# Chapter 1
# Polymer Nanoparticles for In Vivo Applications: Progress on Preparation Methods and Future Challenges

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**Abstract** Polymer nanoparticles are one type of the arsenal of nanomedicines that are developed to improve efficacy and specificity of drug delivery and to design new contrast agents enhancing the performance of diagnostic methods based on imaging techniques. To answer the various challenges, it has lead the way to development of suitable nanoparticles. Many types of methods of preparation were proposed designing nanoparticles taking different structures and integrating various functions. The purpose of the introduction to the part I of the book devoted to the methods of preparation of polymer nanoparticles to be used as nanomedicines is to present the different types of polymer nanoparticles that were designed so far and to give an overview on their methods of preparation. It is also important to place these methodologies in a prospective view raising future challenges and bottlenecks.

**Keywords** Methods · Micelles · Polymer nanoparticles · Nanocapsules · Nanospheres · Nanogel · Polyelectrolyte complex · Self-assembling · Precipitation · Polymerization · Emulsion · Polymer solution · Layer-by-layer · Print · Microfluidic · Self-assembling · Complex · Spherical particles · Nonspherical nanoparticles · Multifunctional nanoparticles

## 1 Introduction

In the 1970s, polymer nanoparticles were found to be suitable materials thanks to their small size to serve the purpose of the "magic bullet" born behind the concept of drug targeting that was inspired by Paul Ehrlich, an imminent bacteriologist and immunologist who received the Nobel Prize in Physiology and Medicine in 1908. However, to be used as drug carriers, polymer nanoparticles need to comply with

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regulatory registration and fulfill stringent specifications. Besides, they must integrate all functionalities that are needed to complete a specific medical application. Among others, this includes a composition made of suitable materials for in vivo use and preparation conditions that are compatible with the production of pharmaceutical grade compounds.

## 2 Development of Methods of Preparation of Nanoparticles Made of Polymers: Progresses

By the time polymer nanoparticles were first introduced to be used as drug carriers, they were produced by polymerization methods (Birrenbach and Speiser 1976; See the historical perspective by Kreuter 2007; Couvreur 2013). In addition to regulatory constraints that are an important limitation for the choice of the polymer composing the nanoparticles, nanoparticles designed to become nanomedicines need to fulfill various types of functions. Drugs should be associated efficiently with nanoparticles while protection against degradation should be insured in storage conditions and in vivo during transportation of the nanomedicine toward the target site of delivery of the drug. This implies that the drug remains associated with the nanoparticles during transportation. However, the association needs to become unstable once the nanoparticle has reached the target site, where the drug should be available to express its biological activity. Behind mechanisms controlling the stability of the association of the drug with the nanoparticles, other functionalities are needed to help the nanoparticles to reach the delivery site. The requested properties, which are contradictory for some of them, can be associated customizing the design of new polymers. The number of suitable polymers that can compose nanoparticles developed to be used as nanomedicine produced by polymerization methods is extremely low being a bottleneck for an extensive development of the polymerization methods to prepare polymer-based nanomedicines. Other limitations of these methods include the use of organic solvents and sometimes of large amounts of surfactants, while the majority of polymer nanoparticles synthesized by polymerization methods are nonbiodegradable. Nevertheless, the first rapidly biodegradable nanoparticles were synthesized by emulsion polymerization using alkylcyanoacrylate monomers (Couvreur et al. 1979). A broad range of nanoparticles composed of poly(alkylcyanoacrylate) were synthesized since then and are used to develop innovative therapeutic strategies with many types of drugs with interests for developing treatments of serious diseases (Vauthier et al. 2003a, b, 2007; Andrieux and Couvreur 2009; Nicolas and Couvreur 2009). Today, poly (alkylcyanoacrylate) nanoparticles prepared by polymerization methods continue to generate interest on the international scene (Murthy and Harivardhan Reddy 2006; Vauthier et al. 2007; Graf et al. 2009; Nicolas and Couvreur 2009; Yordanov 2012; Sulheim et al. 2016). Polymerization methods were successful to provide with nanoparticles of interest that were translating to clinics being evaluated in clinical

trial phase II/III for the treatment of hepatocellular carcinoma (primary liver cancer) (Zhou et al. 2009; Soma et al. 2012; Onxeo 2016). However, all nanoparticles developed as nanomedicines and prepared by polymerization methods were synthesized with monomers of the alkylcyanoacrylate family limiting the choice of intrinsic properties that can be given to the particles although some flexibilities are allowed tuning conditions of polymerization (Chap. 5 from Vauthier).

To enlarge the choice of polymers composing nanoparticles to be used as nanomedicines, a series of methods were developed based on the use of polymers that were synthesized independently of the nanoparticles. Obtaining polymer nanoparticles from already prepared polymers was a challenge. The first series of attempts was based on the use of matrices formed by thin emulsions in which the polymer was dissolved in the tiny droplets composing the dispersed phase of the emulsion. The polymer was then forced to precipitate using various artifacts in order to obtain nanoparticles. Evaporation of the solvent contained in the droplets was the approach proposed in the pioneer work in the early 1980s (Gurny et al. 1981). The development of this emulsification-solvent evaporation method was applied first to the production of nanoparticles made of poly(lactide) (PLA), the most used polymer composing medical devices for parenteral administration. Since then, the method has been applied to a large choice of polymers. This method brought a real breakthrough. It was the first time nanoparticles were obtained directly from polymers while they were all obtained before by polymerization methods. It was an important milestone for the development of methods for the preparation of nanomedicines occurring as polymer nanoparticles. In a derived method also based on the precipitation of a polymer dissolved in the emulsion droplets, the polymer solvent is extracted from the droplets diluting the emulsion with a third solvent in which both the continuous and the dispersed phases of the parent emulsion are miscible. This operation causes the immediate precipitation of the polymer contained in the emulsion droplets that compose the dispersed phase of the emulsion. In general, both the emulsification-solvent evaporation method and the emulsification-solvent extraction method can be applied with polymers that are soluble in organic solvents (Chap. 4 from Mendoza-Muñoz et al.). Instead of precipitation, the polymer contained in the droplets of the emulsion can be gelified. This method was addressed to produce nanoparticles composed of hydrogels to associate hydrosoluble drugs with nanoparticles that was challenging with previous methods. The main difficulty with methods based on the use of emulsions is to prepare emulsion with a small size of the emulsion droplets. While the majority of works were based on the use of mechanical techniques to produce the thin emulsion required, several authors have suggested the formulation of miniemulsions and microemulsions as matrices to produce the nanoparticles. More recently, microfluidic techniques have been introduced. Droplets hence nanoparticles are formed one by one in a very well controlled manner (Karnik et al. 2008; Valencia et al. 2012; Pedro et al. 2013; Lim et al. 2014). To avoid the use of organic solvents, supercritical fluid technologies were envisaged (Sun et al. 2005; Meziani et al. 2006; Elizondo et al. 2012; Sheth et al. 2012; Girotra et al. 2013).

In another series of methods, nanoparticles are prepared directly from polymer solutions. Nanoparticles form by causing a rapid change of the physicochemical conditions that induces the nucleation of particles of small size. In general, they form by mixing the initial polymer solution with a second medium with which it is fully miscible. Mechanisms behind nucleation of nanoparticles include precipitation of the polymer, self-assembling of macromolecules providing that they were selected with the required architecture or specific properties, formation of complexes and gelation. Figure 1 illustrates the formation of nanoparticles based on the induction of nucleation from two examples of methods: the formation of polymer micelles resulting from self-assembling of amphiphilic polymers assisted by solvent diffusion (Fig. 1a) (Chap. 2 from Miladi et al. and Chap. 3 from Tang and Prud'homme), and the formation of nanogels triggered by self-assembling of two polymers having complemental groups to form inclusion complexes between alkyl chains grafted on one polymer and cyclodextrins grafted on a second polymer (Fig. 1b) (Gref et al. 2006; Hassani et al. 2012).

In some cases, the nucleated nanoparticles are stabilized in a second step that can be performed in the same vessels. For instance, after nucleation of polymer particles by precipitation, it is generally necessary to remove the solvent of the polymer from the dispersing medium. The so-called nanoprecipitation method in which nanoparticle nucleation is induced by a solvent shift belongs to this category of method (Fessi et al. 1989; Ganachaud and Katz 2005; Minost et al. 2012; Chap. 2 from Miladi et al. and Chap. 3 from Tang and Prud'homme). Nanoparticles obtained by gelation are sometimes stabilized by complexation with another polymer that sticks on the surface to stabilize the particle (Oh et al. 2008; Kabanov and Vinogradov 2009; Maya et al. 2013; Wu and Delair 2015). Interesting features with these methods are their rapidity and scalability because production can be performed with a continuous-based process as demonstrated with the nanoprecipitation method. These methods of preparation can be achieved with a large panel of polymers. Although precipitation methods and methods based on self-assembling of amphiphilic polymers generally require the use of organic solvents (Fig. 1a) (Chap. 2 from Miladi et al. Chap. 3 from Tang and Prud'homme, Weber 1998; Torchilin 2007; Kabanov and Vinogradov 2009; Rowan 2009; Guan et al. 2015; Fuks et al. 2011; Pearson et al. 2013; Robertson et al. 2013), self-assembling methods based on the formation of polymer complexes and those based on a gelation process can be performed in aqueous media avoiding totally the use of organic solvent (Fig. 1b) (Vauthier and Couvreur 2000; Janes et al. 2001; Gref et al. 2006; Kabanov and Vinogradov 2009; Daoud-Mahammed et al. 2009; Delair 2011; Hassani et al. 2012; Maya et al. 2013; Eckmann et al. 2014). Another marked advantage of the last category of method is given by the fact that nanoparticles form in gentle conditions that are suitable to associate very fragile hydrosoluble molecules with the nanoparticles. For instance, the methods based on the formation of complexes and nanogels can be used to associate biologically active peptides, proteins, and nucleic acids with nanoparticles. With methods based on the complexation of polyelectrolytes of opposite charges, peptides, and nucleic acids may compose one of the polyelectrolyte involved in the formation of the complex

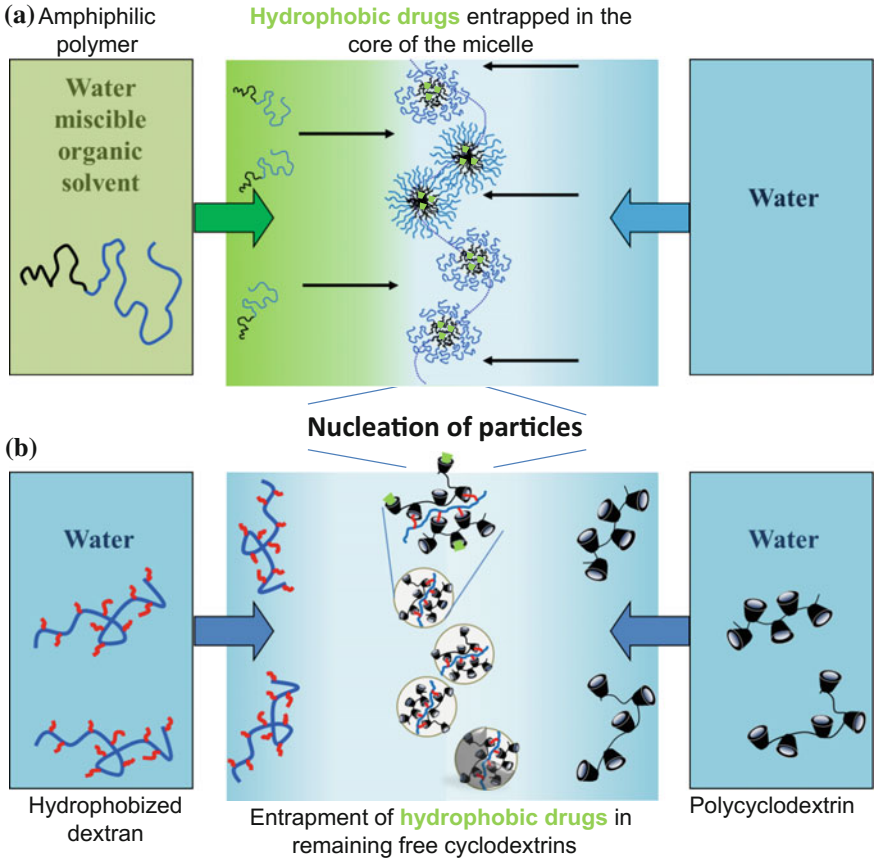


**Fig. 1** Preparation of nanoparticles by nucleation of particles thanks to self-assembling of soluble polymers. Nucleation of polymer particles occurs while mixing two miscible solutions. **a** Formation of polymer micelles assisted by solvent diffusion. This can be applied with amphiphilic polymers. **b** Formation of nanogels by self-assembling of neutral hydrosoluble polymers including a polycyclodextrin and a hydrophobized dextran. The nanogels form, thanks to the formation of inclusion complexes between the cyclodextrins grafted on one of the polymers and alkyl chains grafted on the second polymer (hydrophobised dextran shown on the figure)

included in the final nanoparticles (Kabanov and Vinogradov 2009; Delair 2011; Kataoka et al. 2001; Mukhopadhyaya et al. 2012; Osada 2014; Bekale et al. 2015; Shiraki et al. 2016). All these techniques of preparation of polymer nanoparticles allow production of nanoparticles with a wide range of properties thanks to the nature of polymers that can be used to produce them.

## 3 Producing Polymer Nanoparticles with Different Structures and Characteristics

A broad range of methods of preparation of polymer nanoparticles was requested to permit association of drugs having various biological activities and physicochemical properties. In general, molecules are associated with the nanoparticles while they are solubilized in an appropriate solvent. Solubility properties of drug molecules are important factors to consider and that contribute for the success of drug to nanoparticle association. Although soluble molecules are the majority of compounds that were associated with nanoparticles so far, metal nanoparticles were interesting ingredients to associate with polymer nanoparticles designing a new generation of contrast agents for application in diagnostic based on imaging techniques (Khemtong et al. 2009; Maya et al. 2013; Cormode et al. 2014; See Chap. 17 from Herceg et al.). The solvent in which the drug molecule is soluble or metal nanoparticles occur as a stable dispersion is a key for the choice of the method of preparation. However, in general, methods of preparation need to be customized on a case-by-case basis to design each new nanomedicine. Existing methods can be used to inspire the development of new methods. They were applied to make nanoparticles with polymers of various nature and to produce nanoparticles having different structures to resolve many different challenges found to achieve efficient drug association and releasing issues (Fig. 2) (Chap. 13 from Zandanel and Charrueau, Chap. 14 from Charrueau and Zandanel).

Methods based on general principles that were described above are all suitable to prepare matrix-like-type nanoparticles. Reservoir-type nanoparticles, i.e., nanocapsules could be obtained modifying and adapting protocols of most of the previous methods (Couvreur et al. 2002; Mora-Huertas et al. 2010). Figure 3 summarizes the different methods of production of polymer nanoparticles and gives the type of nanoparticle produced.

Size and shape of nanoparticles are important characteristics to consider as they both influence the pharmacokinetic and cell uptake; hence, they can dramatically affect the efficacy of the nanomedicine (Truong et al. 2015). In general, size can be well controlled by experimental conditions used preparing the nanoparticles. Nanoparticles with a spherical shape are generally prepared by the above-mentioned methods. The obtaining of nanoparticles with a shape that differed from a sphere was reported only in a few cases producing nanoparticles by self-assembling of polymers and amphiphilic materials (Lee et al. 2010; Cauchois et al. 2013; Chap. 6 from Ponchel and Cauchois). New methods were specifically introduced to design nanoparticles with well-controlled nonspherical shapes (Chap. 6 from Ponchel and Cauchois). For instance, rod-like nanoparticles can be produced stretching spherical particles embedded in a stretchable matrix (Mitragotri 2009; Wang et al. 2011a). Print methods were introduced to design polymer nanoparticles with a wide range of shapes (Oh et al. 2008; Wang et al. 2011b; Perry et al. 2011; Sultana et al. 2013) (Fig. 4).

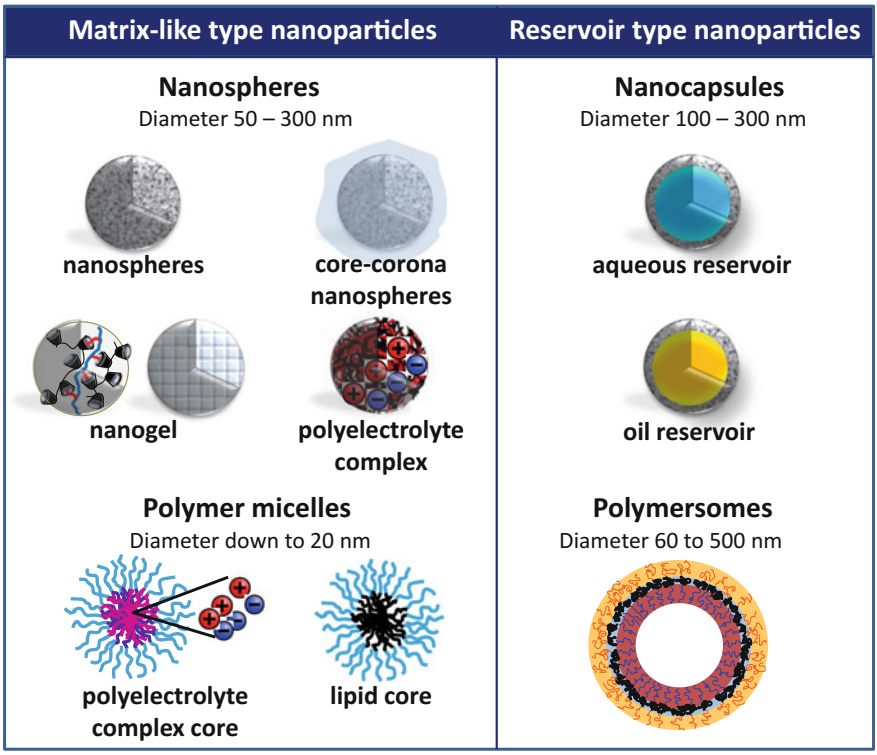


**Fig. 2** Different types of polymer nanoparticles showing the structures

## 4 Future Challenges

In the infant age of their development, polymer nanoparticles were designed as very simple particles based on the association of a drug with a nanosized-scale particle made of biodegradable polymer. The evolution is to design multifunctional nanoparticles that may include diagnostic and therapeutic elements together with equipment's controlling the pharmacokinetic and biodistribution hence improving targeting efficiency of the carrier and its drug releasing properties. Table 1 summarizes the different functionalities that are desired to associate with nanoparticles and gives examples of items found in the corresponding toolbox to achieve each function.

The possibility to design very precise nanoparticles with polymers by tuning nanoparticle properties to optimize the benefit of the treatment for each patient taking into account the individual variability while the safety profile will be high is

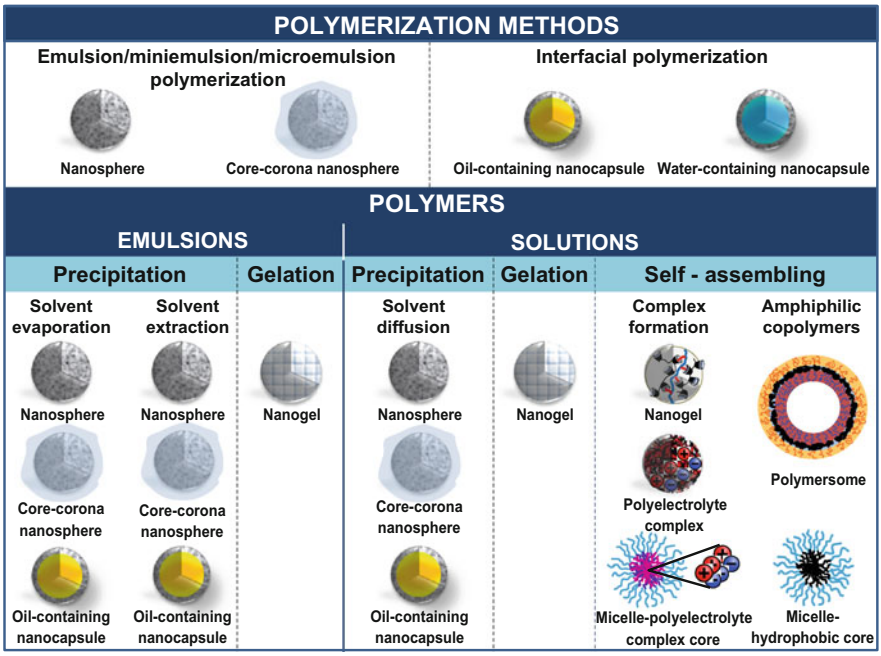


**Fig. 3** Summary of general principles of methods of preparation of nanoparticles from polymerization procedure and protocols based on the use of polymers either included in the dispersed phase of an emulsion/miniemulsion/microemulsion or occurring as a polymer solution. This summary indicates the type of nanoparticles that are produced from these methods illustrating the spherical species

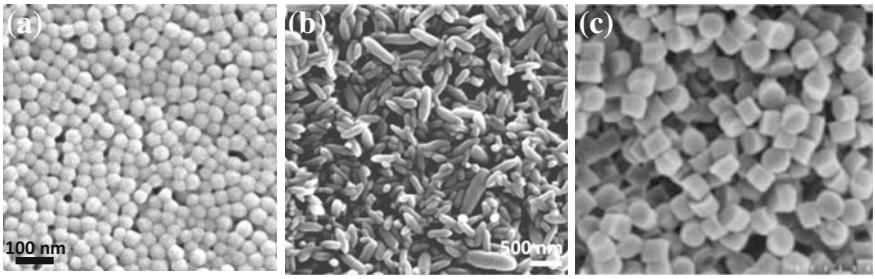


**Fig. 4** Example of polymer nanoparticles obtained with different shapes as shown by scanning electron micrograph. **a** spherical nanoparticles obtained from anionic emulsion polymerization of isobutylcyanoacrylate (C. Vauthier, personal collection), **b** rod-like nanoparticles obtained by nanoprecipitation of poly(γ-benzyl-l-glutamate) (Mw:70 kDa) (Adapted from Cauchois et al. 2013, reproduced with permission), and **c** 200 × 200 nm cylindrical nanoparticles made of poly (lactide-co-glycolide) prepared by a print method (Adapted from Wang et al. 2011b, reproduced with permission)

**Table 1** Functionalities that may be associated with polymer nanoparticles designed as nanomedicines

| Function | Tool | Tool occurrence* | Additional information |
|---|---|---|---|
| Therapeutic | Therapeutic agents | Drug molecule | Small chemical molecules and macromolecules from biology, peptides, proteins, and nucleic acids |
| | | Metal nanoparticles | Gold nanoparticles enhancing efficacy of radiotherapy<br>Metal nanoparticles (gold nanoparticles, magnetic nanoparticles) enhancing treatment based on hyperthermia |
| | | Nanocrystals | Upconverting nanoparticles (UCNP) for photodynamic therapy |
| | Drug releasing control system | Stimuli responsive polymer | Chemical stimuli: pH, oxidant, reductant |
| | | | Physical stimuli: light, temperature, and ultrasound waves |
| | | | Biochemical stimuli: enzymatic degradation |
| Diagnostic | Contrast agent for imaging techniques | Ultrasmall paramagnetic iron oxide nanoparticles (USPIO) | Magnetic resonance imaging |
| | | Perfluorocarbone | Ultrasound imaging |
| | | Fluorescent tracers occurring as molecular compounds or metal nanoparticles (quantum dots) | Optical imaging |
| Guidance | Controlling general interactions with tissues and the immune system | Macromolecules arranged at the nanoparticle surface | Stealthiness, mucoadhesion, diffusion in tissues |
| | Cellular and molecular targeting | Molecular ligand highly specific to a well-defined cell receptor | Antibody or other types of proteins<br>Small molecule (folic acid for instance) |
| | External guidance | Magnetic particles | Targeting from the application of an external magnetic field |

*Examples of items of the toolbox to achieve each function

seen as an opportunity to elaborate personalized therapeutic protocols (Mura and Couvreur 2012). To permit the development of suitable nanoparticles to be used in personalized nanomedicine, nanoparticles should be tailor-made with a great flexibility. Methods for the preparation need to satisfy all exigencies that are required to make the nanoparticles a pharmaceutical compound having a given activity. In the same time, there will be a need for methods fulfilling reproducible preparation of nanoparticles with customized properties. Emerging approaches are based on the development of platforms that allow preparation of nanoparticles which properties can be tuned easily. For instance, those based on self-assembly of polymers are progressing as they can be applied to assemble a family of polymers in which each is bearing a different functionality to be included into one nanoparticle (De Miguel et al. 2015; Bao et al. 2013). Another suitable method that offers possibilities to integrate different functionality in a single nanoparticle is based on the superimposition of polymer layers forming the final nanoparticles layer-by-layer (Caruso 2001; Bao et al. 2013; Yan et al. 2014). These strategies allow the building of multifunctional nanoparticles with high precision. Preparation of multifunctional nanoparticles is also accessible by most of the other described methods providing that the polymer that gives the structure of the nanoparticle also shows the required properties. In general, this can be achieved customizing the design of polymers to give them all desired features as explained in the Chap. 12 from Cammas. For instance, this approach can be used to conceive stimuli responsive nanoparticles delivering their cargo in well-controlled conditions (Mura et al. 2013). Surface functionalization can be adjusted introducing postsynthesis modifications. This is often used to equip the nanoparticle surface with a targeting moiety to optimize precision of the delivery method at the target site (Nicolas et al. 2013). Postsynthesis modifications are predominantly achieved by chemical methods but the layer-by-layer approach is another option to achieve surface modification of nanoparticles (Labouta and Schneider 2010; Poon et al. 2011; Bao et al. 2013; Ejima et al. 2013; Nicolas et al. 2013; Yan et al. 2014). In the movement which tends to increase the number of functionality to associate with nanoparticles, it is nevertheless important to keep in mind that the complexity should not compromise translation to clinic. Bottlenecks to development of highly sophisticated nanomedicines may arise from their method of preparation among other factors. Whatever will be the functions to associate with the nanoparticles, the method of preparation needs to be scalable producing large amount of nanoparticles. It should also be robust to insure the reproducible production of the nanoparticles and to comply with the high rate of quality requested for pharmaceutical grade compounds to insure their safety.

This part of the book was aimed to describe methods that can be used to produce polymer nanoparticles that are interested to develop nanomedicines. Choice has been made to illustrate methods from each group. Chapters 2 from Miladia et al. and 3 from Tang and Prud'homme focus on methods based on nanoprecipitation that are using polymer solutions while the precipitation of the polymer is induced by a solvent shift. Chapter 4 proposed by Alcala-Alcala et al. described methods

based on the use of emulsions. Methods based on polymerization are described in Chap. 5 proposed by Vauthier. The obtaining of nonspherical nanoparticles is the subject of Chap. 6 proposed by Ponchel. All these chapters were written to provide with basic and practical information to inspire the development of nanomedicines made of polymer sharing the authors' expertise on the key methods of preparation.

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