surface grafting polymerizations are carried out through the one-step or simultaneous method, in which the grafting proceeds in the presence of monomer under ionizing irradiation. The two-step or combinatorial technique first introduces dormant groups on substrates under ionizing radiation and, then, the grafting polymerization is initiated by heating or irradiation [119, 120].

Relatively inert materials, such as polypropylene (PP) [121, 122], cotton fabric [123, 124], silicone rubber [125], and polyethylene [126] have been widely used as components of medical devices and endowed with temperature and/or pH-responsive by grafting sensitive polymers at the surface through gamma radiation.

3. Characterization of sensitive polymers

Currently, there are many methods available regarding the characterization of sensitive polymers which rely upon the responsive properties of the smart polymer. This chapter details pH and thermal responsiveness, and thus, the main methods of characterization with regard to pH and thermal sensitivity of the polymeric films are described below.

3.1 Swelling measurements

The equilibrium of swollen materials in distilled water is determined by swelling the dried grafted polymeric samples for different periods of time and weighing them on an analytical balance until a maximum and constant weight is obtained [127-133]. The degree of swelling of the films (%) is calculated according to the formula:

\[
\text{Swelling (\%)} = \left(\frac{W_s - W_d}{W_d}\right) 100
\]

where \(W_s\) and \(W_d\) are weights of the swollen and initial catheter respectively.

3.2 Thermo sensitive polymers

Miscibility in high molecular weight polymer blends is governed mostly by intermolecular interactions because contribution of the combinatorial entropy to mixing is negligibly small. Miscibility for most miscible polymer blends is caused by specific (i.e. attractive) interactions, which leads to LCST behavior, the LCST of different smart polymers are determined by swelling them in water for the equilibrium time at different temperatures and plotting the swelling percentage as a function of temperature. The inflexion point gives the LCST [134-137].

3.3 pH critical point.

The critical pH point is determined in the same way from a plot of swelling percentage in different pH solutions with a buffer of citric acid and sodium phosphate. In pH-sensitive smart materials, the responsive mechanism lies within the side chain groups, branches, and crosslinks of a polymer's chemical structure. In polymer networks that contain weak acid or base groups, absorption and adsorption of water can occur simultaneously. The movement of water into the polymer network results in ionization of the acid and base pendant groups. This phenomenon is controlled by the solution's pH, ionic composition and ionic strength [138-140]. Acrylic acid (AAc) is one of the most popular monomers that have been grafted onto different polymeric matrices, and its polymer or copolymers with pH sensitive response have a capability to undergo further chemical reaction to produce new functional groups [141,142].

3.4 Surface plasmon resonance spectroscopy (SPR)

Is a surface-sensitive characterization based on the evanescent field of the surface plasmon. The latter is an electromagnetic wave traveling along the interface between a metal and a dielectric. Its electric field decays exponentially into both materials over a distance of a few hundred nanometers and the wave has a finite propagation length due to damping processes in the metal. The resulting data are a direct measure of the local average refractive index of the dielectric close to the surface, and with Fresnel calculations either the thickness or the refractive index of thin films at an interface can be determined. Furthermore, a time-dependent measurement mode enables the detection of changes in the local average dielectric constant due to the adsorption of molecules onto the surface or changes in film properties due to an external trigger [143]. Surface plasmons are the quanta of charge-density waves of free electrons in a metal propagating along the interface of a metal and a dielectric medium such as buffer or air. The electromagnetic field of these surface waves reaches its highest intensity at the metal surface and decreases exponentially into the
adjacent phase. Therefore, it is influenced by the optical properties of this phase. The strong dependence of the surface plasmons on the refractive index of the dielectric medium can be used for sensor development purposes [144-149].

3.5 FTIR spectroscopic method for the determination of the LCST.

This is a new and simple method for determining the LCST in both linear and crosslinked polymers by FTIR spectroscopy [150,151]. This technique has been shown to be useful for probing transitions such as a lipid bilayer transition, for the self-association of aqueous surfactants, and for studying changes in hydrogen bonding in polymers. In addition, changes in the infrared spectra provide information on the conformation and bonding state of the functional groups involved in the transition. In this method, the FTIR-ATR spectra of PNIPAAm change dramatically in the vicinity of the coil-globule transition temperature. Although the polymer will aggregate and precipitate at the bottom of ATR crystal above LCST, this exactly indicate the occurrence of phase separation, actually the polymer will also aggregate to some extent above LCST using the IR transmittance measurements. In addition, the generalized 2D IR correlation spectroscopy, proposed by Noda [152,153], could be effectively applied to the examination of IR spectra of polymer solutions [154].

3.6 Thermal transition of responsive materials

Heskins and Gillet were the first to report that an endotherm can be observed at the LCST upon heating an aqueous solution of PNIPAAm [155]. Grinberg [156] studied the volume phase transition in responsive polymers using high-sensitivity differential scanning calorimetry (DSC) and the swelling behavior of the polymers at different scanning rates was considered. It was possible to measure the dependence of the transition parameters on the heating rate. The DSC measurements, by heating at different rates, provide results closely approximating equilibrium. The transition temperature, enthalpy, and entropy of this thermosensitive behavior as well as the transition LCST can be determined. The LCST of the linear polymers (0.5%, w/v) was determined using an aqueous sample (10 mg by weight). The samples were run in a sealed aluminum crucible under a nitrogen purge at 1 °C/min unless otherwise stated. Samples were analyzed in the range from 0 to 60 °C. The transition temperature has been defined in previous studies as either the temperature of onset or the peak temperature. In the current work the phase transition temperature was defined as the maximum of the endothermic transition peak [157].

3.7 Contact angle.

This method consists of the measurement of advancing and receding contact angles by a dynamic method [158], or by the sessile drop method using the optical contact angle [159,160]. The measurements of the contact angles for various samples are carried out at room temperature, 1 minute after water drops are deposited onto the surface of polymeric films, using direct microscopic measurement of the contact angles. The contact angle is an important parameter in surface science. It is a common measure of the hydrophobicity of a solid surface. In the literature, it is well established that meaningful contact angle measurements can be used in the calculation of solid surface tensions. In the past several decades, numerous techniques have been used to measure contact angle which were inspired by the idea of using the equation first derived by Thomas Young in 1805 [161-163].

3.8 Microscopy

Surface morphology investigation and force-curve measurement with atomic force microscope (AFM) was used for determination of stiffness; microscopic infrared imaging is commonly used to found the distribution of specific compounds on the surface. Specially, the use of a confocal laser microscope enables surface morphology measurement of extremely soft surface on the swelled copolymers, which is essential to investigate pH response in buffer solutions. Nano-porous polymeric systems fabricated using fluorescently end-labeled samples of PAAc permitted real-time imaging of changes in internal structure using confocal microscopy (LSCM). The investigation and relationship between the surface morphology and the composition and other condition of the copolymers, and in-situ change of surface morphology induced by the external stimulation such as pH and/or temperature change can be evaluated by the scanning electronic microscopy (SEM), with this technique is possible to visualize the morphology surface by means of a micrograph; furthermore the composition along the surface and at different thickness of the micrometer order of magnitude can be recorded by Raman spectroscopy. Force curve measurement by AFM will be performed using a special home-made tip with a colloidal nano-sphere attached to the cantilever, which is essential to measure an extremely soft surface. These techniques help to investigate the relationship between the surface stiffness and the composition and other condition of the copolymers, and change of surface stiffness induced by the external stimulation such as pH and/or temperature change. Using microscopic infrared imaging, could be investigate the change of spatial distribution of specific chemical species induced by the external stimulation. Combination of these results reveal the actual surface behavior as the response to the applied external stimuli (pH and/or temperature change), and it will enable us to optimize the design of the materials [164,165].
4. Potential Biomedical applications

From a biomedical point of view, the development of smart polymers and materials brought to light alternative solutions to unresolved problems by providing effective and suitable materials capable of responding specifically to the disease, illness to be treated or a specific need [166-167]. Up to now smart polymers have been extensively explored as drug delivery systems, materials for scaffolds and cell cultivation [168], biosensors and implants among others due to their unique ability to respond to stimulus, which assures a better interface with biological tissues and an optimized response as a consequence.

Regarding drug delivery systems, perhaps the most relevant therapeutic advantage over conventional or even controlled release systems relies on the response triggered or regulated according to the symptoms of a disease as they appear, such as fever, metabolic acidosis and so on. In practical terms, the material is capable of sensing changes and providing a drug-release profile regulated by the biological effects/changes caused in the organism [166,168]. As result of the recent advances in the technology, an increasing number of patents over the years, regarding smart polymers for the delivery of specific classes of drugs, such as proteins and peptides has been identified [169].

5. Conclusion

The upsurge of smart polymers unraveled novel possibilities with regard to polymer science, mainly in terms of responsiveness, which was not achieved in the past by any other method. The elegance of these materials lies indeed in their change as a response to stimuli of a wide variety of sources and nature. The responsive properties results and varies according to the intrinsic characteristics of selected monomer, subunit or molecule to be attached to polymer. Of course and not least relevant, the amount, concentration or displacement of such units along the polymer backbone dictate the final characteristics of the material, and correspond to ways of controlling or designing the polymer for a desired purpose.

A deep and careful characterization is mandatory to effectively assure the responsiveness and other properties of the polymer or product based on the material. Apart from the physical, chemical or mechanical characterization, the responsive properties must be carefully assayed; both on a compound and stimuli based approach.

Although the applications of smart polymers are enormous, the constant changes and advances in technology makes it hard to predict how far the applications or the possibilities to combine or improve such materials may reach. By means of biomedical applications, the contribution is directed towards innumerable benefits, with a highlight for controlled and stimuli-based advanced release systems, materials for tissue engineering and cell cultivation, including bone implants, as well as biosensors, which allowed detection and monitoring of biological markers, mediators or compounds, in real time, without the need to be constantly removed from the organism.

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