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Application of Nanoparticle Infused Polymer Matrix for Highly Active, Target Specific Drug Development and Repurosing: A Review

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Abstract: Polymeric nanoparticles (NPs) are one of the most studied organic strategies for nanomedicine. Intense interest lies in the potential of polymeric NPs to revolutionize modern medicine. To determine the ideal nanosystem for more effective and distinctly targeted delivery of therapeutic applications, particle size, material choice, and processing techniques are all research areas of interest. Utilizations of polymeric NPs include drug delivery techniques such as prodrugs, stimuli-responsive systems, imaging modalities, and theranostics. Cancer, neurodegenerative disorders, and cardiovascular diseases are fields impacted by NP technologies that push scientific boundaries to the leading edge of transformative advances for nanomedicine. The complexity of some diseases as well as the involved toxicity of certain drugs has led to an increasing interest in the development and optimization of drug-delivery systems. Polymeric nanoparticles stand out as a key tool to improve drug bioavailability or specific delivery at the site of action. The versatility of polymers makes them potentially ideal for fulfilling the requirements of each particular drug-delivery system. In this review, a summary of the state-of-the-art panorama of polymeric nanoparticles as drug-delivery systems has been conducted, focusing mainly on those applications in which the corresponding disease involves an important morbidity, a considerable reduction in the life quality of patients. A revision of the use of polymeric nanoparticles for ocular drug delivery, for cancer diagnosis and treatment, as well as nutraceutical delivery was discussed.

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1. Introduction

The polymeric nano-revolution in medicine is an exciting prospect as it boasts the potential to transform the conceivable solutions of current therapeutic, diagnostic, prophylactic, and biological challenges to options that are more effective and reliable. However, the challenges lie in the multiple combinations of intricate physiological systems and the overwhelming feature considerations and corresponding effects, which create a complex system to analyze and understand. Cellular responses are critically different at the nano-scale level. Understanding the nanosize and biological interface is complicated but essential, especially considering the toxicity fears that currently exist in the nanomedicine field, there is a need for a set of design controls. Initial research characterization experiments of the nano-bio interactions include studies comprised of both the material properties and biological compositions such as analysis of transport kinetics, clearance, gene expression variations, chemical functionality, surface charge, biomolecular signaling, and toxicity (Albanese *et al.*, 2012). Polymeric nanomaterials have revolutionized how medicine is approached and executed.

According to Duncan and Vicent (2013) 'polymer therapeutics' encompass polymeric drugs, polymer conjugates of proteins, drugs, and aptamers, block copolymer micelles and multicomponent nonviral vectors with covalent linkages. Polymers are of interest in therapeutic applications owing to the design flexibility based on functionalization, macromolecular synthesis methods and polymer diversity (Delplace *et al.*, 2014). Initial uses of polymeric nanoparticles (NPs) for nano-based applications were based on nonbiodegradable polymers, such as poly methyl methacrylate, polyacrylamide, polystyrene, and polyacrylates (Vijayan *et al.* 2013). For nonbiodegradable particles, systems need to be designed such that particles exhibit rapid and efficient clearance through carriers such as feces or urine, do not accumulate or distribute in tissues at a toxic level because they cannot be easily degraded and excreted (Burman *et al.*, 2015) or are physically removed. Nonbiodegradable polymeric particles have been used for various applications, including drug

delivery (Feuser *et al.*, 2015), wound healing (Greenhalgh and Turos, 2015) and antimicrobial activity (Turos *et al.*, 2007). Chronic toxicity and inflammatory reactions were observed with the use of nonbiodegradable materials and thus a shift in focus to biodegradable polymers occurred. Biodegradable polymeric particles became of interest owing to reduced toxicity concerns, ability to influence specific drug release kinetic patterns, and increased biocompatibility.

2. Nanoparticles

Current research focuses on the search to identify the 'ideal nano-system' through the investigation of physicochemical structure properties and the biological interface. The cellular responses and ultimately alterations in phenotype are dependent on the cell receptors' initial surface contacts, which can include cell membrane stretching or compression and protein or ligand interactions, among other factors. All of these responses are related to the chemical composition, geometry, and functionalization of the NP in addition to the cell microenvironment, which includes the cell membrane and subsequent trans-membrane proteins, the surrounding extracellular matrix, and the morphology of the target cells (e.g., spindle-shaped endothelial cells growing on a basement membrane are a dramatically different target than surrounding connective tissue composed of fibro-blasts surrounded by extracellular matrix) (Shang *et al.*, 2014).

2.1 Particle size and geometry

A nanostructure's shape, aspect ratio, particle size, and dimensions directly influence cellular uptake and impact the pharmacokinetics and pharmacodynamics in nanomedicine applications (e.g., circulation time, clearance, selective tissue distribution, and intracellular fate) (Shang *et al.*, 2014). Specifying the details for various nanomedicine applications is a challenge owing to expected batch-to-batch particle geometry and size dissimilarities and the inability to accurately predict the behavior of the NP-cell interactions. A particle's geometry and size impact the formation of the protein 'corona', which is generated upon initial intro- duction of the particle to the biological system. Particle size can be controlled by multiple material selection factors (e.g., polymer, surfactant, and concentrations) and various fabrication method factors (e.g., type, nozzle diameter, flow rate, (Mitragotri and Lahann, 2009) control agent, monomer, initiator, polymerization, and emulsion types) (Rao and Geckeler, 2011). Functions of circulation, targeting, degradation, toxicity, opsonization, and uptake mechanisms, are correlated to particle size (Kulkarni and Feng, 2013). The cell membrane-particle interactions may be affected by the route of NP uptake, which can be defined in two consecutive stages: an adhesion process of the particle to the cell membrane and an internalization process (He *et al.*, 2010). Guidelines for what particle size might be useful for specific NP applications are listed in Table 1 (Win and Feng, 2005).

Table 1: Particle Size Relative to Clearance and Applications

Particle Size (Based on Rigid Sphere)	Nanomedicine Applications
<10 nm	Rapidly cleared through extravasation or renal clearance
10–20 nm	Detection, imaging, potential to cross blood–brain barrier (BBB)
20–100 nm	Drug/gene delivery, cancer therapy, sites of inflammation (optimal range to escape physiological barriers; high circulation potential, reduced filtration by liver and spleen)
100–200 nm	Drug/gene delivery (high potential for prolonged circulation)
200 nm–1μm	Generally cleared by the spleen
>1μm	Usually opsonized and accumulate in liver and spleen, cleared from circulation almost immediately

2.2 Material processing

Innovative and advanced processing techniques have accelerated the advancements in polymer therapeutics. However, the processing techniques may be constrained by the material choice. Requirements of the material such as temperature, solvents, and material stability may restrict the treatment options. Additionally, the process may be chosen based on the anticipated nanostructure outcomes: particle size, distribution, application (Rao and Geckeler, 2011), morphology, tailor ability, and so forth. The material possibilities can be divided into synthetic and natural categories. Liu *et al.* (2011) list prominent synthetic materials used in nanomedicine applications, such as polyethylene glycol (PEG), poly-lactic acid-co-glycolic acid (PLGA), PVA, polyvinyl pyrrolidone (PVP), polyethylene (PE), polyanhydrides, and polyorthoesters, and natural materials, such as starch, polypeptides, albumin, sodiumalginate, chitin, gelatin, cellulose, and polyhydroxyalkanoates. Materials used for nanomedicine applications must abide to the biocompatible and biodegradability requirements for biomedical applications.

2.3 Polymerization

Two generalized routes of polymeric NP synthesis are from preformed polymers or via direct

polymerization of monomers with classic polymerization (Liu *et al.,* 2011); in addition, other NP preparation methods of consideration include PRINT® and mechanical stretching, which have shown tighter control over size and shape and lend themselves to mass production. The appropriate NP synthesis method is based on a number of factors, such as application (drug delivery, imaging modalities, etc.), size requirement (Rao and Geckeler, 2011), material choice (biocompatibility, biodegradability), specificity (stability, surface charge), and morphology. With the numerous synthesis options available, advanced nanostructure designs can be more functional and complex.

3. Polymers in Drug Delivery

One of the most important biomedical applications of biodegradable polymeric nanomaterials can be found in the field of drug delivery. Polymeric nanomaterials offer several advantages, such as (1) provide a controlled release fashion from the matrix structure into a targeted part of the body; (2) encapsulate labile molecules (e.g., DNA, RNA, and proteins) and prevent degradation; (3) option to modify surfaces with ligands; and (4) provide excellent in vitro and in vivo stability (Torchilin, 2014).

3.1 Biodegradable polymeric nanoparticles for controlled drug delivery

Controlled drug delivery happens when the drug of interest is released from the polymeric matrix in a designed fashion (Bao *et al.,* 2013). Over the years, several different morphologies of biodegradable polymers have been fabricated and applied for drug delivery such as nano- fibers and NPs (Li *et al.,* 2014). Among different nanostructure morphologies for drug delivery, NP-based drug delivery shows numerous advantages for controlling the release of biological factors. These advantages include (1) selective targeting, (2) controlled release, (3) protection of deliverable agents, and (4) extension of the circulation time in the body (Torchilin, 2014).

3.2 Responsive polymeric nanoparticles

One of the new approaches in nanomedicine, especially in drug delivery, is using stimuli-responsive materials. Stimuli-responsive nanostructures can provide longer circulation times, targeted delivery, enhanced intracellular delivery of the drugs, and release a drug payload in a spatially, temporally, and dose-controlled manner (Mura *et al.,* 2013). The release mechanism within polymeric NPs is more sophisticated because the biomaterials experience conformational changes caused by a stimulus. Sources of stimuli can be internal and inherent to the body tissue response (Thambi *et al.,* 2014) (e.g., hypoxia, temperature, or enzymatic activity), external forces (e.g., magnetic field or ultrasound), or a combination of both. Among the internally controlled stimuli, pH and temperature are the most convenient ones to apply.

3.2.1 Temperature-triggered drug delivery

Most of the temperature-sensitive polymeric NPs are characterized by a low critical solution temperature (LCST). Temperature-triggered drug release is enabled by the rupture of the polymeric structure when the temperature is raised above the LCST. This can be used as a strategy for designing temperature-sensitive drug carriers because cancerous tissues exhibit hyperthermia (e.g., 42ºC in human ovarian carcinoma). Temperature-sensitive NPs as a drug carrier can cause a triggered release of the agent in the tumor site owing to hyperthermia or local heating. The release mechanism happens because in hyperthermia higher extravasation of drug loaded NPs occurs owing to the increase in both microvasculature and blood flow (Dan *et al.,* 2014). Liposomal systems show the most potential for temperature- sensitive polymeric NPs in clinical applications. The most critical challenge related to these systems is the design and the choice of safe and sensitive nanobiomaterials that can respond to changes on small temperature range close to the physiological temperature (37ºC) (Cheng *et al.,* 2012).

3.2.2 pH-triggered drug delivery

The physical tumor microenvironment can provide a situation (changes in PO_2 and pH) to overcome a solid tumor's resistance to therapy. Owing to hypoxia and high glycolytic activity in solid tumor areas, a significant secretion of H+ and lactate to the extracellular environment can be observed, causing an acidic extracellular space in a tumor site (Danhier *et al.,* 2010). Studies also confirmed that an acid pH gradient typically is created inside the tumor environment, which is not typically found in normal tissue. The acidic environment of tumors provides an avenue for the design of pH-sensitive NPs for onsite drug release. These pH-sensitive NPs consist of building units that protonate at a low pH, causing drug release based on the destabilization of the drug-loaded NPs (Pennakalathil *et al.,* 2015).

3.3 Polymeric micelles

Polymeric micelles (PMs) are spherically shaped NPs made of hydrophobic and hydrophilic units in aqueous solutions. In polymeric micelles, hydrophobic anticancer agents can be stored in a hydrophobic core reservoir, while hydrophilic shells interact with the aqueous solution. The hydrophilic shell of the PMs acts as a brush to keep the hydrophobic core away from biological invasion and reduces adsorption of proteins on the micelle. PMs have been used for drug delivery applications owing to their unique properties. These properties include flexibility in the variety of selecting hydrophobic regions, nanoscale size, and increase in the solubility and stability of anticancer agents (Ahmad *et al.,* 2014). Regulating the mass ratio of hydrophilic/ hydrophobic units and selecting different hydrophobic units can adjust the physicochemical properties of PMs.

These advantages make PMs a great clinical candidate for cancer treatment.

3.4 Polymer–DNA and small RNA complex

Nucleic acids, such as DNA and siRNA, have attracted much attention as a promising tool for treating genetic disorders and cancer therapy. However, there are some challenges in using this method, such as low cellular uptake, serum nucleases degradation, and fast rapid renal clearance after application. Biodegradable polymeric NPs have been found to be safe and effective as drug carriers, by protecting the nucleic acids from degradation and cellular uptake of nuclease without the help of transfection agents. Tzeng and coworkers developed a method for treatment of malignant glioma using polymeric NPs to deliver DNA (Guerrero-Cazares *et al.,* 2014). Biode-radable poly (β-amino ester) (PBAEs)/DNA NPs were applied in both in vitro and in vivo and resulted in higher transfection and intrinsic tumor cell specificity in glioblastoma cells compared with naked DNA (Guerrero-Cazares *et al.,* 2014).

4. Application of Nanoparticle Infused Polymer Matrix

4.1 Pro-drugs

The prodrug approach, developed more than 50 years ago, involves covalently linking a drug to a polymer scaffold or macromolecule to help move drugs across physiological barriers (Bildstein *et al.,* 2011). Prodrugs require an in vivo chemical or enzymatic transformation(s) to release the active drug. In carrier-linked prodrugs, a promoiety is a nontoxic removable protecting group linked onto an active drug molecule to improve the delivery or effectiveness of the drug; typically, it is quickly excreted from the body following activation of the prodrug unit. The prodrug platform creates more powerful treatments by improving aqueous solubility, minimizing toxicity effects, enhancing site specificity, increasing cell uptake, and reducing the 'burst release' effect of many drug delivery systems.

4.2 Imaging

Molecular imaging (MI) is a technique that monitors changes in vivo at the molecular level in order to detect diseases at an early stage. With the help of MI, physicians can develop a personalized therapy for a patient by closely examining the region of interest in the body (Bao *et al.,* 2013). Contrast agents play an important role in enabling visualization of a target with most conventional MI techniques [e.g., magnetic resonance imaging (MRI), optical imaging, and X-ray computed tomography (X-ray CT)]. However, most of the current agents suffer from instability in vivo, poor targeting, and a burst release of imaging agents upon *in vivo* (Li *et al.,* 2014). To overcome these challenges, polymeric NPs have been utilized to deliver fluorescent contrast agents. Polymeric NPs offer several advantages because of their physicochemical properties, including: (1) nanoscale sizes to facilitate endocytosis and probing of cells;(2) high drug payloads; (3) ability to functionalize their surfaces with a variety of molecular signaling and receptor targeting molecules; and (4) theranostic ability to enable both detection and treatment of targeted diseases (Srikar *et al.,* 2014). Some of the polymeric NPs in MI techniques are MRI, optical imaging, CT, and positron emission tomography (PET).

4.2.1 Magnetic resonance imaging (MRI)

Physical encapsulation of contrast agents within polymeric NPs is a commonly used method for MRI. Polymeric NPs can be used to encapsulate and subsequently deliver T1 and super-paramagnetic iron oxide NP [SPION (T2)] MR agents. The encapsulated agents can be released to a target area by responsive conditions. For example, enzyme-activated fatty acid-coated gadolinium diethylenetriamine pentaacetic acid (GA- DTPA-FA) NPs have been synthesized to validate the use of NPs as a targeted agent for early detection of acute pancreatitis. Both in vitro and in vivo studies confirmed that the release of Gd-DTPA fatty acid NPs could significantly enhance the imaging signal (Zhang *et al.,* 2014). Several studies have shown encapsulation of SPIONs using self-assembled amphiphilic polymers. A polymeric micelle system can be a good candidate for targeted MRI and drug delivery of SPIONs (Zhang *et al.,* 2014).

4.2.2 Optical imaging

Recently, optical imaging has shown an exponential growth in MI because of its noninvasive nature and the development of robust near-infrared fluorescence (NIRF) imaging instruments. Several polymer nano-constructs are used to encapsulate the indocyanine green (ICG) and noninvasive NIRF dye used for optimal imaging in the human body (Liu *et al.,* 2013). Liu *et al.* (2013) have developed novel sensitive ICG NPs with theranostic potential. The NPs possess the ability to be activated from an off state to on state in the intracellular environment and can be used for accurate imaging and photo- thermal therapy. ICG NPs can be used for photothermal therapy with NIRF laser irradiation, which suggests that this system maybe an effective theranostic agent for cancer imaging and therapy (Liu *et al.,* 2013).

4.2.3 X-ray computed tomography

Both encapsulated and covalently linked contrast agents have been used in CT imaging and in vivo characterizations of these types of nanostructures. For covalently linked agents, for example, mPEG-polylactide cross-linked with biocompatible poly (iohexol) NPs was employed for in vivo CT imaging. These types of polymeric NPs exhibited extended retention within the tumor compared with conventional small-molecule contrast agents. This approach can improve diagnosis accuracy for a longer time without the need for multiple administrations. In addition to covalently linked agents, several polymeric matrices

have been successfully used to encapsulate contrast agents for CT imaging (Mieszawska *et al.,* 2013).

4.2.4 PET scan

PET is a nuclear imaging machine that detects a small amount of radioactive tracer, which is introduced into organs and tissues. It has been introduced as an increasingly favored functional imaging technique for physiological and/or pathophysiological processes. Recently, researchers have introduced several PET agents based on polymeric NPs. The choice of radiotracer is determined by the required circulation time of the NP. For the measurement of a long circulation time frame of NPs after injection, longer half-life radio-isotopes are required (De Barros *et al.,* 2012).

4.3 Theranostics

Theranostics, a combination of therapeutics and diagnostics, is a new wave of nanomedicine developed for both molecular detection and diagnostic as well as targeted treatment (Li *et al.,* 2014). Briefly, theranostic systems provide a proper method to administer the right drug dosage to the right area at the right time by imaging the extent of the disease, delivering treatment, and monitoring real- time therapeutics efficacy. The drug carrier plays a key role in theranostics; thus, it should provide three elements at the same time: delivery of imaging contrast agents, bioactive molecules, and an optimal distribution of agents. Numerous combinations of these three factors and corresponding features have been investigated (Mura *et al.,* 2013). Among all the MI methods, MRI is the most frequently used method for therapeutics owing to its very high resolution and capability to cover most of the organs. More importantly, many MRI contrast agents can be encapsulated into NPs. Optical imaging can also be utilized as a medical imaging modality in nanotheranostics; however, the application of optical imaging is limited owing to the visible light spectrum scattering in the soft tissues' region. Using longer wave- lengths in the NIR (biological window) can decrease the scattering for optical imaging and many fluorophores. Kim *et al.* (2010) used NIR dye Cy5.5 label PTX- loaded chitosan-based NPs for nanotheranostics. In vivo experiments clearly showed that Cy5.5-labeled PTX-chitosan-based NPs (PTX-CNPs) are extremely useful for simultaneous early-stage cancer detection and treatment. Cy5.5-labeled PTX-CNPs can pro- vide the possibility of both detecting biodistribution and noninvasively monitoring tumor growth changes in response to the treatment.

4.4 Cancer treatment

In order to improve drug efficacy in cancerous cells, it is desirable to encapsulate the anticancer agents and deliver them in a controlled manner to the tumor site. To further improve the therapeutic efficacy of anticancer agents, polymeric NPs can be utilized; these polymeric NPs play a more effective role on treatment compared to conventional chemotherapy. Polymeric NPs can not only diminish the drug toxicity to the surrounding normal tissues but can also increase aqueous solubility of anticancer agents (Louage *et al.,* 2015). Cheng *et al.* (2011) showed that cisplatin-cross-linked carboxymethyl cellulose (CMC) NPs, made from PLGA-monomethoxy PEG (PLGA-mPEG) copolymers, could release cisplatin in a controlled fashion and enhance the treatment effectiveness of cisplatin against IGROV1- CP cells compared to intravenous administration. In another recent study, Zhao *et al.* (2013) showed that Docetaxel (DTX)-loaded NPs overcome multidrug resistance of tumors owing to their stimulus-responsive nature of polymer. By examining these dual-functional pH-sensitive polymer and D-α-tocopheryl poly- ethylene glycol succinate-mediated P-glycoprotein inhibition copolymer NPs loaded with DTX, they successfully solubilized the DTX, provided a well-con- trolled release, and enhanced the cell cytotoxicity of the DTX in a tumor area. Sufficient efficacy and improved toxicity profiles were demonstrated in their in vivo preclinical tumor models. Polymeric NPs hold great promise as next generation treatment in improving the quality of life for cancer patients by overcoming the limitations of conventional chemotherapy treatments.

4.5 Neurodegenerative disorders treatment

Another area of using polymeric NPs in medicine is neurodegenerative disorders (NDs), such as Alzheimer's disease (AD) and Parkinson's disease (PD). NDs treatment still remains a challenge owing to limitations presented by the preventive BBB surrounding the central nervous system (Goldsmith *et al.,* 2014). To address this challenge, polymeric NPs are utilized to facilitate drug penetration through the BBB. Recently, Zhang *et al.* (2014) developed a dual-functional drug delivery carrier based on PEG-PLA polymer to target and potentially treat AD. The surface of NPs was modified with a 12-amino acid peptide, TGNYKALHPHNG (TGN) and a D-enantiomeric peptide, QSHYRHISPAQV (QSH), which can be screened by targeting peptides to target AD lesions. This dual-functional drug delivery system can diminish cytotoxicity to normal tissues and help to improve early diagnosis or treatment of AD. Another formulation designed to treat PD includes NPs composed of chitosan (CSNP) for delivery of neurotransmitter dopamine (DA). In vivo microdialysis studies showed that intraperitoneal acute administration of DA/CSNPs in a rat brain resulted in a dose-dependent increase in striatal DA output. CSNP containing DA represents an interesting technological platform to treat PD (Trapani *et al.,* 2011).

4.6 Cardiovascular disorders treatment

Another area of nanocarriers for drug delivery is for the treatment of cardiovascular diseases, such as atherosclerosis and restenosis (Yin *et al.,* 2014). Chan *et al.* (2011) developed a NP system for systemic and targeted delivery of an antiproliferative agent to the

injured vasculature. Together, a controlled delivery system with vascular targeting can offer a safe method for treating coronary artery disease. Kim *et al.* (2014) noted the translocation of lipid polymer hybrid NPs through the atherosclerotic endothelial layer relied on the permeability of the microvasculature. To validate the in vitro model and results, NPs translocation in an in vivo rabbit model of atherosclerosis was examined. In addition to the aforementioned drug delivery systems, polymeric NPs can be used for other diseases, such as viral infections and osteoporosis.

5. Nanomedicine

Many nanoparticles are thought to have improved pharmacokinetic properties due to their physical nature and reduced size; they can target specific cells for selective action dependent on the particle type. These particles can easily penetrate target cells and accumulate into subcellular structures to modify cellular processes, which may be beneficial in the treatment of lifelong diseases such as diabetes, cancer, and kidney diseases (Barua and Mitragotri, 2014). Nanoparticles that are popularly used in research for therapeutic purposes include encapsulated mRNA (siRNA) or DNA (in gene therapy), inorganic metal and metal complexes, or chemotherapeutic agents with pharmacologic abilities (Khurana *et al.*, 2019; Sharma *et al.*, 2022). However, some of these nanoparticles do not easily traverse the cell membrane, requiring delivery systems to alleviate such difficulties. Thus, different nanoparticle delivery systems have been developed, some of which include liposomes, micelles, chitosan, and synthetic dendrimers. The entrapment of both hydrophobic and hydrophilic drugs into liposomes is possible, and this helps to bypass the toxicity associated with anticancer drugs.

5.1 Micelle nanocarriers for ocular delivery

Most commonly used polymers for the synthesis of micelles as DDSs is the poly (lactic-co-glycolic acid) (PLGA), due to its high biocompatibility and biodegradability. It was approved for clinical use in 1989, by the US Food and Drug Administration (FDA) (Park *et al.*, 2019). It has been tested for the sustained delivery of different drugs formulated with polyvinyl alcohol (PVA). Varshochian *et al.* (2015) used the PLGA/PVA system to prepare bevacizumab-loaded micelles for the treatment of ocular neovascularization. This molecule has widely demonstrated its effect in the treatment of retinal and choroidal neovascularization, however, its short half-life in vitreous humor requires frequent intravitreal injections. Surprisingly, bevacizumab-containing micelles provided a sustained release, and the drug concentration in vitreous humor endured above 500 ng/mL, the minimum concentration that completely blocks the vascular endothelial growth factor-induced angiogenesis, for about two months. Dexamethasone, a powerful anti-inflammatory, was also delivered in this type of NP. Qiu *et al.* (2019) proved that the use of these micelles improved retinal dysfunctions, inhibited retinal leukostasis, diminished retinal vascular leakage and regulated the over expression of vascular endothelial growth factor (VEGF) at eight weeks after the application.

5.2 Dendrimeric nanocarriers for ocular delivery

Although most of the explored polymeric nanocarriers have focused on micelle-based NP systems, dendrimeric structures have also been investigated. The archetypical dendritic polymer for the preparation of nanosystems for drug delivery to the posterior segment of the eye is based on polyamidoamines. Yang *et al.* (2019) examined the potentiality of dendrimers prepared from a PEGylated polyamidoamine and modified with cyclic arginine–glycine–aspartate hexapeptide and penetratin, as drug carriers. They demonstrated that these functionalized NPs were present in the ocular posterior segment after more than 12 h of a non-invasive administration. Lancina *et al.* (2018) studied a dendrimer based on a polyamidoamine, the dendrimeric core was derivatized with a timolol analog, a common drug used for the treatment of ocular hypertension. Their results displayed an intraocular pressure reduction of 30% in normotensive adult Brown Norway male rats, after 30 min of topical application, in addition to the absence of irritation or toxicity after one week of daily administration.

5.3 Other types of polymeric nanocarriers for ocular delivery

Although they are less utilized for ocular drug administration, cyclodextrins (CDs) and polymeric vesicles (PVs) are another type of polymeric nanocarriers. CDs are a special type of cyclic oligo- or polysaccharide constituted of six or more units of glucose bound by α-1, 4 glycosidic bonds (Tian *et al.*, 2020). This characteristic configuration entails truncated cone geometry with an outer surface presenting a hydrophilic character and an internal cavity with hydrophobic feature. This makes them a good option as DDS for hydrophobic active ingredients (Wankar *et al.*, 2020). In addition, the polarity of these systems can be modulated depending on the number of glucose units that form the cyclodextrin and the variety of their substituents. Jansook *et al.* (2019) used γ-cyclodextrin and randomly methylated β-cyclodextrin to enhance solubility of celecoxib, a non-steroidal anti-inflammatory administered for age-related macular degeneration and diabetic retinopathy. By combination of these nanoaggregates with mucoadhesive polymers, such as hydroxypropyl methylcellulose or hyaluronic acid, they obtained eye-drop formulations that demonstrated improvements in drug permeation through transcorneal and transscleral routes, with no cytotoxicity shown. In a similar approach, Lorenzo-Veiga *et al.* (2019) prepared ocular natamycin nanocarriers. Currently, this is the only drug approved for fungal

keratitis treatment. They used a combination of Soluplus and Pluronic P103 and α-cyclodextrin to generate a library of micelles and poly (pseudo)rotaxanes containing the drug. The latter were found to be the most promising candidates since they displayed good diffusion, cornea and sclera accumulation and sclera permeability coefficients.

5.4 Polymeric nanoparticles in cancer diagnosis and imaging

According to the WHO, cancer is the second leading cause of death worldwide, with an estimated 9.6 million deaths in 2018. These data indicate cancer to be one of the diseases with the highest rate of morbidity and mortality nowadays. Finding effective methodologies for early detection, diagnosis and treatment has become a fundamental objective when developing NPs as DDSs (Zhou *et al.*, 2018). Ordinary imaging and diagnosis techniques can only detect tumor mass when it is at least one-centimeter in size, being notably difficult to detect cancer at early stages. This is the reason many researchers are currently trying to develop new and smaller composites able to identify malignant cells related to cancer processes, in order to inform medical staff to devise a treatment strategy. Polymeric NPs have thus emerged as an alternative to limit ordinary contrast agents due to their surface modification abilities and their capacity to regulate solubility of the embedded agents in order to enhance imaging of cancerous cells.

5.5 Gold-based polymeric nanoparticles used in cancer diagnosis

Gold metallic NPs (AuNPs) and their derivatives are the most important investigation topic when describing new composites able to improve diagnosis and imaging techniques. Due to their versatility, they can be used in multiple imaging methods, providing high resolution and low or non-existent toxicity (Maham and Doiron, 2018). Computed tomography (CT) is one of the most commonly used diagnosis techniques in cancer imaging, mainly due to its low cost, high imaging resolution and compatibility with all types of patients. Scanning of soft tissues carried out by this technique requires contrast agents absorbing X-ray radiation. AuNPs have generated great interest as these agents, since they are nontoxic and present up to three-fold more efficiency in X-ray absorption than the current iodine-based CT contrasts agents. Other benefits related to AuNPs are the possibilities of designing and modifying their shape, size and surface. Although there are other NPs with a higher capability of X-ray radiation absorption, like bismuth-sulfide NPs, the control of their characteristics and the modification of their surface are more complicated (Kim *et al.*, 2014). In order to emphasize AuNPs contrast properties, encapsulation of these metallic NPs in polymeric NPs have been tested. Al Zaki *et al.* (2014) designed and optimized polymeric micelles (AuMs) where 1.9-nm-size AuNPs were encapsulated within the hydrophobic core of micelles constructed from amphiphilic copolymer PEG-PCL. Blood pool contrast was obtained for 24 h and enhanced tumor margin delineation was observed, via CT, when AuMs were injected in living mice. Improvements in survival time when radiotherapy was applied were also demonstrated in these animals when treated with AuMs, compared to those which were not. Dedrimeric NPs were also investigated for the stable encapsulation of AuNPs for CT cancer diagnosis.

AuNPs can also be utilized in many other bioimaging techniques such as two-photon nonlinear microscopy, to study the binding coefficient between NPs and target cells and their absorption (Park *et al.*, 2018). Single-photon excitation is a similar technique employed in vitro to establish AuNPs accumulation in cells cytoplasm. Wang *et al.* (2016) designed biodegradable polymeric NPs based on silica-coated AuNPs for photoacoustic imaging (PAI). This technique allows researchers to obtain images from biologic structures of different shapes and forms, even from organelles. It consists of the generation of wideband ultrasonic waves (called PA waves) due to thermoelastic expansion when a tissue is irradiated by near-infrared (NIR) light, which is absorbed by the target. It is a very reliable technique to be linked to commonly used clinical diagnosing techniques. The gold nanospheres where synthesized, coated with silica, fluorinated and then introduced in a previously synthesized PLGA NP.

5.6 Gadolinium polymeric nanoparticles (gdnps) used in cancer diagnosis

Magnetic resonance imaging (MRI) allows three-dimensional high-resolution images to be obtained. It is useful for delimiting morphologic characteristics in tumors without producing ionizing radiation that could be harmful for the patient. This has become one of the best strategies in clinical cancer diagnosis. To optimize this technique, contrast agents are utilized to enhance the variations between the different tissues, by lowering water relaxation parameter values (longitudinal or T1 and transverse or T2). There are many different types of contrast agents, but gadolinium-based materials are the most widely used and mainly those formed by the chelated metal. While gadolinium-chelated complexes are easily eliminated from the organism by the kidneys because of their low molecular weight (<11 nm), if they are too big, they can be phagocytosed by macrophage cells (>200 nm). Nanotechnology has tried to overcome this inconvenience by designing new gadolinium-based contrast agents with enhanced imaging time, contrast effect and lowered toxicity, as well as granting passive targeting properties. In order to modulate these characteristics, NP surface modification and full-size control is necessary. Some investigations have allowed enhancing of imaging by targeting key elements present in cancer cells, such as overexpressed surface proteins.

To this end, Liu *et al.* (2011) synthesized a novel multifunctional polymeric GdNPs-based contrast agent (Anti-VEGF PLA-PEG-PLL-GdNP). These nanoparticulate systems were designed with anti-VEGF antibody, which facilitates delivery to cancer cells in hepatocellular carcinoma (HCC) in order to improve its detection in early phases.

Gadolinium has also been used as an imaging platform in PAI technique. The great depth penetration that NIR light reaches, makes NIR-light-absorbing materials (650-900 nm) such as organic materials, the ideal candidates for this technique (Kim *et al.*, 2014) even if they are optically unstable. Gadolinium-based agents could overcome this issue, enhancing both imaging time and resolution. Developing polymeric GdNPs where Gd-complexes can be attached and immobilized in macromolecules (Hu *et al.*, 2013), red blood cells (Li *et al.*, 2012), monoclonal antibodies, is a tedious and complicated process.

5.7 Perfluorocarbons polymeric nanoparticles (PFCNPs) used in cancer diagnosis

Perfluorocarbons (PFCs) are molecules whose structure is similar to common organic compounds (e.g., alkanes). The difference between PFCs and regular organic compounds is that every hydrogen atom is replaced by fluorine (^{19}F) in PFCs, the most electronegative element in the Periodic Table. This exchange grants new and interesting properties that can be useful for medical applications. Nuclear magnetic resonance (NMR) is usually based on the ^{1}H signal from the water of the body's tissues and mobile hydrocarbon compounds. There are also other nuclei such as ^{19} F (Wallat *et al.*, 2017), which can be used in this technique to improve diagnosis and imaging effects. Unlike hydrogen atoms, most of the fluorine found naturally in the organism are located in bone structures, which as solid structures, restrict fluorine signal for MRI assays. One of the major problems connected with the use of PFCs, is their solubility, due to the fact that they have high hydrophobicity. Research and development of new systems able to load contrast agents and enhance their biodistribution, has led to the design of nanoparticulate systems which raise their imaging effects. Wallat *et al.* (2017) designed and characterized a polymeric NP containing fluorine compounds for enhanced NMR effect and passive targeting using a described copolymer, obtained from polyethylene glycol methyl ether methacrylate (PEGMEMA) and trifluoroethyl methacrylate (TFEMA) monomers with an azide functional group. NPs were synthesized through atom transfer radical polymerization (ATRP) in order to obtain a small polydispersity index and provide precise molecular weights and sizes. This system also showed passive diffusion into tumors and irrelevant ^{19}F NMR signal alteration.

5.8 Polymeric nanoparticles in oncologic treatment

Cancer has become a leading cause of death in developed countries. In fact, experts claim that over the next 20 years, the incidence of this disease is expected to increase by approximately 70% (Calzoni *et al.*, 2019). The classic therapeutic approach to deal with cancer consists of surgery, chemotherapy and radiotherapy. Chemotherapy is the treatment of choice in most cancers, but it does present high toxicity due to the affection of both healthy and cancerous cells. Nanomedicine, defined as the use of materials in nanometric scale in medicine, offers a more specific alternative. Its main objective in oncology is to transport the drug only to cancer cells selectively in order to improve its efficacy and reduce its toxicity (Calzoni *et al.*, 2019).The potential application of nanomedicine can also provide early detection tools in cancer as well as combination therapies that can result in both better efficacy of treatment and prognosis.

5.9 Polymeric nanoparticles as nutraceutical agents

Although there is no official accepted definition of nutraceuticals, they are mostly referred to as pharma-foods, a powerful toolbox to be used as a complement to the diet and before prescribing drugs, in order to improve health and prevent and/or treat pathologic conditions (Santini *et al.*, 2018). Substances from similar sources are classified differently, such as plant-derived drugs, for example, digoxin from foxglove leaves is in the group of the medicinal products, while extracts from green tea leaves are regarded as nutraceuticals. In animal models of ulcerative colitis (UC), codelivery of conventional drugs related to UC therapy, together with alternative therapeutic molecules or their combinations have been reported. Hyaluronic acid-functionalized polymeric NPs, to direct the specific drug (siCD98) and curcumin have shown anti-inflammatory effects in colonic epithelial cells and macrophages, protecting the mucosal layer and offering a structurally simple platform to be orally administered (Xiao *et al.*, 2016). In that sense, a pH-sensitive NPs of curcumin-celecoxib combination reduces the overall toxicity and total dose of celecoxib, providing enhanced efficacy for mitigating UC by synergistic action of these two agents. This novel form of carriers could represent a new strategy to deliver drugs directly to target cells in UC therapy. As it is possible to observe, the use of NPs has been effective to improve the curcumin low systemic bioavailability. In a recent study, the protective effects of curcumin-loaded PLGA NPs, against mono-iodoacetate-induced osteoarthritis in rats, have been reported. The results reveal that curcumin could reverse hypocellularity and structural changes of articular cartilage in animal models of osteoarthritis. However, the increase in cellularity and matrix is more pronounced when it is encapsulated in PLGA (Soukoulis and Bohn, 2018).

Other nutraceuticals that offer health benefits have been nanoencapsulated to increase delivery, mobility,

cellular uptake, bioaccessibility and stability. Carotenoids, widely distributed in fruit and vegetables, induce health beneficial properties mainly through their antioxidant activity, although their bioavailability is often compromised due to incomplete release from the food matrix, poor solubility and degradation during digestion (Soukoulis and Bohn, 2018). Yi *et al.* 2015) confirmed that whey protein isolate (WPI) NPs are good carriers for delivering beta-carotene, by means of the homogenization-evaporation method. This is due to the low release profile in gastric fluids and high release profile in intestinal fluids.

5.9.1 Toxicity

Most commonly used nutraceuticals are compounds derived from herb food, plants, fruit and vegetables. Widely consumed nutraceuticals include flavonoid, flavonols and polyphenols, such as resveratrol, catechins and quercetin. A small number of these products do have a toxic potential, associated with hepatotoxicity, genotoxicity and mutagenicity (Nowak *et al.*, 2017). In addition, the safety of some nutraceuticals can be compromised via contamination with toxic plants, metals, mycotoxins, pesticides, fertilizers or drug-supplement interactions (Gupta *et al.*, 2018). Chemical structures of polyphenols could alleviate cytotoxicity induced by NPs through the inhibition of oxidative stress, hydrodynamic size, zeta potential and solubility caused by some NPs, such as the ones derived from zinc oxide (ZnO) (Zhang *et al.*, 2018). The use of silver NPs (AgNPs) in several dietary supplements, utilized due to their strong antimicrobial properties, may leak out into the food and be consumed, creating severe health risks when reaching the small intestinal epithelium with their surface characteristics altered or dissolved into silver ions, which could alter their subsequent absorption and toxicity (Wu *et al.*, 2018). On the contrary, biopolymers, which are used for NP delivery systems, have well-documented biodegradable, biocompatible, mucoadhesive properties, and they do not decrease cellular viability in different cell lines when loaded with bioactive compounds (Vozza *et al.*, 2019).

6. Conclusions and Future Perspectives

Presently, a variety of NPs have been designed and applied in both preclinical and clinical studies. The potential for polymeric NPs in drug delivery, imaging, therapy, and theranostic applications is significant. Several unique NPs presently at the primary design stage have potential to improve and facilitate both cancer imaging and therapy. During the last decade, polymeric NPs, such as biodegradable NPs, micelles, and stimuli-responsive NPs, have developed quickly with rapid growth owing to NP's unique physical properties such as selective targeting, controlled release, protection of deliverable agents, and extension of the circulation time in the body. In cancer therapy, polymeric micelles provide new tools to load poorly water-soluble anticancer agents and increase the longevity of the molecules to create innovative therapeutic entities. Stimuli responsive polymeric NPs offer extraordinary controlled release profiles resulting in more effective anticancer effects both in vitro and in vivo. Polymeric NPs provide an excellent contrast enhancement for almost all medical imaging modalities, which provide the opportunity to monitor tumor activity by tracking NP kinetics. NPs can also be utilized in theranostics for MI. If high NP accumulation is exhibited in tumors, a burst release of the drug occurs by applying a physical source to NPs, which may be NIR lasers, external heat, or by lighting photosensitive components. The future of nanomedicine, especially through polymeric NPs, will improve and facilitate the conventional therapies to assist humans on both individual and worldwide levels. The continuous research on polymeric NPs in both preclinical and clinical studies will fundamentally change and improve the diagnosis, treatment, and prevention of diseases.

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12/12/2023