Polymeric Nanoparticles for Cancer Treatment

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Contributor: Carlos Alonso-Moreno

Over the last decade, polymeric NPs have been designed to overcome the limitations of free therapeutics for the treatment of cancer. Polymeric NPs have shown a more favorable pharmacokinetic profile than the free chemotherapeutics, but optimization of the formulation, in terms of the polydispersity and size of the NPs, is still needed to improve efficacy. In the same way, drug release from polymeric NPs can be more precisely controlled, with a range of polymers designed specifically for that purpose.

Keywords: nanomedicine ; polymeric nanoparticles ; drug delivery system ; cancer treatment

1. Introduction

At the end of the nineties, nanomedicine arose as a panacea for the diagnosis and treatment of diseases. However, today, nanomedicine is still there, waiting for its potential to be fully tapped.

The first visualization of <4 nm structures took place in 1902, and was performed by Richard Zsigmondy and Henry Siedentopf. Fifty years later, the disposition of the atoms over surfaces was reported, for the first time, by Erwin Müller in 1951 using ion field microscopy. In this regard, the development of the first atomic force microscope in 1986 allowed us to finally see nanostructures in high resolution [1]. These findings attracted great interest in the field of medicine, and a surge of scientific studies and research allowed us to come up with the term “nanomedicine” [2].

Looking back, we saw the first nanoparticles (NPs) as drug delivery systems (DDS), reported in the late 1960s by Peter Paul Speiser [3]. This event is considered one of the greatest moments in the history of nanomedicine, because it represented the first “Targeted Nanotherapy”. There were other important findings aimed to implement nanotechnology in the field of medicine, such as the use of dendrimers [4] or chips [5], but, undoubtedly, the use of nanomaterials in tissue engineering paved the way for considering nanomedicine as an area of expertise in science [6]. In fact, it accelerated the registration and marketing approvals of key pharmaceuticals in developed countries [7].

Nanomedicine provides hope to improve current cancer treatment. In this sense, nanoparticles can offer several advantages in comparison to conventional chemotherapeutics based on the enhanced permeability and retention (EPR) effect. The drug can be delivered in high concentrations to the site of interest, reducing the effects to the surrounding tissues (**Table 1**collects the advantages of nanomedicines comparted to conventional chemotherapeutics). Apart from all the advantages of the use of DDS for cancer treatment, polymeric DDS are notable for clinical translation, due to the biocompatibility of the raw materials and the easy modulation to improve efficacy.

Nanomedicine can be divided into the following three main areas depending on its application: nanodiagnosis, regenerative medicine, and nanotherapy [8]. The main aim of nanodiagnosis is the early detection of diseases by the use of nanomaterials [9][10][11]. The in vivo diagnosis consists of the administration of different nanodevices for the quantification of several parameters, compounds or metabolites in the organism, while in vitro diagnosis achieves disease detection through samples obtained from patients. One of the principal nanomaterials for nanodiagnosis is the nanobiosensor, which can detect a number of compounds in real time [12].

On the other hand, regenerative medicine consists of the repair or substitution of damaged tissues and organs by nanomaterials [8]. The most commonly used nanomaterials employed for this purpose are based on carbon nanotubes, hydroxyapatite nanodevices, nanocomposites, and biodegradable polymers [13].

Unfortunately, therapeutic agents are not free of side effects and contraindications. In fact, there is a significant proportion of patients who experience adverse effects with the current therapies. On the other hand, minor, but frequent, side effects produced mean that many patients report low levels of adherence to treatments [14]. In this context, nanotherapy seems to provide solutions by therapeutic encapsulation in controlled-release systems.

Lipid-based NPs are simply formulated and are able to carry large payloads [15], but they are rapidly retained by the reticuloendothelial system, and modifications to extend their half-time circulation are requested for clinical use. However, the low therapeutic loading, and accumulation in the liver and spleen limit their options for clinical development [15]. Amongst the many materials used in nanomedicine, with promising properties as therapeutic carriers, the following one stands out: biodegradable and biocompatible polymers [16][17]. To date, many polymeric NPs are in clinical trials (**Table 3**)

2. From Raw Materials to Polymeric NPs

Polyesters are the most used raw materials for polymeric DDS generation. Ideally, the polymers selected must be biocompatible and biodegradable, and therefore the existence of ester bonds in the macrostructure make these devices easily broken in biological environments. Despite their biocompatibility, biodegradability and non-toxic properties, these raw materials present limitations to clinical translation, due to the high variability in batch productions and high immunogenicity of some natural polymers. On the other hand, synthetic polymers can be designed to modulate delivery parameters such as loading efficiencies, therapeutic release kinetics, surface charge, stability, responsivity, and size and polydispersities of the polymeric NPs.

PLA is an FDA-approved polymer, due to its biodegradability, low immunogenicity, low toxicity and high biocompatibility. PLA is degraded to lactic acid, which, in turn, is used in other metabolic routes [18]. Some studies with PLA NPs showed that lactic acid was metabolized fast, to H2O and CO2, and, therefore, was easily eliminated by the body [19]. Representative examples for the development of new cancer treatments using PLA NPs are the work carried out by Coolen et al., where PLA NPs were used for cell transfection [20], or the work reported by Feng et al., to encapsulate fisetin for breast cancer therapy [21].

PGA was used for the generation of the first bioresorbable suture in the seventies [22]. PGA is a biodegradable thermoplastic that produces glycolic acid after degradation, and is then excreted in urine. The low solubility in organic solvent, low stability in water, and quick enzymatic degradability limited the use of PGA for NPs formulation. Indeed, the use of PGA is focused on tissue engineering for bone, tendons, cartilage, teeth, and spinal regeneration [23].

The degradation products of PLGA are lactic acid and glycolic acid, which are innocuous for humans [24]. The incorporation of polyethylene glycol into the macromolecular structure allows the circulation time of the NPs to increase [25], and the bio-adhesion to different immune cell lines or different plasmatic components to decrease [26][27]. As an original strategy, Pan et al. reported hyaluronic acid-decorated hybrid PLGA nanoparticles as 17-allylaminogeldanamycin delivery carriers for targeted colon cancer therapy. In vivo studies showed much better therapeutic efficiency than the free therapeutic [28].

PCL is a biodegradable and biocompatible FDA-approved polymer, obtained from fossil resources [29]. It is soluble in a wide range of organic solvents and presents slow degradation rates (2–3 years). Once again, its use is focused on tissue engineering [30]. However, it has also been used as a raw material for DDS generation, in the form of copolymers with other low degradation rate polymers, such as PLGA or PEG [31][32].

Poly(anhydrides) [33], poly(orthoesters) [34] are examples of other polymers used for the generation of DDS. In many cases, successful devices have been formulated, such as the one reported by Fusser et al., using poly(2-ethylbutyl cyanoacry-late) to encapsulate cabazitaxel for breast cancer treatment [35], or the poly(ester amides) NPs reported by Villamagna et al.

3. Methods to Formulate Polymeric NPs

There are several methods to formulate polymeric NPs. The methods can be broken down in two main strategies, top-down and bottom-up methodologies (**Figure 6**).

In top-down methodologies, the NPs are obtained from preformed polymers; meanwhile, in bottom-up methodologies, the polymerization of the monomers is achieved during formulation [36][37]. The nanoprecipitation and displacement solvent method, several techniques of emulsification and evaporation, solvent diffusion, dialysis methods, salting-out, electro-static spraying and micro-fluids are the most important ones in the case of top-down methodologies. Bottom-up strategies have not been widely explored, but, among them, emulsion polymerization, interfacial polymerization, interfacial polycondensation and the coacervation approach are the most used [37]. The following is a more detailed explanation of the most widely used methods for the generation of polymeric NPs (see illustrations in**Figure 7**).

In this approach, the therapeutic and polymer are solubilized in immiscible organic solvents, such as ethyl acetate or dichloromethane, within the aqueous phase containing surfactants [38]. The phases are emulsified with the help of a high-speed homogenizer or sonicator. Once the nano-emulsion is stabilized, the solvent is removed. This methodology is characterized to give rise to large particle sizes [39].

It was designed to encapsulate hydrophilic therapeutics and proteins. This approach consists of the formulation of two nano-emulsions, once a simple nano-emulsion preparation is added to an external aqueous phase, and again emulsified to obtain the double nano-emulsion. NPs are formed when the organic solvent is removed. This approach was designed in order to attain higher encapsulation efficiencies for hydrophilic therapeutics [40].

The common choices of salting-out agents are magnesium chloride, calcium chloride or sucrose. Fast mechanical stirring is used to emulsify, and the solvent is removed via reduced pressure. The mixture needs ultracentrifugation and repeated washing to eliminate the salting-out agents and surfactants [41]. The main disadvantage of this methodology is that the salting out agents are, in many cases, incompatible with therapeutics [42].

The polymer and therapeutic are solubilized in miscible organic solvents, and then the mixture is added in a controlled manner over an aqueous solution during continuous stirring [43]. During nanoprecipitation, NPs are formed instantly and the therapeutic is entrapped in the polymer matrix. In this case, the solvent is removed by reduced pressure [44]. The formation of NPs is governed by the Gibbs-Marangoni effect, which describes a mass transfer in an interphase between two fluids, due to a gradient of superficial tension [45].

The basic principles of this approach are based on the application of electrostatic charges to manufacture the NPs. For this approach, a charged solution where the therapeutic and polymer are dissolved is used, and the concentration, caudal, voltage and other parameters are adjusted to generate little drops with different defined shapes and sizes in the matrix solution. This technique achieves very high therapeutic loading efficiency with a low polydispersity index [46].

The microfluid devices are designed to manipulate fluids in microscale channels. Obtaining NPs in microfluid systems is carried out by microdevices with internal dimensions of less than 1 mm [47][48].

Emulsion polymerization is the fastest scale-up method to manufacture polymeric NPs. There are two types [49], emulsion polymerization with a continuous organic phase, which consists of the dispersion of the monomer into an emulsion, and emulsion polymerization, with a continuous aqueous phase in which the monomer is dissolved in an aqueous solution without surfactants. The former is less used because of the use of toxic solvents, surfactants, and initiators, which are difficult to be removed [49].

In this case, the mixture of the therapeutic, monomers and initiator are extruded through a needle over an aqueous solution within a surfactant. During the process, NPs are spontaneously formed by monomer polymerization. Later, the solvent is removed, and the NPs are obtained. The advantage of this approach is the high encapsulation efficiency in the one-step formulation.

4. Polymeric NPs in Clinical Investigations

There are more than 15 nanomedicines on the market for cancer treatment [50]. Concerning the polymeric NPs (see **Table 3**), PICN®is a polymeric formulation of paclitaxel that is approved in India for metastatic breast cancer [51]. The non-targeted PICN®is currently in clinical trials in the USA [50]; Genexol®, produced by Samyang Biopharm, is a polymeric micelle formulation of paclitaxel that is clinically approved to treat breast cancer in South Korea [52][53][54]. Early results in patients with solid tumors showed dose-dependent intracellular localization in tumor cells.

The identification of genomic alterations, such as gene amplifications or mutations, in cancers has permitted the design of chemical entities against those alterations. Similar findings can be described for targeted agents, such as the kinase inhibitor against HER2 neratinib that shows an inadequate toxicity profile in relation with diarrhea. Another example is the mucositis and glucose deregulation observed with everolimus, which produces treatment discontinuations [55]. In this context, it is expected that strategies targeting pan-essential genes will be toxic, having an inverse therapeutic index [56] [57].

In addition, the pharmacokinetic (PK) profile can influence the toxicity and particularly when the toxicity itself is not reversible [58]. To resolve this problem, encapsulation of compounds to improve their PK profile, limiting their exposure to non-transformed tissue, is a main area of research. The encapsulation of PROTACs is an example of success [59], but there is still a long way to go, which requires safety and efficacy experiments in different animal models. Novel methods for the encapsulation of targeted agents, such as small chemical entities, are under evaluation.

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