Polymeric Nanogels and Nanoparticles in Medical Applications

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Key Points

- Definitions and classifications of macro-, micro- and nanogels have been given.
- Radiation-induced synthesis of nanogels has been discussed.
- Examples of nanogels and nanoparticles based on synthetic and natural polymers have been given.
- Biomedical applications of nanogels and nanoparticles have been presented.

Abstract

Nanogels and polymeric nanoparticles have been intensively studied for diverse applications due to their unique and tuneable properties. Nanogels are hydrogels—three-dimensional network of polymer chains with water filling the spaces between them—in nanometer size, which allows them to penetrate biological barriers and be of high interest for several medical applications. Polymeric nanoparticles are differentiated from nanogels by the swelling property. While nanogels have high capacity of water absorption that may lead to size changes, polymeric nanoparticles are mostly a solid mass. Both, nanogels and nanoparticles may be obtained from synthetic and natural polymers though different synthesis processes. The radiation-induced intramolecular crosslinking was proposed as a great alternative, eliminating the need of toxic crosslinking agents and providing a final sterile material. In this review, we intended to

present a focused discussion on the radiation-induced synthesis technologies, the most frequent used polymers to obtain nanogels and nanoparticles, and their biomedical applications showcasing their potential to revolutionize healthcare.

Introduction

Hydrogels (Wichterle and Lím, 1960), whether physical or chemical, synthetic or natural, random or regular in architecture, and varying in size, have become an object of intensive study due to their unique properties, such as high water content, biocompatibility, tunability, and responsiveness. Their potential applications span diverse fields including medicine, pharmacy, agriculture, robotics, and sensors, with specific uses in drug delivery, regenerative medicine, and wound healing. The study of hydrogels intersects various scientific disciplines like materials science, chemistry, biology, and engineering, driving innovation in this field (Boateng et al., 2008; Gupta et al., 2002; Hoare and Kohane, 2008; Hoffman, 2002; Peppas et al., 2000; Rosiak and Yoshii, 1999; Slaughter et al., 2009; Tibbitt and Anseth, 2009; Zhang and Khademhosseini, 2017). Despite their wide range of applications, hydrogels remain challenging to define and classify. Nearly a century ago, Dorothy Jordan Lloyd remarked, "the colloidal condition, the gel, is one which is easier to recognize than to define" (Jordan-Lloyd, 1926). Since then, more precise definitions have been developed. Today, hydrogels are defined as two- or multi-component systems consisting of a three-dimensional network of polymer chains with water filling the spaces between the macromolecules. According to the IUPAC (2014), a hydrogel is a gel in which the swelling agent is water. This definition highlights the hybrid nature of hydrogels, combining a solid polymer network with a fluid presence. The water content in a hydrogel typically exceeds the polymer content, necessitating the use of moderately hydrophilic polymers. High degrees of swelling are often achieved using synthetic polymers that are water-soluble when not crosslinked. Although many biomedical hydrogels are synthetic, crosslinked natural polymers, mainly polysaccharides, are also being used.

Classification of Hydrogels

Understanding classifications (Ahmed, 2015; Peppas et al., 2000) and their unique properties allows for the precise design and application of hydrogels in a wide range of fields, maximizing their potential benefits and effectiveness. Hydrogels are generally classified into two main types based on their network structure:

Physical gels (pseudogels): these hydrogels have polymer chains connected by electrostatic forces, hydrogen bonds, hydrophobic interactions, or chain entanglements. They are non-permanent and can often revert to polymer solutions under conditions such as heating or changes in pH or ionic strength.

Chemical gels (true, permanent hydrogels): these hydrogels have polymer chains linked by covalent bonds, resulting in a stable and permanent network.

Beyond this basic classification, hydrogels can be further categorized based on various criteria such as origin, polymer composition, physical structure, response to stimuli, and charge. The main classifications are:

1. Based on origin (Varghese et al., 2020; Zhang and Huang, 2021)
   - Natural hydrogels: derived from natural sources such as proteins (e.g., collagen, gelatine) and polysaccharides (e.g., agarose, alginate, chitosan).
   - Synthetic hydrogels: made from synthetic polymers like poly(vinyl alcohol) (PVA), poly(ethylene glycol) (PEG), poly(acrylic acid) (PAA), and poly(2-hydroxyethyl methacrylate) (PHEMA).
2. Based on polymer composition (Mougin et al., 2003)
   - Homopolymer hydrogels: consist of a network made from a single type of monomer.
   - Copolymer hydrogels: formed from two or more types of monomers.
   - Multipolymer Interpenetrating Networks (IPNs): consist of two or more interpenetrating polymer networks that are physically or chemically crosslinked.
3. Based on physical structure (Agrawal et al., 2008; Divakaran et al., 2015; Hu et al., 2018)
   - Amorphous hydrogels: have a non-crystalline, randomly organized polymer structure.
   - Semi-crystalline hydrogels: contain both amorphous and crystalline regions.
   - Hydrogels with porous structures: have a well-defined porous structure, which can be macroporous, microporous, or nanoporous.
4. Based on response to stimuli (Chawla et al., 2014)

   Stimuli-responsive hydrogels: can change their properties (such as swelling behavior) in response to environmental stimuli like temperature, pH, light, magnetic fields, or electric fields.
   - Temperature-sensitive hydrogels: exhibit changes in swelling or solubility with temperature changes (e.g., poly(N-isopropylacrylamide) (PNIPAAm)).
   - pH-sensitive hydrogels: swell or shrink in response to pH changes (e.g., hydrogels made from poly(acrylic acid) (PAA) or chitosan).
   - Light-sensitive hydrogels: respond to light exposure.

- Magnetic and electric field-sensitive hydrogels: respond to magnetic or electric fields.

5. Based on charge (Li et al., 2021a,b)
   - Neutral hydrogels: have no charge and are generally made from non-ionic polymers (e.g., poly(N-vinyl-2-pyrrolidone) (PVP)).
   - Anionic hydrogels: contain negatively charged groups (e.g., poly(acrylic acid) (PAA)).
   - Cationic hydrogels: contain positively charged groups (e.g., chitosan).
   - Zwitterionic hydrogels: contain both positively and negatively charged groups, balancing each other out.

Hydrogels can also be classified based on their degradability, application, and functionality:

6. Based on degradability (Kharkar et al., 2013; Mahoney and Anseth, 2006; Zustiak and Leach, 2010)
   - Degradable hydrogels: designed to break down over time within the body or environment. They are particularly useful in biomedical applications such as temporary scaffolds for tissue engineering or as carriers for drug delivery that degrade after releasing their payload.
   - Non-degradable hydrogels: these hydrogels are designed to remain stable over long periods. They are used in applications where a long-lasting presence is required, such as in contact lenses, sustained drug release systems, and implantable devices.
7. Based on application
   - Biomedical hydrogels (Caló and Khutoryanskiy, 2015; Chai et al., 2017; Hoffman, 2002; Klouda and Mikos, 2008): used in various medical applications, including drug delivery systems, wound dressings, tissue engineering scaffolds, and contact lenses. These hydrogels are designed to be biocompatible and often biodegradable.
   - Agricultural hydrogels (Chen et al., 2018; Kabiri et al., 2011; Zohuriaan and Kabiri, 2008): used to retain soil moisture, reduce irrigation frequency, and improve soil structure. These hydrogels help in water conservation and are particularly useful in arid regions.
   - Environmental hydrogels (Dai et al., 2018; Thakur et al., 2018): employed in applications such as wastewater treatment and pollutant removal due to their ability to absorb and retain large quantities of water and contaminants.
   - Industrial hydrogels (Ahmad et al., 2024; Ahmed, 2015; Damodaran and Sifri, 2005; Saxena et al., 2020): used in products like diapers, sanitary pads, and other hygiene products due to their high absorbency. They are also used in sensors, actuators, and other smart materials.
8. Based on functionality (closely related to the stimuli responding hydrogels)
   - Bioactive hydrogels (Catoira et al., 2019; Malda et al., 2013; Zhu, 2010): incorporate bioactive molecules such as growth factors, enzymes, or drugs to enhance biological interactions and therapeutic effects. They are often used in tissue engineering and regenerative medicine.
   - Conductive hydrogels (Balint et al., 2014): contain conductive polymers or nanoparticles to enable electrical conductivity. These are used in biosensors, soft robotics, and wearable electronics.
   - Magnetic hydrogels (Courant et al., 2012): contain magnetic particles that allow them to respond to external magnetic fields. They are used in targeted drug delivery, magnetic resonance imaging (MRI) contrast agents, and remote-controlled actuators.

Finally, hydrogels can also be classified based on their size (Oh et al., 2008; Shewan and Stokes, 2013; Thorne et al., 2011; Ulański et al., 1998; Vinogradov, 2006):

- Bulk hydrogels: macroscopic hydrogels that are large enough to be handled and shaped manually. They are used in applications requiring a substantial volume of material, such as wound dressings, tissue engineering scaffolds, and contact lenses.
- Microgels: small particles typically in the micrometer size range. They have a high surface area to volume ratio, making them suitable for controlled release and targeted drug delivery systems.
- Nanogels: nanoscale hydrogels typically ranging from 1 to 100 nm. Their small size allows them to penetrate biological barriers and deliver drugs at the cellular or subcellular level, making them highly effective for targeted drug delivery, gene therapy, and diagnostic applications.

One should also notice that beside nanogels, polymeric nanoparticles (NP's) are also recognized in the literature as objects of the same size and quite often of similar chemical composition or synthetic procedure. The most significant difference is the swelling property. Nanogels, as swellable materials, could change its size depending on number of properties or interactions e.g., crosslink density, environmental interactions etc., while polymeric nanoparticles (mostly nanospheres or nanocapsular shaped) are matrix particles whose overall mass is generally solid (Khan et al., 2019).

In this review, we aim to continue our previous work on the presentation of macro, micro, and nanostructured hydrogels for different applications (de Lima et al., 2020), with special attention to polymeric nanogels and nanoparticles obtained using radiation-induced technologies.

Synthesis

A number of excellent review papers and book chapters have been published, presenting various methods for the synthesis of polymeric nanogels (Funke et al., 1998; Hamzah et al., 2017; Kabanov and Vinogradov, 2009; Mauri et al., 2021; Oh et al., 2008; Soni et al., 2016; Ulanski and Rosiak, 2004; Yin et al., 2020). Each of these developed techniques offers unique advantages aimed at optimizing the methods and providing advanced nanomaterials for potential applications. These methods can generally be

classified based on the nature of the process (physical vs. chemical), the type of substrate (monomers for methods involving simultaneous polymerization and crosslinking vs. polymers for crosslinking-based techniques), the type of network (random vs. regular), and the processes involved in synthesis (e.g., photolithography, micromolding, microfluidics, nanoreactors, particle replication in nonwetting templates).

Special attention should be given to the method based on non-classical initiation, namely radiation-induced intramolecular crosslinking (Ulański et al., 1998; Ulanski and Rosiak, 1999). Since it requires only aqueous polymer solution (without initiators, crosslinkers etc.) and source of ionizing radiation it has been proposed as an excellent alternative for synthesis of medicine relevant materials. Below more detailed description of this technique with its drawbacks and advantages will be presented.

Radiation-Induced Techniques

Possibility of nanogel synthesis with the use of ionizing radiation stars with idea of water radiolysis (Caër, 2011) i.e., chemical decomposition of water molecules due to exposure to ionizing radiation, such as gamma rays, X-rays, or high-energy particles. This process leads to the formation of various reactive species, including free radicals and molecular products. The primary step involved in the radiolysis of water is its ionization and excitation. When water is exposed to ionizing radiation, energy is absorbed by water molecules, resulting in ionization (1) (ejection of electrons) and excitation (2) (raising electrons to higher energy states):

$$H_2O \rightarrow H_2O^+ + e^- \tag{1}$$

$$H_2O \rightarrow H_2O^* \tag{2}$$

These are followed by formation of free radicals (3−4) when ionized water molecule can further dissociate into hydroxyl radicals (•OH) and hydrogen radicals (•H):

$$H_2O^+ \rightarrow OH^\bullet + H^+ \tag{3}$$

$$H_2O^* \rightarrow H^\bullet + OH^\bullet \tag{4}$$

Finally free radicals can recombine or react with each other (5−6) and with other water molecules to form stable molecular products such as hydrogen peroxide H_2O_2 and hydrogen gas H_2.

$$2OH^\bullet \rightarrow H_2O_2 \tag{5}$$

$$2H^\bullet \rightarrow H_2 \tag{6}$$

The overall set of reactions in the radiolysis of water is complex and can produce a variety of reactive oxygen species (ROS) and other intermediates. However, from the perspective of hydrogel synthesis (Rosiak and Ulański, 1999; Ulański et al., 1998; Ulanski and Rosiak, 1999), the formation of hydroxyl (•OH) and hydrogen radicals (•H) is the most important. These radicals are capable of abstracting hydrogen from the polymer molecule, leading to the formation of macroradicals. These macroradicals can shift along the chain or undergo single radical decay (degradation) or two radical recombination reactions, which can be either intermolecular or intramolecular, resulting in disproportionation and crosslinking.

The dominance of chain scission or recombination in an irradiated system depends on the chemical composition of the polymer (Osamu, 1958). This competition is influenced by several reasons. One significant factor is the presence of oxygen in the irradiated medium, which shifts the macroradical reaction mechanism towards chain scission. Another important issue, particularly relevant to nanogel synthesis, is the number of radicals present on a single macromolecule at the same time. Irradiating concentrated polymer solutions or delivering energy at a low dose rate promotes intermolecular recombination since, statistically, one or fewer radicals are present on each polymeric chain. This increases the molecular weight and size of the macromolecules, ultimately resulting in a macroscopic "wall-to-wall" gel.

Conversely, high dose rate irradiation (e.g., electron beam) of solutions below their critical hydrodynamic concentration leads to a much higher number of radicals per macromolecule. These conditions are crucial for the synthesis of nanogels, as they result in the stability of molecular weight and a pronounced decrease in size due to increased coil density.

Temperature and pH are other parameters that can influence the formation of crosslinks in nanogels (An, 2010). At elevated temperatures, the polymer chain "collapses" as hydrogen bonding between the polymer and water molecules is disrupted. The same happens for polyelectrolytes: reduction of the charge density to a minimum while avoidance of aggregation by hydrogen bonding leads to the shrinking of macromolecules to the desired level. The collapsed chains adopt a stiffer conformation and produce smaller nanogels upon irradiation. This occurs due to a decrease in the distance between carbon-centered radicals on the same chain, which favors intramolecular crosslinking. However, intermolecular reaction also occurs. Despite the closer proximity of radicals on the same chain, higher temperatures increase the diffusive motion of chains, allowing more contacts and opportunities for intermolecular crosslinks to form. Under these conditions, intramolecular crosslinking is dominant, as evidenced by the smaller dimensions of the final nanogels. Nonetheless, the increased molecular weights of these gels suggest some intermolecular crosslinking is present. The decrease in pervaded volume at higher temperatures also implies less "empty" space (areas occupied

only by solvent molecules). Larger pervaded volumes increase the likelihood of hydroxyl radicals decaying before interacting with the polymer. When this happens, hydroxyl radicals often react with each other to produce hydrogen peroxide, reducing the number of radicals available to abstract hydrogens from the polymeric backbones (Ashfaq et al., 2021).

Irradiation of polymers in dilute aqueous solutions results in the formation of nanohydrogels, while radiation-induced polymerization and crosslinking (Chapiro, 2004), using a monomer or a mixture of monomers as substrates, serve as efficient methods for synthesizing nanoparticles. Various preparation techniques for producing monodispersed beads have been developed, including suspension polymerization, emulsion polymerization, and dispersion polymerization (Güven, 2016; Ikeda et al., 2008; Pasanphan et al., 2015; Ye et al., 2003).

Radiation polymerization is generally considered one of the most convenient methods due to its temperature-independent initiation (via gamma or electron beam) and the high yield characteristic of radiation chemistry. Additionally, the radiation process can easily produce monodisperse polymers without contamination from chemical initiators.

Nanogels and Nanoparticles

Nanogels Based on Synthetic Polymers

Poly(vinyl alcohol)

In early 1960s Sakurada and Ikada have found that the critical concentration for gel-formation corresponds to the polymer concentration where the polymer spheres just begin to be in contact with each other (Sakurada and Ikada, 1964, 1966). Gamma irradiation of initially transparent poly(vinyl alcohol) solutions at concentrations only 0.01% lower than the critical one resulted in a turbidity of solution irrespectively of the degree of polymerization of the samples used, indicating the formation of intramolecular crosslinking. Based on results obtained together with Hosono and Tamamura (Sakurada et al., 1964) sizes of obtained microgels have been calculated. Later on Wang et al. (1997) continued to analyze the gelation process of aqueous oxygen-free solutions containing poly(vinyl alcohol) by γ-ray irradiation as a function of polymer concentration. Mechanism of microgel formation has been proposed: initially, small and branched polymers are obtained through intermolecular crosslinking, independent of polymer concentration. When irradiation continues beyond the gelation dose at concentrations higher than a critical threshold, these branched polymers further crosslink with each other, forming a macroscopic gel. Conversely, at concentrations below this critical overlapping concentration, the small branched polymers combine to form a larger branched polymer. Subsequently, intramolecular crosslinking within this larger branched polymer leads to the formation of microgel particles. This process is accompanied by phase separation, resulting in solution turbidity, as previously observed by Sakurada and Ikada.

In their pioneering work, Ulański et al. (1998) on the synthesis of PVAl-based nanogels, proposed not only the irradiation of a diluted polymer solution but also the use of an electron beam instead of gamma irradiation. This method resulted in a significantly higher initial average number of radicals generated on each chain, promoting their intramolecular recombination. Analysis of the irradiation products showed a marked decrease in intrinsic viscosity with an absorbed dose, despite an increase in molecular weight. Similar effects (a significant decrease in viscosity and radius of gyration, coupled with a slight increase in molecular weight) were also described by Brasch and Burchard (1996) as a result of chemical inter- and intramolecular crosslinking of PVAl with glutaraldehyde. In addition to product analysis, kinetic experiments demonstrated that a dispersive kinetics model with a time-dependent rate constant (Plonka, 1994) can describe intramolecular processes, as proposed for poly(ethylene oxide) (Ulański et al., 1995).

Poly(N-vinyl-2-pyrrolidone), PVP

Building on the initial study of nanogel formation in PVAl, Ulanski and Rosiak extended their research to poly(N-vinyl-2-pyrrolidone) (PVP) (Ulanski and Rosiak, 1999). Static light scattering measurements revealed a significant decrease in the radius of gyration of EB-irradiated, oxygen-free PVP solution, while the weight-average molecular weight remained almost constant. Kadlubowski's review on the synthesis of PVP-based nanogels (Kadlubowski, 2014) highlighted the impact of polymer concentration on the competition between inter- and intramolecular recombination. At a 10 mM concentration, radicals formed on macromolecules primarily recombined to form intramolecular bonds. However, at nearly twice this concentration (still below the critical value), a decrease in macromolecule size was observed alongside a significant increase in weight-average molecular weight due to higher intermolecular crosslinking yield. Regardless of the polymer concentration examined, the products exhibited higher coil densities than the initial polymers, as determined by the ratio of radius of gyration to hydrodynamic radius and confirmed by Atomic Force Microscopy.

Continuing Rosiak's work, Kadlubowski et al. (2012) proposed a variation of the preparative pulse radiolysis technique. This method allows for the synthesis of internally crosslinked macromolecules with independently chosen molecular weight and dimensions, such as nanogels with a specific coil density. The proposed two-stage process involves sequential gamma- and electron-beam irradiation. In the first stage, a PVP solution at a concentration higher than the critical one was irradiated with gamma rays to induce intermolecular crosslinking, forming branched structures and increasing the molecular weight to the desired value. In the second stage, after diluting the solution to a concentration below the coil overlapping concentration, it was subjected to electron beam irradiation. This induced intramolecular crosslinking. Significant reduction of the polymeric coil dimensions was accompanied by a nearly constant molecular weight.

Interesting approaches for the radiation-induced synthesis of PVP-based nanogels have been proposed by An (2010), An et al. (2011) and Sütekin et al. (2023). Previous research has confirmed that one of the crucial parameters involved in intramolecular

recombination is a coil contraction of precursor coils. For aqueous solutions of poly(N-vinyl-2-pyrrolidone) it can be achieved in two ways:

(a) by addition of a cosolvent, namely acetone breaking tridimensional structure of water, hence disrupting the H-bonds bridging polymer coils and causing separation and shrinkage in their sizes. Irradiation of these solutions has led to the formation of intramolecular crosslinks within the coils resulting with nanogels with sizes smaller than precursor coils, while in the absence of a cosolvent more pronounced intermolecular recombination proceeds. The same procedure has been also used for synthesis of nanogels based on poly(N-isopropylacrylamide) (Sütekın et al., 2023).
(b) by inducing coil collapse through temperature. Although PVP is not a thermosensitive polymer, at temperatures above 55 °C, the coils start to shrink due to the loss of water of hydration, eventually collapsing into tight coils. When thermally collapsed PVP macromolecules are irradiated at relatively high temperatures, intramolecular crosslinks form, leading to the creation of nano- and microgels in the size range of 30−200 nm.

In addition to the works utilizing electron beams as the source of ionizing radiation, gamma rays have also been employed for the synthesis of PVP-based nanogels (Balogh et al., 2022; de Lima et al., 2020; Duygu Sütekin and Güven, 2019; Güven, 2021; Sütekın et al., 2023). By varying the initial polymer molecular weight, concentration, saturation, dose rate, and total absorbed dose, nanogels with different molecular weights, sizes, and consequently, crosslink densities have been obtained. This research has once again demonstrated that ionizing radiation, whether through electron beam or gamma radiation, is a highly convenient method for synthesizing PVP nanogels in a single step, without the need for initiators, crosslinking agents, or high temperatures.

Poly(acrylic acid), PAA

While PVAl and PVP are polymers that primarily undergo crosslinking, poly(acrylic acid), one of the simplest polyelectrolytes, exemplifies materials that experience both recombination and chain scission when exposed to ionizing radiation. Both of these processes were analyzed in detail by Sakurada and Ikada (1963a,b). Similarly to the observations for poly(vinyl alcohol) below critical concentration decrease in viscosity and turbidity of gamma irradiated solutions has been attributed to formation of intramolecular crosslinks i.e., microgel formation. The key factor was presence of the salt in irradiated solution responsible for expansion and segmental repulsion.

Ulanski et al. analyzed mechanism and kinetics of PAA derived macroradical reactions in oxygenated and deoxygenated aqueous solutions (Ulanski et al., 1995, 1996a,b) pointing out experimental conditions promoting inter- and intramolecular crosslinking. Finally experimental data on radiation-induced synthesis of poly(acrylic acid)-based nanogels has been presented by Ulanski et al. (2002). Typical feature of intramolecular crosslinking, i.e., a strong decrease in solution viscosity (coil dimensions) without an accompanying decrease in molecular weight with only minor participation of side processes like chain scission and intermolecular crosslinking has been presented. Kadlubowski's et al. work is a development and continuation of this research. It has been shown that adjusting the polymer concentration and radiation dose, molecular weight and dimensions of nanogels can be controlled (Kadlubowski et al., 2003). The products of preparative pulse radiolysis have been analyzed by static light scattering, viscometry, and Atomic Force Microscopy, while the anticipated previously for PVAl nonclassical kinetics of intramolecular recombination has been followed by time-resolved spectroscopy. It has been proved that synthesized nanogels are much more resistant to free-radical-induced degradation than the parent linear chains. Other works devoted to radiation-induced synthesis of PAA-based nanogels discuss in more detail the mechanism of the cross-linking process and the influence of parameters such as the molecular weight of the starting polymer (Matusiak et al., 2018, 2020).

One step process to synthesize poly(acrylic acid) nanogel containing silver nanoparticles involving electron beam irradiation has been proposed by Choi et al. (2013). Synthetic procedure consisted dissolution of silver nitrate in water followed by solubilization of the polymer and mixing with hexane. In this conditions simultaneous radiation-induced intramolecular crosslinking and $AgNO_3$ reduction proceeded. With the doses up to 150 kGy PAA nanogels with the sizes below 100 nm have been obtained. Synthesized nanogels exhibited good antibacterial activity against both Gram-negative and Gram-positive bacteria as well as good effect in the results of the *in vivo* wound healing.

Poly(vinyl methyl ether), PVME

Thermosensitive materials (Jeong et al., 2002; Klouda and Mikos, 2008; Pelton, 2000; Russo and Villa, 2019; Senff and Richtering, 1999) are one of the most intensive examined, synthesized or modified, including radiation processing, materials. Number of polymers are utilized for this purpose with poly(N-isopropylacrylamide) (Rzaev et al., 2007; Zhang et al., 2004) as most intensively studied one. However poly(vinyl methyl ether) because of its lower critical solution temperature close to 37 °C also has gained substantial interest (Arndt et al., 2001; Kishi et al., 1993; Schmidt et al., 2003).

Possibility of intermolecular crosslinking and gel formation in poly(vinyl methyl ether) aqueous solution has been successfully presented by Sakurada and Ikada (1962). Further detailed study on radiation crosslinking and scission of PVME in aqueous solution has been presented by Janik et al. (Janik et al., 1999; Janik and Rosiak, 2002). Idea of synthesis of micro- and nanogels based on poly(vinyl methyl ether) has been proposed by Schmidt et al. (2005). A diluted aqueous polymer solution has been irradiated in preparative pulse radiolysis regime at temperatures, below the lower critical solution temperature. With increasing radiation dose the average molecular weight increased, while the dimensions (both radius of gyration and hydrodynamic radius) decreased, up to 10 nm, as typical for nanogel synthesis. ρ-parameter (ratio of radius of gyration to hydrodynamic radii, Rg/Rh) calculated for synthesized nanogels has been found in the range of $\rho = 0.5-0.6$ that corresponds to freely draining globular structures, as

proposed by Burchard (1999). It has been also found that the phase-transition temperature of PVME nanogels, as determined by cloud point measurements, decreased around 20% because of the formation of intermolecular crosslinks evidenced by increase in molecular weights. Similar performance for a pre-irradiated PVME (γ-irradiation) with higher molecular weight due to intermolecular crosslinks was observed.

Multicomponent Nanogels: Interpolymer Complexes, Grafted Structures

Secondary interactions between polymers in aqueous solution can lead to interpolymer complex (IPC) (Dou et al., 2003; Ivopoulos et al., 2006; Tsuchida and Abe, 1982) formation through hydrogen bonding, Coulombic and dispersion forces, or hydrophobic interactions (Bekturov and Bimendina, 1981; Jiang et al., 1999). Hydrogen-bonding complexes, such as those between poly(ethylene oxide) (PEO) or poly(N-vinyl-2-pyrrolidone) (PVP) and weak polyacids like poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA), have been extensively studied for applications in wastewater treatment and biomaterials (Caló and Khutoryanskiy, 2015; Dautzenberg et al., 2001; Khutoryanskiy, 2007; Matsudo et al., 2003; Mende et al., 2002). These complexes depend on molecular weight, concentration, degree of dissociation, and solvent character (Osada, 1979). Studies show that PVP and oligoacids form sphere-like structures, transitioning to core-shell types with higher molecular weights, and aggregation kinetics are influenced by pH and preparation methods.

Henke et al. (2011) conducted detailed studies on the formation of PVP−PAA hydrogen-bonded complexes and their aggregates in dilute aqueous solutions. They found that PVP and oligoacrylic acids formed interpolymer complexes with a sphere-like structure and uniform segmental density. As the polyacid molecular weight increased, the IPCs transitioned to a core-shell structure. The aggregation of the PVP-PAA system produced clusters with fractal properties and exhibited diffusion- and reaction-limited cluster aggregation kinetics. The aggregation mechanism was strongly influenced by solution pH and preparation methods, which significantly affected the resulting particle structures.

A comprehensive analysis of IPC formation provided a strong foundation for synthesizing polymeric nanogels from interpolymer complexes. Henke et al. (2005) developed a method to produce nanogels from poly(N-vinyl-2-pyrrolidone)−poly(acrylic acid) IPCs using preparative pulse radiolysis, focusing on intra-complex radical recombination. They observed that viscosity and radius of gyration decreased with increasing absorbed dose, indicating intramolecular crosslinking. However, some intermolecular cross-linking also occurred, as evidenced by changes in apparent weight-average molecular weight.

Abd El-Rehim et al. (2013a,b), Swilem et al. (2020) have also described the synthesis of nanogels from poly(N-vinyl-2-pyrrolidone)−poly(acrylic acid) interpolymer complexes however using gamma radiation-induced template polymerization. They monitored changes in the transparency of the PVP/AA solution during irradiation, determining the minimum dose required for nanogel synthesis. This indicated that PAA of suitable length was polymerized to form complexes with PVP. Further irradiation facilitated chemical crosslinking among nanoparticle chains. The low polydispersity index of the irradiated PVP-*g*-PAA demonstrated that the resulting nanogels had a monomodal, narrow size distribution.

Gamma irradiation has been also used by Guven and his group for synthesis of nanogels based on poly(N-vinyl-2-pyrrolidone) and poly(acrylic acid) (Ghaffarlou et al., 2018; Sütekin et al., 2021). It has been found that the sizes of the nanogels were smaller than the size of the precursor IPC coil sizes due to the formation of intramolecular crosslinks.

Multifunctional PVP-based nanogel synthesis has been proposed by Dispenza and colleagues (Adamo et al., 2016; Dispenza et al., 2012; Grimaldi et al., 2014). Acrylic acid has been added to a polymer solution, at concentration low enough to avoid significant electric charge repulsion between the polymer and monomer, and EB-irradiated. At this condition the polymer radical can add to the monomer's double bond at a nearly diffusion-controlled rate. This results in the monomer grafting onto the polymer chain. Introducing charged functional groups into the network further increases the electrical charge on the polymer chains, causing repulsion or attraction between macroradicals. This interaction influenced crosslinking, leading to either smaller or larger nanogel particles. At higher monomer concentrations, if there is no charge repulsion among the monomer molecules, homopolymerization competed with grafting. In this case, the polymer initially presented in the system served as a template for the polymerization of the second polymeric component, as proposed by Abd El-Rehim et al. (2013a,b).

Poly(ethylene oxide)-poly(acrylic acid) nanogels were synthesized from their interpolymer complexes through radiation-induced intramolecular crosslinking (Rattanawongwiboon et al., 2018). Before irradiation, acetone has been used to reduce the size of the complexes, as a non-solvent for both polymers. The permanent covalent bonding in IPC nanogels ensured stability in size and surface charge across varying temperatures and pH values. The dual functionality provided by PEO and PAA is advantageous for biomedical applications, as it enhances compatibility and effectiveness in the human body.

An interesting idea of poly(acrylic acid) and pullulan complexes and its radiation-induced stabilization has been presented by Ghaffarlou et al. (2023). Nanogels with a fixed spherical shape were obtained by irradiating PAA-pullulan self-assemblies with gamma radiation in an aqueous solution and later on modified with folic acid-conjugated Bovine Serum Albumine to formulate a drug carrier system with folate receptors.

Nanogels and Nanoparticles Based on Natural Polymers

As mentioned previously polymers under action of ionizing radiation undergoes, both in solid state and in solution, number of different processes with recombination (inter- and intramolecular) and chain scission as the one determining final product properties. Depending on the chemical structure of the polymer and experimental properties one can influence the competition between degradation and recombination (Osamu, 1958). In case of polymers of the natural origin (e.g., polysaccharides, peptides) chains scission is mostly

anticipated during irradiation. However one can find examples of natural, or natural but modified, polymers used for radiation-induced nanogel and nanoparticle synthesis (chemical methods are much more versatile in this case). Below examples of nanogels and nanoparticles from this group of polymers obtained with radiation-induced techniques will be presented.

Albumin

Natural polymers, such as albumin, are frequently used in the synthesis of nanogels and nanoparticles due to their biocompatibility and lack of toxicity. This globular protein, a natural polyelectrolyte, dissolves in water and forms gels and emulsions when heated. Due to its medical relevance, abundant availability, low cost, ease of purification, unique ligand-binding properties, and wide acceptance in the pharmaceutical industry, albumin is widely utilized in drug delivery (Radeva et al., 2024; Wang et al., 2016).

Albumin is the most abundant plasma protein, totaling 55% of human serum proteins. A molecule formed by 584 amino acid chains results in a polypeptide with a molecular weight of around 66.4 kDa with 5 nm (LeVine, 2016; Queiroz et al., 2016). The main albumin functions are to regulate blood pH, maintain circulating plasma volume, and modulate the distribution of fluids between body compartments, responsible for 80% of oncotic pressure. Furthermore, albumin is involved in transporting endogenous and exogenous compounds such as fat-soluble molecules of fatty acids, hormones, metal ions, peptides, proteins, and drugs, increasing its bioavailability stability in biological fluids (Fanali et al., 2012; Ferreira et al., 2024).

As a raw material for the manufacture of nanocarriers, albumin is stable under physiological conditions (its biological half-life is about three weeks), in solvent presence, and at heterogeneous pHs. Furthermore, due to its natural properties as an endogenous and exogenous molecule carrier, it can be combined with therapeutic, diagnostic, and theranostics agents to improve pharmacokinetics (Parodi et al., 2019).

Nearly two mechanisms are responsible for the successful albumin nanoparticles use in biological systems for cancer diagnosis and therapy: active transport mediated by GP60 receptors and caveolin-1 (transcytosis) also the functional binding tumor albumin-drug complex through the SPARC protein (secreted protein acidic and rich in cysteine) (Ergul et al., 2014).

The GP60 receptor is a protein present in vascular endothelium cells that increase membrane permeability for the absorption of circulating proteins (Larsen et al., 2016). The albumin-receptor binding activates the caveolin-1 membrane protein, which induces small vesicle formation on the cell surface. The Caveolae migrate through the cytoplasm, releasing their content in the cellular interstitium, which is the mechanism that facilitates the transcytosis of albumin, protecting it from proteolysis (Cohen et al., 2004; Parat and Riggins, 2012).

On the other hand, SPARC proteins are compounds secreted within the extracellular microenvironment and present regulatory functions which affect tumor proliferation and invasion, and angiogenesis (Chong et al., 2012). They are described as associated molecules with extracellular matrix communication and as receptors for albumin nanoparticles. SPARC is overexpressed in different types of cancer of the breast, prostate, esophagus, colorectal, liver, and lung. The SPARC's ability to inhibit or promote tumors depends on cell type, tumor stage, and interaction with different components present in the cell microenvironment (Arnold and Brekken, 2009). Both internalization mechanisms confer great potential for useful applications of albumin nanoparticles in oncology.

Several research groups have focused on synthesizing nanosystems by crosslinking albumin through ionizing radiation (gamma rays and electron beams). Reports indicate the formation of covalent bityrosine bonds while maintaining the bioactivity of albumin and nanoparticle growth. Additionally, it is possible to modulate the size of the nanoparticles formed by adjusting reaction conditions such as albumin concentration, radiation dose, pH, and buffer type (Achilli et al., 2015; Ferreira et al., 2024; Queiroz et al., 2016; Radomska and Wolszczak, 2022; Varca et al., 2016a; Wasko et al., 2024).

Collagen

Collagen, the most abundant protein in the human body, is a fibrous macromolecule essential for the structure and function of various connective tissues, including skin, bones, cartilage, and tendons. Its significance extends beyond humans, as it is also found in various animals and plays vital roles in nature (Siadat and Ruberti, 2023). Collagen's unique triple helix structure, composed of three polypeptide chains rich in amino acids like glycine, proline, and hydroxyproline, gives it high tensile strength, flexibility, and the ability to form fibrils and extracellular networks (Sorushanova et al., 2019).

Collagen's biocompatibility and low risk of rejection in implants make it an ideal biomaterial for numerous medical and biotechnological applications. Its biodegradability is advantageous for tissue engineering and regenerative medicine, as it allows the biomaterial to be replaced by new tissue during healing (Wang et al., 2023). Additionally, collagen exhibits bioactive properties, meaning it can interact with cells and mediate various biological processes, including cell adhesion, proliferation, migration, and differentiation. This bioactivity makes collagen a promising material for developing scaffolds and other biomaterials for tissue engineering (Zheng et al., 2023).

Widely used in various fields of medicine and tissue engineering, collagen's unique properties have led to its application in creating 3D scaffolds that support cell growth and differentiation, enabling tissue regeneration or the development of new tissues for transplantation (Park et al., 2023). It can coat medical implants, such as bone and joint prostheses, reducing the risk of rejection and infection. Collagen is also used in wound dressings to accelerate healing by promoting cell proliferation and extracellular matrix deposition (Peng et al., 2022; Sharma et al., 2022). Moreover, collagen is a common ingredient in anti-aging creams and lotions, as it can improve skin hydration, elasticity, and firmness (Avila Rodríguez et al., 2018; Sionkowska et al., 2020).

In nanotechnology, collagen has been used to develop enhanced nanoparticles, nanogels, nanofibers, and scaffolds. These collagen-based nanomaterials offer advantages such as increased specific surface area, improved biodistribution, and controlled drug release (Lo and Fauzi, 2021). Techniques like electrospinning to create collagen nanofibers, nanoemulsion, electrospray deposition, and milling are used to produce these materials. Nano-collagen can be applied in various medical areas, including bio-

scaffolds or fillers to enhance wound healing, and regeneration of skin, bone, vascular grafts, nervous tissue, and articular cartilage. It also assists in drug administration and cosmetic applications (Lo and Fauzi, 2021; Makkithaya et al., 2022).

Ionizing radiation processing, such as electron beams, gamma rays, or even UV light, can be used to modify the properties of collagen and make it more suitable for various applications. Ionizing radiation can induce physical crosslinking by creating cross-links between collagen chains, with effects that vary according to radiation dosage, temperature, hydration conditions, and electron beam intensity, thereby increasing its mechanical strength, thermal stability, and enzymatic resistance (Gu et al., 2019).

Another effect can occur when collagen is irradiated: peptide bonds can be destroyed due to amino acid deformation, and hydrophilicity is improved by the formation of hydrogen bonds. Gamma radiation-induced collagen cross-linking has been reported to increase the biocompatibility of Ti implants and bone adhesion in beagle mandible models (Cho et al., 2021).

Gelatin

Gelatin, a natural biopolymer derived from collagen, transcends its rich history of applications to become a promising material in the most advanced medical technologies. Its biocompatibility, biodegradability, and versatility make it ideal for developing innovative systems in various areas, including drug delivery, tissue engineering, and 3D printing of human tissues (Narayan et al., 2023). However, gelatin presents a challenge: its instability at physiological temperatures due to the reversible sol-gel transition between 25 and 40 °C (Terao et al., 2003). To overcome this limitation, radiation crosslinking emerges as a powerful tool, enhancing gelatin's properties and enabling precise control of characteristics such as viscoelasticity, swelling, degradation, and stability, significantly expanding its potential applications (Wisotzki et al., 2017).

The literature describes the formation of gelatin nanogels through radiation crosslinking. An important aspect of this process is the increased light scattering in irradiated gelatin solutions, which evidences the growth of high-molecular-weight particles (10 nm) during irradiation. This phenomenon is attributed to the disintegration of original aggregates by gamma rays, which previously hindered light scattering (Furusawa et al., 2004). Similarly, gamma-ray crosslinked gelatin microspheres (2.4−3.6 μm) are described as potential drug delivery systems with adjustable peptide sorption properties and enzymatic biodegradability (Terao et al., 2004). In an innovative study, Matsuura et al. explored the application of radiation-crosslinked gelatin hydrogel to coat arterial grafts in revascularization surgeries, successfully mimicking the native extracellular matrix of blood vessels (Matsuura et al., 2021).

While radiation-crosslinked gelatin technologies are still under development, the results so far are promising and open a range of possibilities. Encouraging results indicate that this innovative material may be the key to developing new biomaterials with diverse applications in the healthcare field.

Papain

Recent scientific developments in papain nanoparticles and nanogels have advanced significantly, reflecting the growing interest and potential of this enzyme in various biomedical applications. Papain, a protease with a molecular weight of 23.4 kDa extracted from the latex of *Carica papaya* green fruit, is widely recognized for its proteolytic, anti-inflammatory, and antioxidant properties. Belonging to the cysteine proteases family (classified as family C1), papain plays a crucial role in several biological processes across different living organisms. It is notable for its specificity regarding proteins and low molecular weight substrates, cleaving peptide bonds at arginine, lysine, and phenylalanine residues (basic amino acids) (Amri and Mamboya, 2012).

Papain's primary applications span across various industries. In the pharmaceutical sector, it is used in detergent formulations, leather treatment, meat tenderizers, and beer clarification (Azarkan et al., 2003). Medically, papain is employed to treat edema, allergic sinusitis, leaky gut syndrome, gluten intolerance, hypochlorhydria, and other digestive disorders (Zhang et al., 2006). Additionally, it is used for cavity removal. Its debriding properties stimulate wound healing, leading to its use in skin ulceration treatments for conditions such as diabetic and chemotherapy-induced injuries, leprosy, and Fournier's syndrome (Leite et al., 2012). Papain also possesses valuable pharmacological properties for medical applications, including antibacterial, antifungal, and antioxidant properties, along with anticancer, antiproliferative, and antimetastatic activities. These properties have been validated through experimental studies *in vitro*, *in vivo*, and clinical studies in patients with breast, colorectal, and plasmacytoma cancers (Beuth, 2008; Budama-Kilinc et al., 2018). In the studies on lung carcinoma and melanoma models, papain has been proven effective in inhibiting primary tumor growth and systemic dissemination, resulting in increased survival rates in treated animals (Wald et al., 2001). Additional studies in various cell lines have corroborated that papain can modulate cell signaling pathways in the immune system, apoptosis, and cancer development (Chandran and Nachimuthu, 2018).

A novel approach to synthesizing papain-based nanomaterials involves ionizing radiation using gamma rays and electron beams. This method offers an alternative pathway for protein crosslinking, producing final products that can serve as drug carrier systems and bioactive nanoparticles. Ionizing radiation allows precise control over the size and properties of the resulting nanomaterials, making it a promising technique in biomedical applications (Fazolin et al., 2020; Varca et al., 2016b).

Papain nanoparticles also represent an exciting application for intravesical chemotherapy administration in bladder cancer. Hydrogels prepared with native papain or papain nanoparticles have been explored to enhance permeability through bladder tissue. These gels demonstrated mucoadhesive properties, and the papain enzyme exhibited mucolytic action, resulting in increased resistance to urothelial washout and enhanced permeability of chemotherapeutic agents. This innovative approach highlights papain-based nanomaterials' potential in improving the efficacy of bladder cancer treatments (de Lima et al., 2023).

Chitosan

Another highly promising material for the synthesis of nanogels and nanoparticles is chitosan, a natural biopolymer obtained by the alkaline deacetylation of chitin, which is found primarily in crustaceans, insects, and microorganisms. It is a linear polysaccharide of cationic nature, composed of β-(1−4)-2-acetamido-D-glucose and β-(1−4)-2-amino-D-glucose units (Harugade et al., 2023). Chitosan's properties, notably its biocompatibility, biodegradability, and mucoadhesive properties, make it ideal for various biomedical applications. These characteristics facilitate cell adhesion, proliferation, and differentiation while providing antimicrobial properties. However, chitosan's solubility in water is limited, as it only dissolves in acidic environments, which restricts its applications (Harugade et al., 2023; Kou et al., 2022).

With its versatility and unique properties, nanoparticulated chitosan has emerged as a material of significant interest in the medical field. It gains enhanced properties when transformed into nanoparticles or nanogels, opening a wide range of innovative applications. These include drug delivery, where it can encapsulate various therapeutic molecules, protect them from degradation, and enable controlled release. Its mucoadhesive properties also make it suitable for non-invasive administration routes, such as nasal and oral, thereby improving drug bioavailability (Ali and Ahmed, 2018; Parhi, 2020). In gene therapies, it serves as a non-viral vector for delivering nucleic acids, protecting the genetic material from degradation, and facilitating internalization (Dong et al., 2024; Santos-Carballal et al., 2018). In regenerative medicine, its antimicrobial properties and ability to promote tissue regeneration promote wound healing (Biswal et al., 2023; Liu et al., 2021). In tissue engineering, it is used in scaffolds that mimic the extracellular matrix, providing an ideal environment for the growth of new tissues and in antimicrobial applications (Mohebbi et al., 2019; Rodríguez-Vázquez et al., 2015; Sahariah and Másson, 2017).

Due to its cationic nature, chitosan can form physical hydrogels through electrostatic crosslinking, resulting in nanometric structures depending on the concentration. Additionally, the functional groups in chitosan facilitate its modification to form covalent networks when reacted with crosslinking agents. The chemical crosslinking of chitosan chains allows the free diffusion of water and bioactive materials and enhances the material's mechanical properties. This method is based on the use of crosslinking agents, which covalently link the molecules and promote nanoparticle formation. Aldehydes, such as glutaraldehyde and epoxides, are among the most frequently used crosslinking agents for modifying chitosan. However, if not properly removed, residues of crosslinking agents can induce undesirable reactions and toxicity to biological systems (Muñana-González et al., 2023).

Recent studies have utilized ionizing radiation-induced crosslinking as an alternative method, where it is possible to control the size of nanoparticles with preserved bioactivity and structural characteristics for effective biomedical applications. This method offers advantages over conventional ones, as it is not restricted by the absence of monomers in the process. Simultaneously with the formation of nanoparticles, the interior of the reaction vial is sterilized. It is important to note that this method generally involves both intra- and intermolecular crosslinking (Radwan and Ali, 2021).

Piroonpan et al. (2024) investigated the formation of chitosan-PAA IPC-based nanoparticles through a process involving a chitosan macromolecular template and free radical graft copolymerization, initiated by electron beam irradiation in a homogenous aqueous solution. They examined how the length of the chitosan template chain, the concentrations of acrylic acid, and the absorbed dose impacted the degree of graft copolymerization, as well as the morphologies, size, and size distribution of the nanoparticles. Additionally, they analyzed the chemical structures, packing structures, weight loss, particle morphologies, and particle size and distribution of the chitosan-PAA IPC nanoparticles. The study also explored the effect of pH on the kinetic water absorption, swelling, nitrogen entrapment, and controlled release properties of the chitosan-PAA IPC nanoparticles.

Silk

Bioactive molecules fractionated from natural feedstock e.g., silk fibroin (SF) are attracting great interest as antioxidant in number of applications including cosmetic and biomedical industry. Raw silk fibers are composed of a fibroin core polymer (75%−83%) and of sericin, a glue-like protein (17%−25%) forming a coating around twisted fibrils. SF is composed of three distinct polymer fractions differing by their composition and average molecular weight.

Wongkrongsak et al. (2022) examined different aspects of the radiation-induced modification of silk fibroin in an aqueous solution in order to fabricate micro- and nanogels with improved antioxidant capabilities. Aqueous silk fibroin solutions exposed to electron beam irradiation with doses higher than 20 kGy exposed the presence of nanogels with an average size less than 100 nm. Influence of ionizing radiation was not only limited to the size of the product but also to its properties including increased antioxidant activity and promotion of keratinocyte cells growth.

Biomedical Applications

Drug Delivery and Gene Delivery Systems

Drug delivery systems have been explored since 1980s as a more efficient approach for different kinds of treatments, ensuring specifically targeting and release rate of the drug (Sung and Kim, 2020). Systems based on polymeric nanoparticles provide several advantages such as the ability to encapsulate a wide range of therapeutic agents, including small molecules, proteins, peptides, and nucleic acids, providing protection to the active substance from degradation and, thereby, enhancing its stability and bioavailability. Additionally, the controlled release of the drug over a longer period is a strategy that enhances therapeutic efficacy, reduce dosing frequency, and decrease side effects.

The use of biodegradable and bioabsorbable polymers provides a safe platform for delivering treatment without impairment of the organism (Sung and Kim, 2020). These materials are ideal for applications in which a temporary presence of the implant is needed. Among many others, some of the polymers frequently used for this purpose are: biodegradable polycarbonates, polycaprolactone, poly(vinyl alcohol), poly(glycolic acid), hyaluronic acids, gelatin, natural polysaccharides such as chitosan, sodium alginate, and gellan gum (Sung and Kim, 2020).

Concerning cancer treatment, selectivity towards tumor cells is still one of the main challenges to upgrade current therapies. Nanoparticle based drug delivery systems can improve therapeutic efficacy by modulation of the pharmacokinetic and pharmacodynamic profiles of the nanocarrier. Passive targeting happens because of physical interactions between the nanoparticles and the microenvironment, such as the "enhanced permeability and retention" (EPR) effect. In this case, the abnormalities of the tumor vasculature characterized by large fenestrations with diameter between 100 and 800 nm facilitates the accumulation of the nanoparticles in tumor rather than in health tissues. Additionally, the inefficient drainage of the tumor tissue due to the absence or ineffectiveness of lymphatic vessels contributes to an enhanced retention of the nanoparticles. On the other hand, nanoparticles can be conjugated with tissue-specific ligands (antibodies, peptides, macromolecules, etc.) on the particle surface and specific ligand-receptor interactions will provide an accumulation of the nanoparticles in the site of interest by active targeting (Gagliardi et al., 2021). For prostate cancer, one strategy that has been studied was the conjugation of doxorubicin and A10 RNA aptamer that is capable to bind to the prostate-specific membrane antigen (PSMA) (Pack et al., 2005; Sung and Kim, 2020). Lung cancer is another condition that has cough attention of innovative engineering on polymeric nano-carriers with diagnosis, screening, imaging and treatment of primary and metastatic tumors (Pandey et al., 2019; Sung and Kim, 2020).

Several stimuli-responsive polymer-drug conjugates have been studied and designed in the last 20 years as a strategy for targeting tumor cells. pH and redox-responsive polymeric nanoparticles are two of the most used strategies. As cancer cells present an acid environment (pH 6.5−7.2), some systems are composed by covalent attachment of the drug to the polymeric nanoparticle with an acid-labile bond, allowing the release of the medicine in the target. Also, a larger redox potential difference between the intra- and extracellular microenvironment of cancer cells is observed due to the increased concentration of glutathione in the cytosol and subcellular organelles. This increased redox potential can also be used as a trigger to release the drug from a smart DDS containing a redox-sensitive functional group in the polymeric nanocarrier (Avramović et al., 2020). **Fig. 1** illustrates the diverse strategies to deliver treatment to tumors using polymeric nanoparticle systems.

Nanogels are also great platforms for drug delivery as they have the ability to shrink or swell according to external environment, allowing controlled release. In tumor microenvironment, for example, pH-sensitive nanogels can effectively deliver drugs to the tumor, improving therapeutic efficiency. Several polymers may be used to prepare pH-sensitive nanogels: natural ones such as hyaluronic acid, chitosan, dextran, alginate, carboxymethyl cellulose, and synthetic ones as poly(N,*N*-dimethylaminoethyl methacrylate), polypeptide, and poly(methacrylic acid) (PMAA) (Li et al., 2021a,b).

Liu and colleagues reported the development of a biodegradable and pH-sensitive nanogel system prepared by self-assembly of carboxymethyl cellulose and bovine serum albumin via electrostatic attraction. Albumin crosslinking was induced by heat

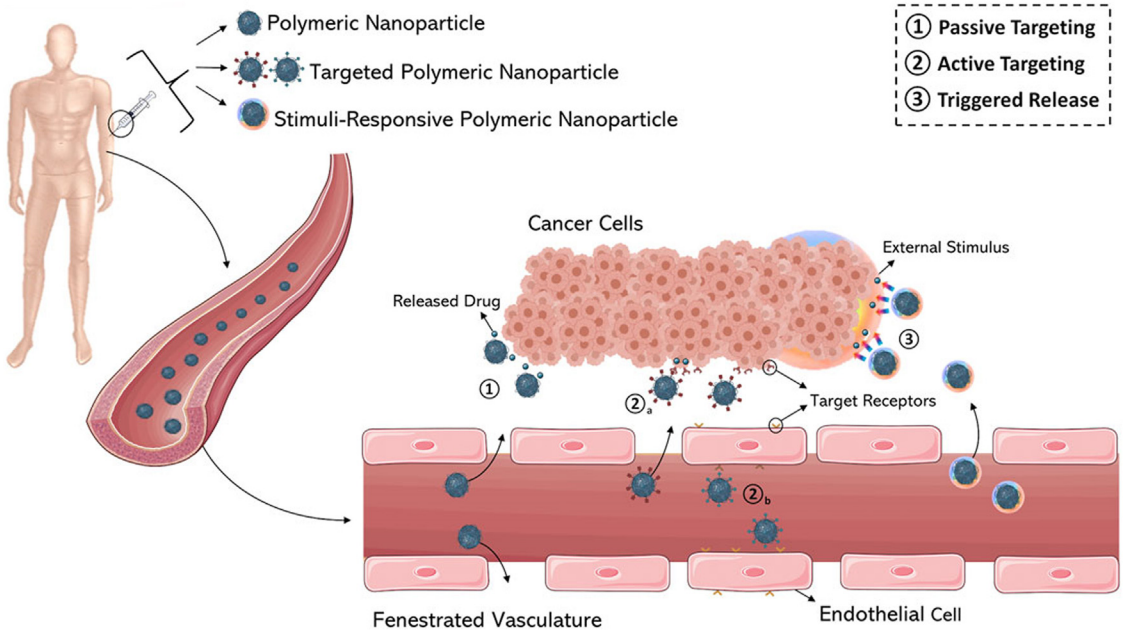

Fig. 1 Schematic representation of various drug targeting approaches (1−3). (1) Passive targeting of nanocarriers through fenestrated vasculature of tumor tissue by extravasation. Active targeting of cancer cells (2a) and (2b) tumor endothelium using ligand-modified nanocarriers. (3) Stimuli-responsive nanomedicines able to release the anticancer agent by internal or external triggers. Reproduced from Gagliardi et al. (2021).

treatment and the nanogel loaded with the radionuclide ^{131}I and camptothecin producing a system for combinatorial chemotherapy and radiotherapy. The results showed that the hybrid nanogel was able to enhance drug accumulation at tumor, improve cell uptake, and prolong circulation in the blood (Liu et al., 2018).

Nanogels also present large potential to transport drugs to the central nervous system, by navigating the blood-brain barrier. A recent research reported the development of a nanogel prepared with poly (ethylene glycol)-g-chitosan for immunotherapy delivery to glioblastoma cells. The results reveled that the nanogel presented greater effectiveness when compared to the Matrigel® regulation in destroying cancer cells. It was also demonstrated that the nanogel cellular compatibility with the T-lymphocytes that once encapsulated in the gel, could maintain their antiglioblastoma function (Kar et al., 2017; Manimaran et al., 2023). Picone et al. have developed a nose-to-brain drug delivery system based on a PVP nanogel synthesized via e-beam irradiation covalently attached to insulin. Insulin has been demonstrated to be an important therapy for some neurodegenerative pathologies such as Alzheimer disease. Their results demonstrated that no immunogenic response of the nasal mucosa was activated after the nanogel injection. Additionally, an enhancement of the delivery of insulin was observed in different brain sites indicating the great potential of the nanosystem to be used as a therapeutic agent (Picone et al., 2018).

Gene therapy is also a promising technique for the treatment of cancer, infectious diseases and immune system disorders. For this type of therapy, it is crucial to deliver the therapeutic gene to the target cell, depending, therefore, on an efficient delivery vector (Sung and Kim, 2020). For the treatment of osteoarthritis, for instance, gene therapy is an effective approach to target specific propagation mechanisms, treating the causes of this condition. Chitosan, hyaluronic acid, polyethylenimine (PEI) are some of the polymers already used as non-viral vectors for osteoarthritis therapy, as the nanoparticles can protect the pDNA from degradation (Rahimi et al., 2021).

Despite the promising advancements, challenges such as scale-up production, reproducibility, and regulatory approval are still concerns of some formulation. Ongoing research efforts continue to optimize different polymeric nanoparticles systems for drug delivery promising improved treatment modalities in the near future.

Biomaterials for Tissue Engineering

Tissue engineering or regenerative medicine is an interdisciplinary field of research that integrates medicine, biology, and engineering to develop biomaterials that restore, maintain, or improve tissue functions. Scaffolds are used as support for cells to their differentiation and proliferation, help regenerate extracellular matrix (ECM), and also may deliver biochemical factors. Thus, these structures are capable of mimicking the structural and physiochemical features of natural tissues. The use of nanotechnology has allowed the development of materials that mimic the ECM conditions more precisely as its network of protein and glycosaminoglycans forms a boundary between tissues and a supportive meshwork around the cells, providing them anchorage (Rahmati et al., 2021).

The manipulation of the physicochemical properties of biomaterial surface for each target application is one of the biggest challenges as this is a key role feature in supporting the cell survival and stimulating the autologous tissue growth in situ. The mechanical properties may also be appropriate as it should stimulate the neo-tissue formations. To meet these criteria, several techniques of biomaterial fabrication are applied, such as self-assembly, template synthesis, phase-separation, melt-blowing, and electrospinning (Rahmati et al., 2021).

Many research have used electrospun three-dimensional porous nanofibers to produce scaffolds for regenerative medicine in diverse applications as bone, cartilage, vascular, cardiac, skin, and neural tissue engineering, among others. Cartilage defects are one of the most common and difficult to treat health issues. Electrospun oriented poly(ε-caprolactone) (PCL) nanofibers seeded with hMSCs were successfully used for cartilage regeneration (Rahmati et al., 2021; Wise et al., 2009).

Concerning bone injuries, when a small (less than 8 mm) defect happens, the tissue is able to bone remodeling and self-healing. On the other hand, bone remodeling is not capable of repairing larger traumatic injuries demanding surgical intervention and bone substitutes. Autologous graft or allograft are often used in these cases, even though they have restricted application due to factors such as limited graft sources (for autologous) and risk of rejection and disease transmission (for allografts). In cases like these, tissue engineering can also represent an alternative to repair the tissue, as polymers and stem cells can create a framework for bone reconstruction. The most useable natural polymers used in bone regeneration are chitosan, collagen, silk fibroin, gelatin, cellulose, alginate and starch (Guo et al., 2021).

The reconstruction of blood vessels and production of tubular scaffolds was also possible using this technique as the high porosity and aspect ratio of nanofibers enhance nutrient and gaseous exchange leading to angiogenesis (Yazdanpanah et al., 2015).

Skin regeneration is another important field of study as auto/allografting present several drawbacks such as risks related to surgery, imperfect donor sites, slow healing rate and scar formation (Atiyeh and Costagliola, 2007). A scaffold developed for skin healing can provide protection to the tissue from dehydration and infection, delivery growth factors and matrix components to the wound site. Added to that, it supports ECM regeneration and allows cell attachment, proliferation, and migration leading to the formation of new skin tissue (Mitchell et al., 2016; Mogoşanu and Grumezescu, 2014; Rahmati et al., 2021).

In neural tissue engineering, nerve growth factor has been loaded in poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles to be used in therapies of neurodegenerative disorders, neural regeneration, differentiation and outgrowth of neurons (Johnson et al., 2008; Péan et al., 1998). PLGA is one of the main polymers used for neuroengineering as its degradation results in water and carbon

dioxide, and therefore, is safe for not forming toxic byproducts. PEI nanoparticles with retinoic acid also have been developed for the use in neural differentiation after ischemia (Kumar et al., 2020; Maia et al., 2011).

Conducting polymer-based nanomaterials are of great interest to the development of electrodes for neural activity monitoring and scaffolds for neural tissue engineering. The use of this conducting polymers on the surface of scaffolds can help control the direction of neural regeneration un advanced neural tissue engineering (Kumar et al., 2020).

Nanoscale fibers fabricated by electrospinning have been explored as a platform for the understanding, assessing, and manipulating the differentiation of stem cells. A study reported revealed that aligned-nanofiber-based scaffolds are more suitable for neural stem cells differentiation than scaffolds made of randomly distributed nanofibers (Kumar et al., 2020; Prabhakaran et al., 2009).

Nanogels can also be used in regenerative medicine for 3D cell cultures in which it is possible to mimic native extracellular matrix improving the similarity with human physiology. Different 3D cell culture systems have been created such as cellular tissues cultured on 3D scaffolds (Zhao et al., 2020), fibers of aggregated cells (Onoe et al., 2013), and spheroids (Imamura et al., 2020). In terms of cell spheroids, the use of nanogels is more interesting than the traditional methods using cell aggregates or stacks because in these cases, necrosis due to their limitation in the diffusion and exchange of nutrients and metabolites is a frequent problem. On the other hand, the nanogel can provide space between cells, avoiding their necrosis (Duan et al., 2023).

Polymeric Nanomaterials for Immunotherapy and Vaccine Delivery

Vaccines are one of the most important achievements in the health sector as they are a successful and most important method for the prevention of deaths caused by infectious diseases. They are able to protect human organism by establishing immunological memory, giving the body the tools to react to a foreign disease before it can cause systemic harm (Kumar et al., 2022). Adjuvants are substances added to the vaccines to enhance the immunogenic responses of antigens, improving its efficacy. Vaccine delivery systems are able to deliver the antigen to phagocytic cells or dendritic cells and release it sustainably (Yan et al., 2020). The use of nanoparticles in vaccine can provide the enhancement of immunogenicity and antigen storage at the same time as it can target delivery and sustain release. Diverse kinds of nanomaterials, including polymeric ones, have gained attention in the last decade as they can not only stabilize vaccine antigens, but also act as adjuvants. That is because their nanoscale particle size facilitates absorption by Antigen-Presenting Cells (APCs) resulting in effective antigen recognition and presentation (Kumar et al., 2022).

In the last years, nanotechnology has been used as a tool for the development of new vaccine adjuvants and delivery systems. Likewise protecting the antigens from degradation and enhancing their immunogenicity, biodegradable materials can also present properties such as immunomodulation, turning them into recognized ideal materials for vaccine adjuvant. Nanoparticles of biodegradable materials ranging from 24 to 100 nm are able to induce humoral, cellular and mucosal immune responses, besides acting as a drug delivery system (Yan et al., 2020). In **Fig. 2** it is possible to see a scheme of how modern vaccine delivery systems may provide enhanced immunogenicity.

The coronavirus pandemic brought about the use of nanomaterials with the development of vaccines and therapeutic antibodies to prevent and treat COVID-19. Beyond the conventional vaccines, the use of nanoparticle-based ones, such as Spikevax (Moderna) with lipid nanoparticles, provided a new, promising and unique approach, starting a new era of advanced vaccines (Rauf et al., 2022). Several nanotechnology method-based strategies for COVID-19 are still in progress, including nanomedicine-dependent

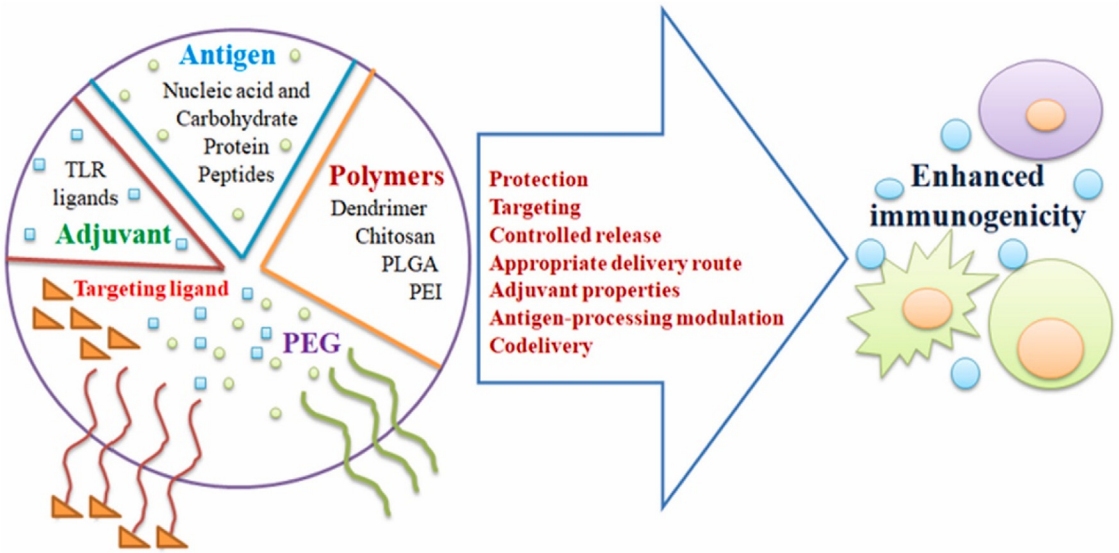

Fig. 2 Modern vaccine delivery systems containing polymeric nanoparticles and their properties. Reproduced with permission from Kumar et al. (2022).

mRNA vaccines, Pfizer-BioNTech (bnt162B2), and Moderna (Mrna-1273) that were approved for emergency use (Tajnur et al., 2023).

Other types of vaccine administrations also have been explored by scientists. Absorption of medicines via nasal mucosa, for example, has cough attention as a possible route to achieve faster, greater drug absorption, and avoid first-pass metabolism. In addition, advantages such as large surface area and ease access are also highlighted (Kumar et al., 2022). Natural and synthetic polymers particle carriers were engineered to improve vaccines performance. Synthetic polyesters as polyurethane (PU), poly(lactic acid), poly(latic-*co*-glycolic acid), and) PCL, are heavily used on the vaccine field as they are highly biocompatible and present a wide range of hydrophilicity and lipophilicity. Additionally, they can be tuned with different surface chemistries to target specific cells, and present different stimuli-responsive behavior to release their loading content. The most used polyesters are PLGA copolymers as they present an outstanding safety profile, being considered safe for sustained release vaccine delivery vehicles by the FDA. Polysaccharides as alginate, chitosan, cellulose, dextran, starch, and hyaluronic acid have also been used in research to develop nanoparticles-based vaccine delivery. These natural materials present advantages as simplicity of manufacture and ease chemical modification (Kumar et al., 2022).

Solid polymeric nanoparticles, micelles, nanogels, polymersomes, and core-shell nanoparticles are some of the polymeric nanomaterials that have been used in the development of vaccine delivery systems. Several antigens can be encapsulated and/or attached to the surface of these structure, including antigens based on lipids, carbohydrates, peptides, proteins, antigen-encoding nucleic acids (RNA or DNA), bacterial lysates, and inactivated viruses (Wibowo et al., 2021).

Chitosan nanoparticles loaded with the plasmid DNA of Newcastle disease virus F gene were successfully developed and improved immune response by mucosal vaccination in chickens. Also, a prolonged sustained release of the plasmid DNA was observed (Zhao et al., 2014). Hyaluronic acid has also been used in the development of a bioadhesive vaccine to delivery LKT63 influenza antigen. The study revealed that the formulation administered intranasally presented a substantial immune response against influenza (Singh et al., 2001; Yan et al., 2020).

PLGA nanoparticles have also been used in vaccines to load antigens such as hepatitis B, tetanus toxin, *Plasmodium vivax* and *Bacillus anthracis*. It was demonstrated that PLGA/PLA nanoparticles could delay the release of antigens and delivery them to antigen-presenting cells in controlled way. PLGA was also considered an important mucosal adjuvant as it could induce cellular and humoral immune responses (Jaganathan and Vyas, 2006; Yan et al., 2020).

In cancer treatment, immunotherapy has caused great impact in the last years. Vaccines are one of the modalities of immunotherapy for cancer, and they have been demonstrated to be capable of bringing out a sustained antitumor immune response and durable tumor regression (Geng et al., 2019; Zhou et al., 2020). The neoantigens are tumor-specific antigens that can elicit tumor-specific antitumor immunogenicity and that have been broadly studied for immunotherapy and minimizing central and peripheral autoimmunity. However, insufficient activation of the dendritic cells for antigen processing and presentation is still a limitation of these vaccines (Zhou et al., 2020).

Distinctly from the other therapies in which the objective is to target cancer cells, the immunotherapy activates the body's immune system. The tumor-immunity cycle happens in 4 steps: (i) first a sufficient effector T cells *in vivo* are generated; (ii) then these effector T cells are infiltrated into the tumor and overcome the inhibition of tumor microenvironment; (iii) followed by the direct recognition of tumor antigen by effector T cells that generate anti-tumor immune response; and lastly, (iv) the persistency of anti-tumor response and the increase number of effect T cells. After these steps, the tumor cells are removed by the body's enhanced immune responses, reshaping the tumor microenvironment. In other words, the immunotherapy intensifies the immune response mediated tumor cell lyses by promoting the production of relevant immune cells to directly recognize tumor cells via tumor antigens. Nevertheless, tumor immunotherapy still has challenges to overcome such as tumor permeability and low tumor cell uptake (Zhu and Li, 2023).

Nanogels are also very effective in loading, protecting, and releasing antigen in a controlled way in antigen-presenting cells, and therefore, are considered a promising strategy for nanovaccines. Nanogel-based vaccines are frequently developed to encapsulate tumor associated antigens, which when by themselves are not able to lead to strong cell-mediated immunity. Additionally, nanogel based vaccines can protect antigens from degradation on the way to lymphatic system and present strong capacity to activate cytotoxic T cells to attack cancer cells (Duan et al., 2023).

Theranostic Nanoparticles

Nanotheranostics is an approach that allows simultaneously monitoring drug distribution, drug release, and evaluate therapeutic efficacy using a single nanoscale carrier (Indoria et al., 2020). Although progress has been made in radiation technology, the challenging of maximizing the dose deposition in cancer organs without reaching other vital healthy organs still remains. The use of nanocarriers promises to improve radiotherapy by delivering radiosensitizers or radionuclides to the tumor, boosting the treatment efficacy. Also, combining the radioisotopes to nanoparticulated systems allows the monitoring of *in vivo* distribution via emission tomography (PET) or Cerenkov Luminescence (CL) or positron or single-photon emission computed tomography (SPECT) (Indoria et al., 2020).

Theranostic nanoparticles can present several characteristics that make them ideal for the application, such as targeted rapid delivery, delivery morphological and biochemical features of the targeted site, sufficient drug delivery, no side effects, and fast clearance. However, in spite of all research in the area, all of these criteria haven't been achieved by one system yet (Hosseini et al., 2023).

To imaging goals, radioactive polymeric nanosystems can be designed using two different protocols: having the radioactive element inside a nanosized cluster or attached to a nanoparticle surface (radiolabeling), as represented in Fig. 3. For example, the radiolabeling of nanoparticles with technetium-99 m, the most widely used SPECT radionuclide, increased the understanding of their biodistribution. Radioactive polymeric nanoparticles can carry high payloads of radionuclides allowing their use for nuclear imaging or radiotherapy, depending on the radionuclide present in the formulation. Added to that, they have potential to improve the medical outcomes by enhancing accumulation of the drug in the tumor by enhanced permeability and retention effect (EPR) (Wu et al., 2020).

Polymeric nanoparticles also provided imaging agents a long-term shelf life, formulation stability, biocompatibility, and allow higher resolution and sensitivity during imaging. The imaging agents and biological markers can be conjugates, chelated or physically bonded to the polymer nanoparticles. Decorating nanoparticles with polyethylene glycol, carbohydrates, acetyl groups, or protein moieties is a strategy to enhance bioavailability (Hosseini et al., 2023).

Plethora of polymeric theranostic systems have been developed, such as FA-PEG-PCL-SPIONs theranostic system for MRI contrast enhancement, ^{18}F-labeled HPMA for PET imaging, ^{177}Lu-labeled dendrimers for vector imaging, among others (Allmeroth et al., 2013; Hosseini et al., 2023). In terms of natural polymers, hyaluronic acid (HA) has been of great interest in cancer treatment research as it is known that many cancer cells present a hyaluronic receptor called CD44. A recent study showed that a HA-paclitaxel conjugate complex was more cytotoxic to cancer cells than to CD44 deficient cells (Hosseini et al., 2023; Lee et al., 2008).

Polymer based superparamagnetic nanoparticles—devices with the ability to respond towards external magnetic field - also permit several uses, including but not limited to treating cancer with magnetic hyperthermia, contrast enhancement agents, magnetic resonance imaging guided drug delivery, and cell tracking (Indoria et al., 2020). Fluorescent polymeric nanoparticles have been studied as potential systems for simultaneous cancer detection and treatment. These systems are composed of fluorescent protein, inorganic quantum dots, commercial organic dyes, and biocompatible biopolymers (Indoria et al., 2020).

Nanogels as well have been extensively studied as platforms for theranostic purposes. Ulanski's group (Matusiak et al., 2021; Rurarz et al., 2023) has recently developed a nanoplatform based on poly(acrylic acid) nanogels functionalized with Lys1Lys3-bombesin(1−14)—to target gastrin-releasing peptide receptor from prostate cancer cells—and modified with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10 tetraacetate) chelator to deliver Lu-177 and Y-90 radionuclides. The nanogel was synthesized by irradiation with accelerated electron beam short pulses of poly(acrylic acid) with different molecular weights. The nanosystem had its biological effects evaluated concerning cellular uptake, tissue distribution, and excretion. Its *in vitro* behavior was very promising for theranostic purposes, maintaining high radiochemical purity of >90% in labeling buffer and human serum for up to 14 days. Additionally, a 30% specific uptake in PC-3 prostate cancer cells was observed after 4 h was observed. However, *in vivo* assays showed that a significant portion of the nanocarrier was retained in the liver and spleen, leading to the need of further optimization of the proposed system.

Podgórna and colleagues have prepared a gadolinium and alginate nanogel by reverse microemulsion method to carry hydrophilic and be traced by Magnetic Resonance Imaging (MRI). The system was non-toxic and stable for 2 months, without the presence

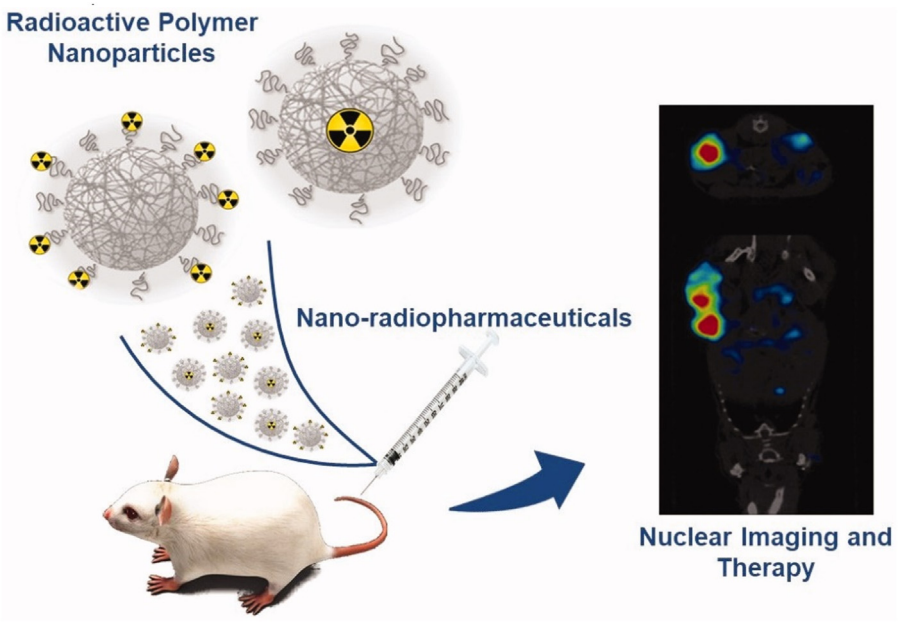

Fig. 3 Scheme representation of two types of radioactive polymeric nanoparticles and their application in imaging and/or therapy. Reproduced from Wu et al. (2020).

of non-complexed gadolinium (III) ions—which are toxic—and was capable of significantly reduce the relaxation time relative to alginate nanogel and water, confirming it could act as contrast-enhancing agent in MRI (Podgórna et al., 2017).

More examples of multifunctional nanoplatforms can be found in an excellent review about drug target delivery and theranostic applications of PVP based radiation-synthetizes nanogels that have been recently published by Dispenza and her group (Sabatino et al., 2020). The authors carefully explore the use of ionizing radiation for the engineering of nanogels, their physical-chemical properties and the possibilities of fluorescent labeling for biological applications.

The main advantage of theranostic approach is the possibility of tracking and monitoring the disease state by combining molecular imaging and therapy. Accordingly, outcomes as safe dose estimation, recognition of adverse effects pattern, and real-time monitoring of therapeutic effects are achieved, substantially improving treatment efficiency. Thus, in cancer treatment, these features are of high interest as they can solve conventional therapies limitations as drug resistance, low specificity to desire tissues, and damage to healthy tissues. Furthermore, theranostic nanoparticles can also increase solubility in photodynamic therapy. Other superiority properties of nanoparticles in the development of target contrast materials are related to the possibility of functionalization with or more target groups in a wide range of densities, adjustable plasma half-life, loading contrast agents and drugs in different concentrations (Hosseini et al., 2023).

Photodynamic Therapy and Photothermal Therapy (PDT)

Photodynamic therapy is a non-invasive method of light-mediated treatment by using photosensitizers. The photosensitizers are molecules that can be stimulated by light in a specific wavelength to create ROS (reactive oxygen species) in the form of singlet oxygen ($^1O_2$) from the molecular oxygen ($^3O_2$). These ROS are capable of killing tumor cells and microorganisms through different biologic mechanisms (Chen et al., 2022).

PDT presents some limitations such as photosensitizers aggregation in physiological conditions because of their hydrophobic structures and severe side effects like phototoxicity due to their low selectivity for tumors. Therefore, nanocarriers have been developed with the goal of solving these problems (Park et al., 2020). Systems composed of photosensitizer conjugates or photosensitizer-loaded nanoparticles—including polymeric ones—have also been developed for the use in image-guided therapy of cancer with enhanced PDT efficacy. More than that, these theranostic conjugates may also deliver hypoxia-responsive drugs to improve the efficiency of the treatment as in the transformation of the triplet oxygen into singlet oxygen in the PDT, the intracellular molecular level decrease, facilitating this condition. For instance, researchers have developed semiconducting polymer based nanocarriers with fluorescence imaging features, that could produce light-activated ROS and hypoxia-responsive nm) anticancer drug release. The system was composed of a conjugated (semiconducting) polymer as a photosensitizer, PVA as a stabilizer and doxorubicin hydrochloride as chemotherapy agent. Under irradiation of near-infrared light (808 nm) and hypoxic condition, the nanoparticles dissociated and released the drug, providing dual chemo and PDT cancer treatment (Chen et al., 2022; Qian et al., 2016).

Nevertheless, PDT procedure still holds drawbacks as dependence on molecular oxygen and poor photodynamic efficacy in solid tumors. As an alternative to these challenges, photothermal therapy (PTT) gained much attention. In PTT no molecular oxygen is required in the process as photothermal agents absorb the light and convert the energy directly into heat through a non-radiative pathway (Chen et al., 2022).

Temperatures equal or above 43 °C can induce a heat-shock response in cancer cells, causing their death. Even though cancer cells are more vulnerable to hyperthermal damage than normal cells, conventional hyperthermal requires external thermal stimuli, like radiofrequency or NIR irradiation, which can result in severe side effects as they are non-selective. Besides, external thermal stimulation creates a temperature gradient with higher temperature on the body's surface that dissipates when it goes through the tissues. As a solution for those disadvantages, hyperthermal agents for PTT have been developed to generate heat in situ in response to non-hyperthermal external stimuli (Park et al., 2020). Organic photothermal agents have been widely explored in PTT approach once they present better biocompatibility and lower toxicity when compared to inorganic materials. Thus, NIR-I light absorbing conjugated polymer materials have been used as efficient photothermal agents (Chen et al., 2022; Sun et al., 2018; Wang et al., 2018).

Semiconducting polymers have also been applied in the development of PTT, PDT, and their combination to achieve a multi-effect on better therapeutic outcome. These materials are interesting due to their aromatic structure with π-π interactions that are capable of generating heat once exposed to NIR light. Polyanine (PAN), polypyrrole (PPy), polydopamine (PDA) are some examples of semiconducting polymers used to create nanoscale level structures for phototherapies. As a novel class of organic optical nanosystems, semiconducting polymer nanoparticles present several advantages like brilliant opto-electrical properties with excellent photostability and easy modification properties with good biocompatibility for biomedical applications. Furthermore, their organic and biologically inert nature diminish the risks of potential toxicity, revealing them to be perfect candidates for theranostic nanoagents in different photo-therapeutic, including PDT and PTT (Rejinold et al., 2021).

Conclusion

Hydrogels are polymer networks swollen with water. Their unique properties, including high water content, biocompatibility, tunability, and responsiveness, make them versatile materials with applications across medicine, pharmacy, agriculture, robotics, and sensors. They are classified based on their network structure into physical (non-permanent) and chemical (permanent) gels. They can be further categorized by origin (natural or synthetic), polymer composition, physical structure, responsiveness to stimuli,

charge, degradability, application, and functionality. Additionally, hydrogels are classified by size into bulk hydrogels, microgels, and nanogels—notable for their ability to penetrate biological barriers, making them effective for targeted drug delivery and gene therapy. This review emphasized the use of radiation-induced technologies for synthesis of polymeric nanogels and nanoparticles based on synthetic and natural polymers. Selected groups of applications, with an examples of materials used, have been presented. Polymeric nanogels and nanoparticles present a promising future in various medical applications, including drug delivery, cancer treatment, tissue engineering, immunotherapy, and theranostics. Despite the advancements, challenges like production scalability, reproducibility, and regulatory approvals remain. Continuous research is aimed at optimizing these systems to improve treatment modalities.

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