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Formulation and Evaluation of Biodegradable Polymeric Nano-therapy for Targeted Cancer Treatment

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Abstract : Advances in nanotechnology have facilitated the development of novel colloidal formulations capable of modulating the pharmacological and biopharmaceutical properties of drugs. The peculiar physico-chemical and technological properties of nanomaterial-based therapeutics have allowed for several successful applications in the treatment of cancer. To promote and optimize cell and tissue interactions, the size, shape, charge, and patterning of nanoscale therapeutic molecules are parameters that need to be studied and modulated. This review describes the use of polymeric nanoparticles as drug delivery systems for anticancer compounds, their physicochemical properties, and their ability to effectively localize within specific tumor tissues. The nanoencapsulation of antitumor compounds in polymeric systems is a promising approach to improve the efficacy of various tumor treatments.

Keywords- Biodegradable polymeric nanoparticles, targeted cancer therapy, drug delivery systems, PLGA nanoparticles, nanocarriers, controlled drug release, tumor microenvironment, ligand-targeted therapy.

Introduction

Cancer is the second leading cause of death in the world, and was responsible for approximately 9.6 million deaths in 2018 (Bray et al., 2018). Over the next 20 years, the number of new cases is estimated to increase by about 70% (Siegel et al., 2017). Cancer therapy is considered a multidisciplinary challenge requiring close collaboration between clinicians, biologists, and biomedical engineers (Danhier et al., 2010). Current cancer treatments include surgery, radiation, and chemotherapy, but the effects of these procedures may cause damage to normal as well as tumoral cells. The resultant systemic toxicity and adverse effects greatly limit the maximum tolerated dose of anti-cancer drugs, and thus restrict their therapeutic efficacy. In particular, surgery and radiotherapy is the first choice used for local and non-metastatic cancers, while anti-cancer drugs (chemotherapy, hormone, and biologic therapies) are the treatments currently employed in metastatic cancers and adjuvant therapies (Tran et al., 2017). The toxicity of conventional chemotherapeutic drugs, as well as the indiscriminate destruction of healthy cells and the development of multidrug resistance, are the motivating thrust behind research on novel targeted treatments (Perez-Herrero and Fernández-Medarde, 2015; Tran et al., 2017). The main challenge is to improve the selectivity of anticancer drugs for tumor cells and the tumor microenvironment, while sparing healthy cells and tissues. In this context, a promising approach is the targeting of tumor tissue by nanomedicine-based therapeutics (Oerlemans et al., 2010). These formulations are made up of submicrometer-sized carriers containing the active compound(s), which are able to selectively diagnose and treat tumors by suitable targeting vectors, thus improving the therapeutic index and the pharmacokinetic profile of the anticancer drugs that are delivered.

Nanocarriers can retain multiple therapeutic agents not only to enhance their therapeutic effect on a synergistic or additive basis, but also to overcome acquired resistance to single chemotherapeutic drugs. Many tumors develop chemo-resistance through many mechanisms, including induction of the drug efflux rate or the downregulation of uptake mechanisms (Mansoori et al., 2017). Nanoparticulate formulations can overcome this limitation by providing an alternative pathway of cellular internalization. Currently, several therapeutic nanoparticle platforms are being investigated for targeted cancer treatment, including lipid-based, polymer-based, inorganic, viral, and polymer-drug conjugated systems. In the past two decades, over 20 nanotechnology-based therapeutic products have been approved for clinical use. Among these products, liposomal systems and polymer-drug conjugates are two of the most important groups, and many other formulations are under clinical investigation, including chemotherapy, hyperthermia, radiation therapy, gene or RNA interference (RNAi) therapy, and immunotherapy (Wicki et al., 2015). Nanocarriers have unique features such as their nanometric size, high surface area-to-volume ratio, favorable drug release profiles

and targeting features, which can promote their preferential accumulation in tumor tissues (Wicki et al., 2015). Most nanosystems for the treatment of solid tumors are administered systemically and accumulated in the tumor tissues through the enhanced permeability and retention (EPR) effect, which is generally thought to be the result of leaky tumor vasculature and poor lymphatic drainage (Maeda, 2015). However, this interpretation of EPR-dependence is simplistic, because the biodistribution of systemically administered nanosystems can be influenced by many biologic factors, including interaction with plasma proteins, blood circulation time, extravasation, penetration of tumor tissue, and cancer cell uptake (Shi et al., 2017).

Modifications of the surfaces of the nano-systems—which are able to confer specific targeting properties or stimuli-sensitive responses—also affects their overall distribution. Much of our current knowledge about the in vivo behavior of nanoparticulate systems is based on data obtained from animal models. But relatively few investigations have correlated the obtained data in order to determine whether and how the safety and the efficacy of nanoparticles in humans can be better predicted by using these animal models (Hrkach et al., 2012; Zuckerman et al., 2014). There also exist a number of scientific articles which focus on specific aspects and applications as to the development of polymeric nanoparticles. Hence, this work is not intended to be a review of all the research performed in this area, but rather to provide the basic concepts and ideas related to the preparation and use of polymer-based nanoparticles as drug carriers in cancer therapy.

Tumor Microenvironment:

The microenvironment of tumor tissue significantly differs from that of healthy tissue. These differences include vascular abnormalities, oxygenation and perfusion levels, pH, and metabolic status (Abadjian et al., 2017). Solid tumors are characterized by a heterogeneous population of neoplastic cells supplied by an irregular and discontinuous endothelium with large gaps between the endothelial cells, and abnormally thick or thin basement membranes where pericytes are loosely attached to endothelial cells (Figure 2). The irregularity of tumor blood vessels in their distribution, diameter, density, and serpentine shape, can be the cause of poor perfusion that leads to excessive fluid extravasation (Khawar et al., 2015). The two main causes of this heterogeneity are spatial stress, resulting from rapid tumor growth, and the abnormal extracellular matrix, which can compress the vessels and partially block the flow of blood [which causes the escape of plasma and a high interstitial fluid pressure (IFP)] (Jain, 2013). The IFP is highest at the center of stolid tumors and decreases radially, creating a movement of fluid away from the central region of the tumor. This phenomenon contributes to a reduced transcapillary transport of therapeutic drugs as well as their scarce accumulation in the middle of the tumor (Danhier et al., 2010). The elevated IFP and associated peritumoral edema also assist in the transport of growth factors and cancer cells away from the tumor, thus favoring tumor progression, while the abnormal and disorganized tumor vasculature results in inefficient blood flow inside the tumor mass, hypoxia, and low extracellular pH (Khawar, et al., 2015).

Hypoxia plays a crucial role in tumor growth and metastasis through the induction of molecular signaling which is responsible for genetic instability, inflammation, immunosuppression, epithelial–mesenchymal transition and altered metabolism (Jing et al., 2019). It also confers resistance against several kinds of treatment, such as radiation, chemo-, photodynamic and immunotherapies, which require oxygen for efficacy (Jain, 2013). Owing to the hypoxia-inducible factor-mediated pathway, hypoxia promotes angiogenesis. Oxygen can diffuse for maximum 150 µm beyond the capillary wall, which implies that when a tumor reaches a certain size (~2 mm3), a state of cellular hypoxia begins. Angiogenesis is a cellular mechanism, which is upregulated in tumoral microenvironments and creates new blood vessels to further assist tumor growth by supplying oxygen and nutrients (Jászai and Schmidt, 2019). This process consists of five steps: I) endothelial cell activation, ii) basement membrane degradation, iii) endothelial cell migration, iv) new vessel formation, and v) angiogenic remodeling. In the first phase, hypoxia induces an increase of the hypoxia-inducible factor-mediated transcription of pro-angiogenic proteins such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and tumor necrosis factor-α (TNF-α) (Wigerup et al., 2016). The Activated endothelium regulates the migration of endothelial cells through the extracellular matrix during vessel formation, due to the expression of a dimeric transmembrane integrin αvβ3, which interacts with the proteins of the extracellular matrix (vitronectin, fibronectin, etc.) (Demircioglu and Hodivala-Dilke, 2016). Successively, the matrix metalloproteinases synthesized by the activated endothelial cells degrade the basement membrane and the extracellular matrix. This process causes the apoptosis of the inner layer of endothelial cells, leading to the formation of a vessel lumen and remodeling of the immature vasculature, stabilized by pericytes and smooth-muscle cells. Often, this step remains incomplete, resulting in irregularly-shaped, dilated, and tortuous tumor blood vessels. The angiogenic switch is the crucial phase in which a tumor changes from a non-angiogenic to an angiogenic phenotype and allows the dissemination of cancer cells throughout the body (Jászai and Schmidt, 2019).

Hypoxia also results in metabolic acidosis caused by increased glycolysis (the Warburg effect); this lowers the extracellular pH to 6.0–7.0 (De Palma et al., 2017). Acidosis is also a factor in epithelial–mesenchymal transition, and it synergistically contributes to tumor invasion and metastasis (Yang et al., 2016). Because of their rapid growth, tumor cells continue to exploit glycolysis as an ATP-generating pathway when oxygen is available, lowering dependence on glucose oxidation for energy production (Fu et al., 2017). This metabolic preference is mostly due to defective mitochondrial function (Kim et al., 2009). The elevated breakdown of glucose produces large amounts of lactic acid and large amounts of free protons (H+) which are pumped into the extracellular milieu by mechanisms involving the carbonic anhydrases IX and XII (Martinez-Outschoorn et al., 2017). The resulting pH gradients between intra- and extracellular compartments within the tumor tissue, as well as between the tumor mass and the general host tissue, are potential sources of variable and often inefficient partitioning and distribution of drugs. Exposure to chemotherapy may favor the selection of tumor-cell clones with acidic organelles, which are able to entrap the drugs, and if these organelles are part of the secretory pathway, then the drug will be transported out of the cell through exocytosis. All these factors in the tumor microenvironment contribute to multidrug resistance (MDR) phenomenon (Danhier et al., 2010).

OBJECTIVES:

To develop a biodegradable polymeric nanoparticle formulation using PLGA for cancer therapy.
The formulations were evaluated for encapsulation efficiency, particle size, and potential.
The in vitro release profile and cytotoxicity against cancer cell lines were analyzed.
To assess the biocompatibility of the developed system on normal cells.

LITERATURE REVIEW

Polymeric Nanoparticles:

Over the last decade, nanoparticles have become extremely attractive for applications in biology and medicine (Mogoşanu et al., 2016). They have the potential to modulate biopharmaceutical features, pharmacokinetic properties, and the therapeutic efficacy of entrapped drugs (Dang and Guan, 2020). Technically, nanoparticles are defined as being less than 100 nm, but in practice structures up to 300 nm in size are included in this category (Guo et al., 2016), and they can fall into different classes as a function of their morphology, size, composition, and physicochemical properties (Khan et al., 2019).

Polymer-based nanoparticles are colloidal systems made up of natural or synthetic polymers. They furnish many advantages over other nanocarriers such as liposomes, micelles and inorganic nanosystems, and include the feasibility of scale-up and the manufacturing process under Good Manufacturing Practices (GMP) (Van Vlerken et al., 2007). Other peculiar characteristics of polymeric nanoparticles are the significant stability of polymeric nanoparticles in biological fluids along with the wide availability of various polymers, the opportunity to functionalize their surfaces and to modulate polymer degradation and the leakge of the entrapped compound(s) as a function of specific stimuli (Venkatraman et al., 2010; Goodall et al., 2015; Sarcan et al., 2018). Several chemotherapeutics have been encapsulated in polymeric delivery systems, with the aim of increasing antitumor efficacy, inhibiting metastases, and decreasing the effective dose and side effects. Polymers can encapsulate an active compound in their structure or adsorb it onto their surfaces (Masood, 2016). Langer and Folkman were the first to demonstrate the controlled release of macromolecules using polymers, which allowed the development of antiangiogenic drug delivery systems for cancer therapy (Langer and Folkman, 1976).

Ideally, the polymers selected for parenteral administration must be biocompatible, biodegradable, and possess specific mechanical and physicochemical properties (Vilar et al., 2012). The first polymers used to develop polymeric nanoparticles (PNs) were non-biodegradable polymers, such as poly(methyl methacrylate) (PMMA), polyacrylamide, polystyrene, and polyacrylates. The nanosystems made up of these materials exhibited a rapid and efficient clearance, but chronic toxicity and inflammatory reactions were observed. Usually, non-degradable polymers require degradation times longer than their effective duration of application (Anju et al., 2020), whereas the degradation rate of biodegradable polymeric nanoparticles can be influenced by several parameters, including their physico-chemical properties (size, structure, molecular weight) and external factors, such as pH and temperature (Su and Kang, 2020). Although pioneering studies on polymeric nanoparticles have focused on non-degradable materials, the use of biodegradable polymers had a great impact because of their notable biocompatibility and biosafety (Kamaly et al., 2016). Biodegradable polymers include synthetic polymers such as poly(D, l-lactide) (PLA), poly(D, L-glycolide) (PLG), co-polymer poly(lactide-co-glycolide) (PLGA), polyalkylcyanoacrylates, poly-Ɛ-caprolactone. They are considered safe and a few biodegradable polymer products have been approved by the US Food and Drug Administration (FDA) as well as by the European Medicines Agency (EMA) for pharmaceutical application (Palma et al., 2018). In general, biodegradable polymeric particles show reduced systemic toxicity, are more biocompatible, and favor modulation of drug-release kinetics. They are typically degraded into oligomers and monomers, which are further metabolized and eliminated from the body via normal pathways (Ravivarapu et al., 2006; Vilar et al., 2012). Non-synthetic, biodegradable polymers, which include natural polymers such as chitosan, alginate, gelatin, zein, and albumin, have also been used to prepare polymeric nanoparticles (Gagliardi et al., 2018). We will discuss commonly-used polymers for the preparation of drug-loaded PNs for an anticancer therapy later.

Biopolymers for Cancer Nanomedicine:

Biopolymers are one of the most important classes of biomaterials (Anju et al., 2020) and are widely used in biomedical applications because of their biocompatibility and biodegradability (Jaimes-Aguirre et al., 2016). They are macromolecules made up of repeating monomeric subunits linked by covalent bonds (Wen et al., 2018). Based on their origin, biopolymers are divided into natural and synthetic classes (Taghipour-Sabzevar et al., 2019). The advantages and disadvantages of these biopolymers are taken into consideration during selection for the development of a drug delivery system.

Synthetic Biopolymers:

can be derived from natural polymers or chemically synthesized. They have attracted much attention because of their stability, flexibility, low immunogenicity, and biodegradability. Since they resist hydrolysis and can tolerate high temperatures, they can be heat-sterilized without degradation (Rahman and Hasan, 2019). Poly (α-hydroxy acids), polyhydroxyalkanoates (PHAs), poly (lactones), and poly(alkyl cyanoacrylates) (PACA) are the common synthetic biopolymers, among which poly (α-hydroxy acids) are the most employed class of biopolymers for production of PNs. Poly (α-hydroxy acids) is degraded by non-enzymatic hydrolysis of the ester link into non-toxic monomers (lactic acid and glycolic acid). Their degradation rate depends on intrinsic properties such as molecular weight, chemical structure and hydrophobicity (Doppalapudi et al., 2016).

Nanoparticles consisting of these polymers have been developed for the delivery of various hydrophilic and hydrophobic anti-cancer agents such as doxorubicin, 5-fluorouracil, cisplatin, paclitaxel, and docetaxel (Rafiei and Haddadi, 2017; Ashour et al., 2019; Domínguez-Ríos et al., 2019; Maksimenko et al., 2019; Mittal et al., 2019). PLG was the first polymer of this class investigated for biomedical applications (Doppalapudi et al., 2016). It is synthesized through the polycondensation of glycolic acid or ring opening of glycolide, but it is not a good choice for the formulation of nanocarriers for cancer therapeutics because of its rigidity and rapid degradation (Shukla et al., 2019). PLA, another widely-investigated polymer, can be obtained from the polycondensation of lactic acid (LA) or by the ring opening polymerization of lactide; it exists in two isomeric forms, poly(l-lactic acid) and poly(d-lactic acid) (Fonseca et al., 2015). PLA naturally degrades in situ through the hydrolysis of the ester link, rendering LA and its short oligomers as the degradation products. Since the products of PLA biodegradation are cleared easily from the body, its use does not induce severe immune responses (Lee et al., 2016; Casalini et al., 2019). Among polyesters, PLGA is the most widely-used co-polymer for the development of targeted drug delivery systems, and is made up of glycolic acid and lactic acid monomers (Mir et al., 2017; Maity and Chakraborti, 2020). PLGA polymers undergo complete biodegradation in aqueous media and their characteristics can be altered by varying the chemical composition (lactide/glycolide ratio) and the chain length. For example, the degradation rate and the drug-release rate accelerate when the molecular weight of the copolymer is decreased (Molavi et al., 2020). PLGA can be prepared at different lactide/glycolide molar ratios such as 50/50, 65/35, 75/25, and

85/15. Lactide is more hydrophobic than glycolide, so a decrease in the proportion of Lactide increases the rate of hydrolytic degradation of the copolymer, with the consequent rapid release of the encapsulated drug (Gentile et al., 2014). It has been suggested that the degradation times of 50/50, 75/25 and 85/15 PLGA are 1–2, 4–5, and 5–6 months, respectively (Middleton and Tipton, 1998; Anju et al., 2020). Biopolymers produced by microorganisms have shown promise as a substitute for the synthetic polymers currently being used in the industry. For instance, PHAs are naturally produced and accumulated as energy/carbon storage material by many bacteria. PHAs have recently gained great attention because of their biocompatibility, biodegradability, thermoplasticity, low toxicity, and availability (Korde and Kandasubramanian, 2020). They are polyesters of various hydroxyalkanoate monomers that can be produced either through the natural bioconversion process or by chemical synthesis via the ring-opening polymerization of β-lactones (Li and Loh, 2017).
Poly(hydroxybutyrate) (PHB) is a PHA derivative used in targeted drug delivery due to its prolonged degradation time in vivo and its lesser effect on the pH of tissues as compared to the polylactides (Korde and Kandasubramanian, 2020). According to ISO 10993, PHB nanoparticles have been shown to be safe when used on animals (Masood, 2016). Amongst polylactone-based polymers, poly(Ɛ-caprolactone) (PCL) is the most studied polymer for anticancer drug development. It is a semi crystalline compound obtained by the ring-opening polymerization of ε-caprolactone (Witt et al., 2019). PCL exhibits slower ester bond hydrolysis at physiological pH and has a less acidic character than poly-hydroxy acids; what's more, the slower degradation rate of PCL prolongs the release of encapsulated drugs (Doppalapudi et al., 2016). Poly(alkyl cyanoacrylates) (PACA) are another biodegradable polymer class useful for developing nanocarriers. These polymers are mainly degraded through the hydrolysis of the ester bonds of their alkyl chain. The rate of degradation depends on the alkyl chain length: the longer the alkyl chain, the slower the rate. The two resulting products, namely alkyl alcohol and poly (cyano acrylic acid), are both soluble in water (Nicolas and Couvreur, 2009; Doppalapudi et al., 2016). Pacas can retain large amounts of drugs (Sulheim et al., 2017). Poly(isohexylcyanoacrylate) nanoparticles containing doxorubicin (Livatag®—see section “Livatag®.”) have been proposed as an innovative formulation for human primary liver cancer and have reached phase III of clinical trials (Merle et al., 2017).

Natural Biopolymers:
It include animal- or plant-derived proteins and polysaccharides as well as polymers obtained from microbial sources. These are widely used in drug delivery research due to their unique properties such as an abundance in nature, biodegradability, biocompatibility, and low toxicity (Eroglu et al., 2017; Gálisová et al., 2020). However, they can be immunogenic and often require chemical modification before being used for the development of nanoparticles (Karlsson et al., 2018).

Animal-Based Biopolymers:
Natural biopolymers of animal origin used for the development of pharmaceutical formulations include albumin, gelatin, hyaluronic acid, and chitosan (Ventura et al., 2011; An and Zhang, 2017; Iannone et al., 2017; Yasmin et al., 2017). Albumin (MW ∼65–70 kDa) is an endogenous blood protein. Both human serum albumin and bovine serum albumin are used to produce nanosystems for the anticancer therapy. They have similar physicochemical properties and produce nanoparticles having similar characteristics (An and Zhang, 2017). Albumin has been used as a nanocarrier for antitumor compounds because of its long biological half-life, which improves the pharmacokinetic properties of the encapsulated drugs and allows the EPR effect to be taken advantage of for increased accumulation in tumor tissues (Karimi et al., 2016; Hoogenboezem and Duvall, 2018). One of the most important formulations of intravenous paclitaxel used in clinical practice is made up of albumin nanoparticles (Abraxane®—see section “Abraxane or Nab-Paclitaxel”). Gelatin is a heterogeneous mixture of polypeptides derived from the partial hydrolysis of animal collagen (Karlsson et al., 2018). From this process, two types (A or B) of gelatin are obtained. Type B gelatin has been shown to produce nanoparticles with better properties than type A (Yasmin et al., 2017).
Gelatin is enzymatically degraded into its aminoacids as a function of several parameters such as pH, temperature or concentration (Sahoo et al., 2015). Gelatin is cheap and readily available and could be easily modified to carry targeting moieties; at the same time, gelatin cross-linking can be controlled to alter the drug-relase properties of resultant nanoparticles (Elzoghby et al., 2017). Gelatin nanoparticles have also been investigated for the delivery of genetic material (Coester, et al., 2000; Magadala and Amiji, 2008). Although gelatin nanoparticles exhibit low toxicity and efficient cellular uptake in cancer cells, the use of gelatins of animal origin carries the risk of contamination with transmissible infection. This drawback could be overcome with the use of recombinant human gelatins, but its widespread use is limited because of the expensive production processes.
Hyaluronic acid (HA) and its derivatives have been employed for biomedical and pharmaceutical applications, particularly for target-specific and long-acting delivery of anticancer agents. HA is a mucopolysaccharide consisting of D-glucuronic acid and N-acetylglucosamine linked together through alternating β-1,4 and β-1,3 glycosidic bonds.
It is present in the extracellular matrix and intracellular domain of all living organisms (Tripodo et al., 2015). HA undergoes degradation in the biologic environment through hyaluronidases that hydrolyze the β-1,4-glycosidic bonds. The resulting oligosaccharides are degraded by β-D-glucuronidase and β-M-acetyl-hexosaminidase enzymes (Chen et al., 2019a). HA is rapidly cleared from the body, but the linkage of amino acids to the carboxyl or hydroxyl groups of its chain enhances its blood circulation time (Taghipour-Sabzevar et al., 2019). A close association was found between HA receptor expression and malignant tumor progression. HA receptors (particularly CD44, hyaluronan-mediated motility receptor RHAMM, lymphatic vessels endothelial hyaluronic acid receptor 1 LYVE1) is activated in cancer cells to promote cell infiltration and tumor malignancy (Lokeshwar et al., 2014; Lee et al., 2020). HA promotes the uptake of nanoparticles by binding to these receptors (Chiesa et al., 2018; Rho et al., 2018). Another strategy to improve drug delivery and enhance the circulation time of nanoparticles is to covalently conjugate HA onto the surfaces of the nanoparticles (Edelman et al., 2017; Cosco et al., 2019).

Plant-Based Biopolymers:
Plant-derived polymers occur abundantly in nature and generally exhibit less immunogenicity than polymers of animal origin. Although cellulose, starch, soy protein, and zein, are the most widely used plant-derived polymers, numerous other plant-based polymers have been studied and have shown excellent results in drug delivery research (George and Suchithra, 2019; Iravani and Varma, 2019; Gagliardi et al., 2020a, 2020b). Cellulose, the most abundant biopolymer in the world, is a linear homopolymer of 1,4-β glycoside-linked d-glucopyranose, (Fattahi Meyabadi et al., 2014; Halib et al., 2017). It is suitable for the development of nanoparticles because it causes no immune-response and its highly hydrophilic structure suppresses opsonization, which is an

important phase of phagocytic clearance of nanoparticles. Thus, it prolongs the residence time of hydrophobic drugs in the blood stream and enables accumulation in the target tissue (Varan et al., 2019). Starch is also a highly available plant-based polysaccharide. All plants synthesize starch as an energy reserve, though this person is more common in tuberous plants (potatoes) and cereals (corn, beans, wheat, rice, etc.) (Alcázar-Alay and Meireles, 2015). It is metabolized by amylases and glucosidases into glucose units (Elvira et al., 2002). The advantages of this edible polysaccharide in a controlled release field are the improvement of drug solubility and stability, the reduction of toxicity and side effects, and an excellent biocompatibility and storage capacity (George et al., 2019). Soy protein nanoparticles have also been investigated for the development of nanoparticles. Like cellulose and starch, it is also a highly-abundant and low-cost material. The amino acid composition of soy proteins (polar, non-polar, and charged amino acids, such as glutamate, aspartate, and leucine) promotes the heavy entrapment efficiency of hydrophobic drugs; its solubility characteristics in aqueous environments can be exploited for different administration routes (DeFrates et al., 2018; Voci et al., 2020). Zein is a low molecular weight protein (~20 kDa) derived from the cytoplasm of corn cell endosperm (DeFrates et al., 2018; Gagliardi et al., 2019; Gagliardi et al., 2021). It is considered to be a promising biomaterial to obtain nanocarriers containing hydrophobic compounds because it is insoluble in water, except in the presence of alcohol, urea, alkali, and anionic detergents (Elzoghby et al., 2017; Tran et al., 2019).

Microbial Biopolymers:

In the previous section, Phase obtained from microbes was discussed, but they are not the only polymers derived from the microbial world. Many exopolysaccharides originating from microorganisms have also been explored as nanocarriers. Sulfated polysaccharides are amply exploited in nanotechnology because of their unique physicochemical properties such as noteworthy stability, biodegradability, biocompatibility, and fluid dynamics (Raveendran, et al., 2013). Halomonas Maura is a bacterium that produces a highly sulfated exopolysaccharide called mauran. Mauran is made up of repetitive units of mannose, galactose, glucose and glucuronic acid and has a high content of sulfate and uronic acid which confer immunomodulatory and antiproliferative effects on human cancer cells (Arias et al., 2003). This high molecular weight polymer has exceptional rheological properties, and exhibits thixotropic behavior. It is also highly resistant to extreme temperatures, freeze-thaw cycles, pHs, and salt-concentrations (Llamas et al., 2006).

Raveendran, et al. produced 120 nm nanofibers of mauran and poly(vinyl alcohol) and found them to be an excellent biomaterial for the migration, proliferation, and differentiation of mammalian cells, (Raveendran, et al., 2013). The same group also reported composite nanoparticles of mauran and chitosan for the delivery of 5-fluorouracil to glioma and breast adenocarcinoma cancer cells (Raveendran, et al., 2015).

Biopolymers From Marine Organisms

Marine organisms are another rich source of polymers for medical applications. Marine biopolymers such as fucoidan, alginate, carrageenan, and chitosan are renewable, stable, non toxic polymers that can be potentially harvested at low costs (Manivasagan et al., 2017). Fucoidan, alginate, and carrageenan are obtained from seaweed, whereas microbial chitosan can be isolated from marine crustaceans. Chitosan is the most widely used cationic polysaccharide approved by the FDA for drug delivery purposes due to its low toxicity, non-immunogenic behavior, and significant compatibility with tissues and cells (George et al., 2019). What's more, it is the only natural positive polysaccharide and can form stable complexes with negative compounds, making it a good candidate for drug encapsulation and controlled release (Yang et al., 2014). Chitosan is a polymer made up of glucosamine and N-acetyl-glucosamine and is mainly obtained from the hard outer skeleton of shellfish, including crabs, lobster, and shrimp. It can self-assemble into nanostructures that can penetrate the tight junctions between endothelial cells because of its bio-adhesive properties (Safdar et al., 2019). Chitosan-based nanoparticles are degraded by different enzymes, such as lysozymes, chitosanase, cellulases, lipases and pectinases (Taghipour-Sabzevar et al., 2019). Interestingly, chitosan can also be obtained from microbial sources (Kaur et al., 2012; Amer and Ibrahim, 2019), but this development is still in its infancy. Fucoidan, which has been recently studied in anticancer nanomedicine, is a sulfated polysaccharide extracted from brown seaweed, principally made up of L-fucopyranose units and sulfated ester groups, (Wu et al., 2016). Many studies have reported that fucoidan carries on antitumor activity against a wide variety of human tumors as a consequence of its interaction with P-selectin, a molecule expressed on cancer cells that promotes metastasis (Shamay et al., 2016; Lu et al., 2017). Alginate is an anionic linear polymer derived from marine brown algae. It consists of β-d-mannuronic acid and α-l guluronic acid residues linked by 1,4-glycosidic bonds (Venkatesan et al., 2016; Karlsson et al., 2018). These linkages are sensitive to both acid hydrolysis and alkaline β-elimination. In humans, the polymer dissolves in surrounding physiologic media in the absence of specific digestive enzymes (Rottensteiner et al., 2014). Its low cost and capacity to interact with various bioactives led to its use in the development of various nanosystems (Joye and McClements, 2014). Carrageenan is another sulphated polysaccharide, which carries a high negative charge. It can be extracted from different species of seaweed and it is characterized by alternate units of d-galactose and 3,6-anhydrogalactose linked by α-1,3 and β-1,4 glycosidic linkages (Manivasagan et al., 2017). Despite its potential, very few authentic studies exist on the use of carrageenan to produce nanoparticles for anticancer drugs. However, carrageenan has been reported for prolonged drug release in mucosal/epithelial tissues (Kianfar et al., 2013; George et al., 2019).

Methods of Preparation for Polymeric Nanoparticles and the Role of Surfactants:

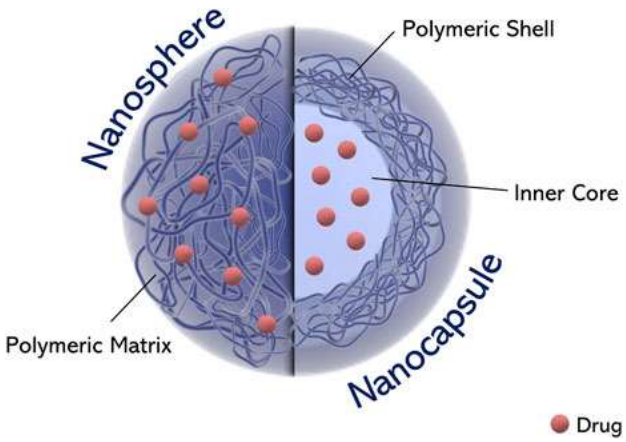
PNs have been developed with the aim of encapsulating hydrophilic and hydrophobic molecules, such as salts, proteins, and high-molecular-weight DNA or antisense nucleic acids (Cosco et al., 2014; Cosco et al., 2015; Lombardo et al., 2018). A variety of drug classes can be delivered by nanoparticles such as anticancer (Cosco et al., 2011), antifungal (Carraro et al., 2016), anti-inflammatory (Gadde et al., 2014), and anti-leishmanial drugs (Palma et al., 2018). Encapsulation favors prolonged and/or controlled release of a drug (Pagels and Prud'homme, 2015), and there is growing interest in nanoparticles for the targeted delivery of entrapped compounds to specific organs or cells (Danhier et al., 2012). The drugs encapsulated in PNs are released by means of diffusion through the polymeric network, erosion of the matrix material, hydrostatic swelling, or by a combination of these mechanisms. A variety of methods has been used to efficiently encapsulate drugs in PNs. The technical choice is dependent on the nature of the polymer selected, desired physicochemical features of the final formulation, and ease and expense associated with the method (Crucho and Barros, 2017). The most important preparation approaches for PNs are emulsification and solvent

evaporation (Yoneki et al., 2015), nanoprecipitation (Rivas et al., 2017; Maggisano et al., 2020), the supercritical anti-solvent method (Kalani and Yunus, 2012), and salting-out (Mendoza-Muñoz et al., 2012). The emulsification and solvent evaporation/extraction technique is the most used method for small and moderate-scale manufacturing of PNs. It is based on the dissolution of polymer in an organic solvent, adding the organic-phase to the water-phase containing stabilizers and surfactants, then emulsification followed by the evaporation of a slowly-boiling organic solvent. Chloroform, dichloromethane, and ethyl acetate are commonly used as organic solvents. Both single oil-in-water (o/w) emuslification (Guo et al., 2015) and double water-in-oil/in-water (w/o/w) emulsification (Cosco et al., 2015) methods are used to obtain an emulsion via high-speed homogenization or ultrasonication. The evaporation of an organic solvent is accomplished by applying heat and vacuum. Spray-drying is the method of choice for getting rid of organic solvents during large-scale production of heat-sensitive PNs (Ozeki and Tagami, 2014). In the nanoprecipitation method, a water-miscible organic phase is added drop-by-drop into an aqueous phase with or without a stabilizer/surfactant (Rivas et al., 2017). The polymer is deposited at the interface following the displacement of a nonaqueous solvent (for example, acetone) from the solution (Fessi et al., 1989). Traditionally, this easily reproducible technique has been mostly employed for the encapsulation of hydrophobic drug molecules. The nanoprecipitation technique was found to be more efficient than the emulsification method for encapsulating cucurbitacin in PNs consisting of PLGA (Alshamsan, 2014), possibly by preventing the loss of drugs during the emulsification process and increasing entrapment in the polymer matrix. Recently, Salatin, et al. reported the development of rivastigmine-Eudragit RL nanoparticles using the nanoprecipitation method; the entrapment efficiency reached 38% and sustained drug release was observed (Salatin et al., 2017). The supercritical anti-solvent method is another way to prepare PNs under mild operating conditions. In particular, a polymeric solution is sprayed as tiny droplets into a high-pressure vessel containing an anti-solvent liquid such as CO2. The rapid diffusion of CO2 into solute favors the formation of nanoparticles. The salting-out method, on the other hand, is based on the addition of a high concentration of salts (electrolytes such as magnesium chloride, calcium chloride and magnesium acetate) or saccharides (non-electrolyte) to a polymeric solution that induces the appearance of a coacervate; they can be also obtained by the modulation of temperature and pH (Masood, 2016). Various parameters, such as the molecular weight of the polymers, the presence of cryoprotectants and stabilizing agents, etc. play an important role in the development of PNs (George et al., 2019). The modulation of the polymer length, which is obtained during the synthesis of the polymer, allows one to predict or obtain the desired physico-chemical properties of the system (Wen et al., 2018). For example, the degradation rate of polymers is related to their molecular weight: polymers with low molecular weight degrade faster than polymers with high molecular weight (Kamaly et al., 2016). The rate of polymer degradation also influences the release rate of the encapsulated drugs from the polymer matrix (Crucho and Barros, 2017). In general, nanoparticles are thermodynamically unstable and attract each other through van der Waals forces in order to decrease their considerable surface energy (Madkour et al., 2019). Therefore, resistance against aggregation is desirable in order to obtain a long shelf life for polymeric nanoparticles. Electrostatic and steric stabilization are the two mechanisms through which nanoparticles are stabilized (Morozova et al., 2019). The former is based on the reciprocal repulsion of similar electrical charges and depends on the balance of forces between charged surfaces and various interfaces, namely, the attracting van der Waals forces (resulting from dipole-dipole interactions) and the repulsive electrostatic forces of the electric double layers surrounding the particles in the medium (Morozova et al., 2019). Steric stabilization, on the other hand, is a protective barrier provided by the adsorption or conjugation of polymers or surfactants onto the surfaces of the nanoparticles (Mo et al., 2016). The use of surfactants is a well-known and widely-employed approach to stabilize polymeric nanoparticles (Heinz et al., 2017). Surfactants stabilize nanaoparticles by reducing the interfacial tension between the solid-liquid phase, which favors interaction between the polymeric system and the suspension medium. Surfactants are classified by their charge which include the following: (i) anionic (negative charge); (ii) cationic (positive charge); (iii) Zwitterionic or amphoteric (charge depends on the pH of the medium), and; (iv) non-ionic (no charge). Generally, non-ionic surfactants are less toxic to the biological membranes than ionic ones and several derivatives have been shown to inhibit the efflux pumps and/or multi-drug-resistance-associated proteins (Rege et al., 2002; Gagliardi et al., 2020c). Examples of common non-ionic surfactants include tweens®, spans®, pluronics,®, vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), and poly(vinyl alcohol). These surfactants can modulate the size, shape, and surface architecture of polymeric nanoparticles, influencing their therapeutic potential (see Physico-Chemical Properties of Polymeric Nanoparticles) (Heinz et al., 2017). Pluronics® are water-soluble triblock copolymers consisting of a hydrophobic core of polyoxypropylene (POP) between two hydrophilic units of polyoxyethylene (POE) (Giuliano et al., 2020). As GRAS (generally recognized as safe) excipients, they have been widely used in the development of many pharmaceutical formulations (Akash and Rehman, 2015; Bodratti and Alexandridis, 2018; Giuliano et al., 2019). Pluronics® are also referred as "functional excipients" as they carry on important and very useful biologic activities (Kabanov et al., 2003; Batrakova and Kabanov, 2008; Giuliano et al., 2018). For instance, Pluronics® is known for their attractive ability to sensitize MDR tumor cells toward chemotherapy and reduce cancer stem cell population by depleting intracellular ATP, inactivating permeability-glycoprotein (Pgp)-mediated drug efflux, and rendering cells pro-apoptotic (Waghray and Zhang, 2018; Khaliq et al., 2019). Moreover, pluronics can stimulate the release of cytochrome C and increase the levels of cytosolic reactive oxygen species (Minko et al., 2005). However, pluronics are not the only surfactants to exhibit anti-MDR effects (Livney and Assaraf, 2013). Tween® 20, Tween® 80, Myrj® 52, and Brij® 30 prohibit protein kinase C (PKC) activity, modulate Pgp-mediated drug efflux, and decrease the apical efflux of the anthracycline epirubicin across human intestinal epithelial (Caco-2) cells (Komarov et al., 1996; Lo, 2003; Tagami et al., 2011; Veeravalli et al., 2020). Tween 80 has been employed as a surfactant in brain tumor targeting (Wen et al., 2018). It enhances the delivery of the active compounds across the blood-brain barrier (BBB) by promoting the adsorption of apolipoprotein E (ApoE) onto the particle surfaces. This place enables transcytosis across the BBB through interaction with the low-density lipoprotein receptor-related protein (LRP) expressed on the brain capillary endothelium (Kreuter, 2014; Li et al., 2018; Tosi et al., 2020). Vitamin E TPGS also inhibits Pgp and enhances drug encapsulation, cellular uptake, therapeutic efficacy, and oral bioavailability of nanocarriers (Guo et al., 2013; Sun et al., 2014; Dong et al., 2016; Choudhury et al., 2017; Peng et al., 2018).

Physico-Chemical Properties of Polymeric Nanoparticles:

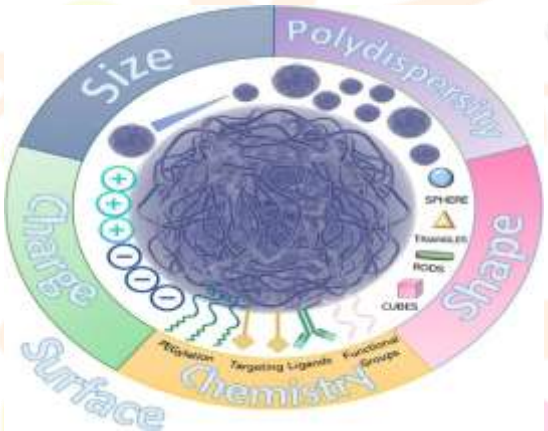
Depending on the process used to prepare polymer nanoparticles, they can be either nanospheres or nanocapsules. Nanospheres are matrix systems in which the drug is dispersed throughout the structure or adsorbed onto the surface, whereas nanocapsules are

systems in which the drug is contained in the core (aqueous or oily) surrounded by a polymeric shell (Paolino et al., 2013; Cosco et al., 2015).



The lack of standardized protocols for the characterization of nanosystems has resulted in translational failure of several formulations that were promising for clinical use (D'Mello et al., 2017; Gioria et al., 2018). The physico-chemical properties of nanoparticles, such as size, shape, stability, drug-release profiles and surface characteristics, can all affect how they behave in complex biological environments. At the same time, pH and ionic strength of the dispersion medium can influence biodistribution, pharmacological efficacy, and safety of the entrapped drug(s) (Figure 4) (Islam et al., 2017). Indeed, these parameters can significantly change in the biologic milieu, due to the adsorption of proteins onto the nanoparticle surface. Recognizing the importance of these physicochemical formulation factors, the European Medical Agency (EMA) and the FDA (Caputo et al., 2019; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UM588857.pdf) both signal the need for the pre-clinical characterization of nanoparticles.

In particular, the European Nanomedicine Characterization Laboratory (EUNCL) and the US National Cancer Institute Nanotechnology Characterization Laboratory (NCI-NCL) have developed several standard operating procedures for nanomaterial assessment, establishing mean size and polydispersity index as the critical quality attributes of a nanoparticle formulation (Gioria et al., 2018).



The size of nanoparticles used as drug delivery systems should be large enough (diameter of ~100 nm) to prevent their rapid escape from blood capillaries and renal filtration, but small enough to avoid mononuclear phagocyte system (MPS) with permission (Yang et al., 2016). Several techniques are used to evaluate the mean diameter and size distribution of nanoparticles, which include laser scattering (dynamic or static light scattering, laser diffraction), field flow fractionation (FFF), electron microscopy (EM), centrifugation (analytical ultracentrifugation and centrifugal particle sedimentation), tunable resistive pulse sensing (TRPS), and particle tracking analysis (PTA) (Caputo et al., 2019). While many of these are still being perfected (Halamoda-Kenzaoui et al., 2019), dynamic light scattering (DLS) is the most common sizing technique. Even though DLS is characterized by a relatively low resolution, it is highly suitable for the assessment of sample integrity and stability during the initial screening of nanoparticles. However, a combination of multiple high-resolution measurements is often required to demonstrate particle size and size distribution in complex biological media. Interaction with a biomaterial could favor the formation of aggregates/particles of different mean sizes, leading to significant differences in cell uptake and distribution, toxic effects, and fate in the cell. Any change in size will also impact the pharmacokinetic profile of nanoparticles, alter localization in tissue compartments, and result in unintended interaction with other biologic substrates and receptors. For instance, it has been demonstrated that renal filtration and nonspecific uptake by the MPS are dependent on the particle size (Scheinberg et al., 2010). The size and the surface chemistry of NPs affect the opsonization as a consequence of the curvature of systems (Hu et al., 2018). The diameter of particles influences their distribution and adhesion in blood vessels, lungs, and the gastro-intestinal tract. Nanoparticles smaller than 100 nm leave the blood vessels through endothelial fenestrations, whereas microparticles are uptaken by Kupffer cells in the liver or physically entrapped in the capillary beds. Moreover, nanoparticles below 200 nm can be internalized through the clathrin-mediated pathway, while nanoparticles of over 500 nm can be taken up through he caveolae-mediated pathway (Di Marzio et al., 2016).

Particle Shape:

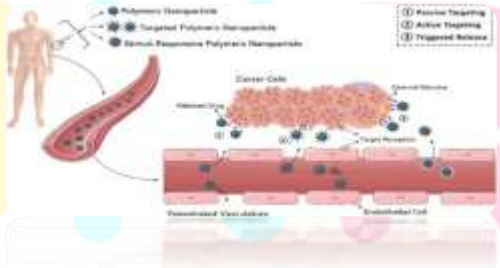
In addition to particle size, the shape of nanoparticles is also an important parameter because it affects their pharmacology and functions (Truong et al., 2015). Whereas spherical nanoparticles are the most desired and versatile types with high surface-to-volume ratio and peculiar optical properties, asymmetrical and non-spherical polymeric nanosystems have also been of interest in tissue engineering, immune-engineering, and for theranostic applications (Banik et al., 2016). Because of isometry, spherical particles have better cellular uptake independently of the way they are presented on the cell surface, but in the case of rod-like systems, the uptake is best when they perpendicularly interact with biologic surfaces (Stylianopoulos and Jain, 2015).

Particle Surface:

characteristics contribute to the solubility of particles, aggregation features, ability to bypass biological barriers, biocompatibility, and targeting properties. The majority of nanoparticles used as drug delivery systems have a hydrophilic surface which is able to favorably interact with the aqueous environment of biological systems. A common strategy for avoiding the MPS uptake of nanomaterials is to introduce neutral hydrophilic polymers in order to decrease the opsonization and hence macrophage phagocytosis. The use of polyethylene glycol (PEG) or poly(ethylene oxide) (PEO) to coat nanoparticles is a prime example of this strategy (Hu et al., 2018). The hydration layer formed by PEG chains around the nanoparticles sterically precludes their interaction with other nanoparticles as well as blood components (Yang and Lai, 2015). In addition, the significant conformational freedom provided by the flexibility of PEG makes the interpenetration of many compounds into the PEG corona thermodynamically unfavorable (Suk et al., 2016). Gref and coworkers developed PEGylated PLGA nanoparticles, which had a prolonged plasmatic half-life and reduced liver uptake, compared to the non-PEGylated formulation (Gref et al., 1994). This approach has been used to modulate the pharmacokinetic profiles of many preparations such as liposomal doxorubicin (Doxil) and micellar-paclitaxel (Genexol) (Barenholz, 2012; Stirland et al., 2013). The biologic behavior of polymeric nanoparticles is also affected by the surface charge or zeta potential (the electric potential at the hydrodynamic slipping plane of a particle) (Shao et al., 2015). Cationic or anionic particles are more stable and able to avoid non-specific cellular uptake by phagocytes as compared to the neutral ones of a similar size (Wang et al., 2010). Cationic nanoparticles are of immense potential as drug delivery systems because of their strong interaction with negatively-charged genetic material and their ability to bind to cell surfaces. They allow the loading of genetic materials that cannot cross cell membranes and ensure efficient cell uptake through endocytosis (Farshbaf et al., 2018). Thus, polymeric nanoparticles can be non-viral vectors for gene delivery with high transfection efficiency (Cosco et al., 2014, 2015; Wen et al., 2018). Several remarkable review papers focusing on the application of polymeric nanoparticles for gene delivery are available in literature (Kafshdooz et al., 2016; Suk et al., 2016; Young et al., 2016; Huh et al., 2017; Zhou et al., 2017; Lai and Wong, 2018; Shen et al., 2019; Roma-Rodrigues et al., 2020). The surface of a nanoparticle is also the place for the conjugation of ligands, with the aim of targeting specific receptors of tissues and organs. As will be discussed below, the patterning of surface groups, also defined by geometric arrangement, influences the geometry of ligands in targeting approaches and also the binding of nanoparticles to the receptors expressed on cancer cells (Banerjee et al., 2016). For this reason, it is extremely difficult to develop “smart” nanomedicines able to selectively interact with cancer cells.

Drug Targeting:

An important goal in nanomedicine is to combine the unique properties of nanosystems in order to enhance the characteristics of an entrapped drug. As previously discussed, drug delivery in nanoparticles can increase therapeutic efficacy by the modulation of the pharmacokinetic and pharmacodynamic profiles exerted by the nanocarrier. These enhancements are partly due to the passive targeting of nanoparticles, which is based on physical interaction between the nanosystems, and the tissue microenvironment (blood flow, lymphatic drainage, etc.). Alternatively, nanoparticles can be targeted by conjugating tissue-specific ligands (antibodies, peptides, macromolecules, etc.) on the particle surface; specific ligand-receptor interactions increase spatial accumulation of nanoparticles in tissues of interest, (Scheinberg et al., 2010).



Targeting:

The targeting approach is based on the conjugation/integration/adsorption of a ligand to the surface of a nanocarrier with the aim of promoting its interaction with overexpressed receptors specifically in tumor tissue while minimizing interaction with healthy cells (Figure 5). Small molecules such as folic acid and carbohydrates, or macromolecules such as peptides, protein's antibodies, aptamers, and oligonucleotides have been used for these purposes (Wicki et al., 2015). Several anticancer therapeutics grouped under the name “ligand-targeted therapeutics,” such as trastuzumab (anti-ERBB2, Herceptin®), bevacizumab (anti-VEGF, Avastin®) etaracizumab, and a humanized anti-αvβ3 antibody (Abegrin), have been conjugated onto the surfaces of drug delivery systems in order to promote their accumulation in specific body compartments (Danhier et al., 2010). The level, selectivity, and homogeneity of expression of the target are important factors in the selection of the ligand-target system for active targeting. An overview of the two principal targets (the surfaces of cancer cells and endothelial tumor cells) is provided in supplementary material. A full discussion of this topic is beyond the scope of this review; however, several excellent review articles have been recently published (Mukherjee et al., 2013; Bazak et al., 2014; Zhong et al., 2014; Choudhury et al., 2019; Das et al., 2019; Molavipordanjani and Hosseinimehr, 2019; Raj et al., 2019).

Stimuli-Sensitive PNs and Trigger Release:

In response to physical, chemical, or biological triggers, stimuli-responsive systems promote the release of drugs as a consequence of the structural modulation of the materials (Figure 5). Triggers can be composed of internal stimuli (patho-

physiologic/patho-chemical condition) which include changes in pH, redox, ionic strength, and shear stress in the target tissues (Li et al., 2013; Lim et al., 2018) and external stimuli (physical) such as temperature, light, ultrasound, magnetic force, and electric fields (Cheng et al., 2013; Liu et al., 2019; Qin et al., 2020). Several studies in literature demonstrate that the acidification of the tumor microenvironment facilitates the pH-sensitive PNs to release the entrapped drugs into the neoplastic tissue. Lee et al. developed poly(l-histidine)-block-PEG (PbAE) core shell nanoparticles able to release the entrapped doxorubicin at a pH below 7.4 (Lee et al., 2003). This response is mainly due to the intrinsic features of PbAE, which enhances drug leakage upon exposure to an acid pH; in fact, the unprotonated polymer is insoluble at the physiological pH (7.4) but becomes instantaneously soluble in aqueous media when the pH of the solution is below 6.5 (Lynn et al., 2001). For this reason, these polymers could be very useful for the delivery of therapeutic agents in solid tumors. Moreover, according to You and August, mild physiologic changes in pH ranges between 0.2 and 0.6, could effectively trigger the pH-sensitive poly (N, N-dimethylaminoethyl methacrylate (DMAEMA)/2-hydroxyethyl methacrylate (HEMA) PNs (You and Oupický, 2007; Fang et al., 2015).

Conclusions and Perspectives:

Despite the fact that PNs have been considered promising formulations for cancer therapy, their successful application is limited by various drawbacks (Kumari et al., 2016). In particular, changes in the physico-chemical properties of nanocarriers (size, surface charge, aggregation, appearance of protein corona) promoted by the components of the blood stream and early drug release in addition to the development of multiple drug resistance by cancer cells, all limit their pharmacological efficacy. Moreover, the toxicity of PNs made up of novel materials, including organic polymers or mixed systems with inorganic materials such as gold, silver oxide and silica are issues for clinical applications. The particle size, shape, sedimentation, drug encapsulation efficiency, desired drug release profiles, distribution in the body, circulation, and cost are some of the parameters used to select suitable formulations for an efficient cancer targeted drug delivery (Biswas et al., 2013). However, although many efforts have been made to develop novel targeted nanocarriers, only a few of them are approved for clinical use by the FDA (Barenholz, 2012). This phenomenon could be due to the lack of knowledge on the distribution and accumulation of targeted nanoparticles after oral or intravenous administration and/or to the deficiency of regulatory aspects (e.g., study design and approval challenges) (Kumari et al., 2016). The future of nanomedicine, especially by means of PNs, will improve the efficiency of conventional therapies by exploiting the concept of personalized therapy as a consequence of the opportunity of modulating the various parameters of nanosystems as previously described.

For instance, the application of PNs for the combined therapy of tumors (simultaneous delivery of multiple anticancer drugs/combination of conventional chemotherapeutics with other treatment modalities) as well as the delivery of anticancer drugs as well as photosensitizing agents, nucleic acids, antiangiogenic compounds may all better exploit the versatility of the proposed systems, and their ability to overcome MDR mechanisms thus maximizing the final anticancer effect. The continuous research on PNs in both preclinical and clinical studies will improve the prevention, diagnosis and treatment of cancer.

Expected Outcomes:

Particle size ranging from 100 to 200 nm, suitable for tumor penetrations.
The encapsulation rate is high, exceeding 70%, and the drug is continuously released for more than 48-72 hours.
It is selectively cytotoxic to cancer cells while sparing normal cells.
Improve the stability and solubility of drugs in physiological environments.

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