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Review

Novel Therapies

Nanoparticles as platforms of molecular delivery in diagnosis and therapy

CS Cordon[1], MBR Piva[2], CM Melo[2], MAS Pinhal[1,2], ER Suarez[1,2]*

Abstract

Introduction

Nanoparticles are polymeric colloidal systems ranging from 10 to 1000 nm, which are able to deliver compounds to the cells. Their size, shape and surface determine the activity of the molecules incorporated. Two main groups of nanoparticles are applied as drug delivery systems: the polymeric nanoparticles, such as liposomes, dendrimers and micelles, and the inorganic particles, including gold, iron oxide, silica and graphene. The aim of this review is to discuss nanoparticles as platforms of molecular delivery in diagnosis and therapy.

Discussion

Dendrimers and liposomes incorporate hydrophobic and hydrophilic agents, but present low biodegradation and leaking of the agents, respectively. Micelles are suitable for hydrophobic molecules, but may use toxic materials. Superparamagnetic iron oxides are efficient agents in magnetic resonance and easily biodegradable; however, at high doses this particle promotes intense oxidative stress. Gold particles are very useful as sensor particles, but they are immunogenic. Silica particles are easy to synthesise and functionalise; however, very less information about their biodegradation is available. The graphene structures, such as carbon nanotubes, have many interesting properties; however, they are very toxic and accumulative.

Conclusion

Nanoparticles are very promising as new diagnosis and pharmacotherapy tools. However, the disadvantages associated with them must be overcome in order to find completely safe and efficient systems.

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Introduction

Nanoparticles are polymeric colloidal systems ranging from 10 to 1000 nm, which are able to deliver compounds to the cells[1]. They can be used alone or associated to several molecules for the treatment and diagnosis of cancer, autoimmune and congenital diseases. For example, showing an increase in the efficacy of these drugs and, mainly, minimising the adverse events. The nanoparticles are classified in two main groups: nanocapsules and nanospheres. The nanocapsules have a polymeric membrane and a cavity where the therapeutic agent can be incorporated, while nanospheres have a polymeric matrix where the therapeutic agent can be adsorbed or dispersed[2].

The size, shape and surface of the nanoparticles are important factors to determine the pharmacological activity of the therapeutic agents incorporated. Particles less than 5–10 nm in size are quickly removed from circulation and eliminated by the kidney, while particles sized 15 µm or more tend to accumulate in organs, such as liver, spleen and bone marrow. Micelles, as an exception, have a reduced size and a half-life of 5 days, due to their ability to escape renal filtration[3]. The biodistribution and uptake of nanoparticles by the tissues are defined specifically by the type of cell[4]. In addition, cells capture particles less than 20 nm by pinocytosis and less than 100 nm by phagocytosis. The immune response is affected by the capture mechanism influencing drug amounts delivered to the target tissue[5]. Particles ranging from 10 to 200 nm have shown better efficacy in the majority of the drug distribution systems[6].

Discussion

Two main groups of nanoparticles, the polymeric and inorganic particles, are applied as drug delivery systems (DDS). Polymeric nanoparticles include liposomes, dendrimers and micelles. Inorganic nanoparticles include gold, iron oxide, silica and grapheme[7]. These systems will be described below.

Delivery systems

Micelles

Micelles are colloidal dispersions of 5–100 nm formed by amphipathic molecules that present a hydrophilic exterior and a hydrophobic interior (Figure 1)[8]. The hydrophobic nucleus allows storage of a large dose of hydrophobic compounds, which would require toxic amounts of organic solvents/surfactants to be diluted[9].

Micelles preferentially accumulate in tumours because of the leaky vasculature of these tissues and poor drainage; this is called the enhanced permeability and retention effect[9]. It helps to concentrate the therapeutic substance in the target tissue. Another strategy to increase tissue specificity and cell uptake is to conjugate specific molecules to the micelles surface[9].

Lipid nanoparticles are synthesised by fusion-emulsification; this technique consists of prior fusion of the lipid, incorporating the active principle by dissolution or dispersion. Then, the lipid phase is emulsified in an aqueous phase containing a surfactant. The emulsion prepared

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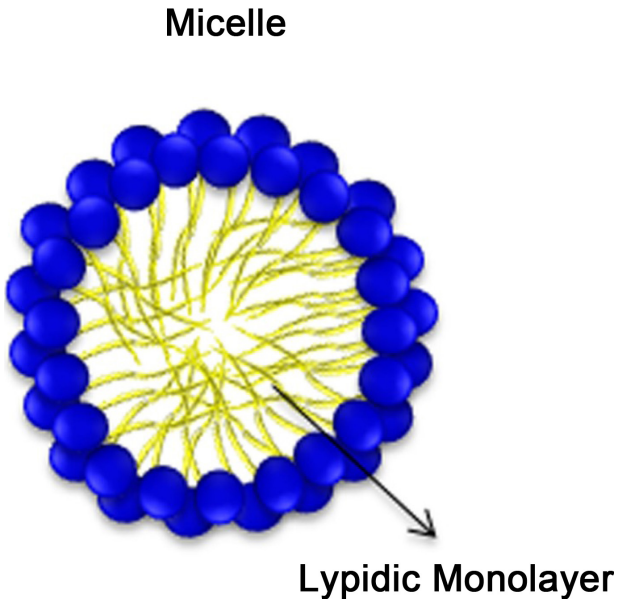

Figure 1: Micelle nanoparticle.

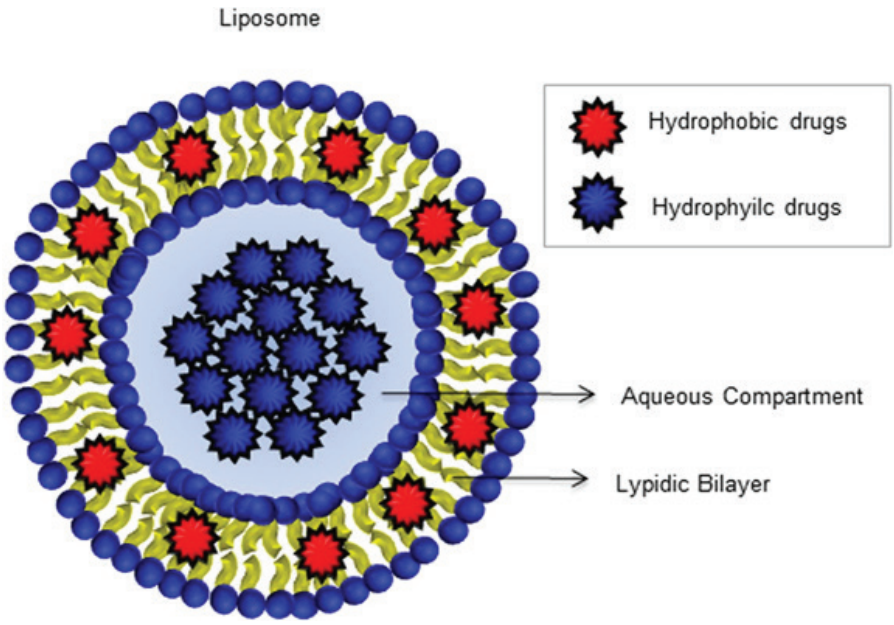

Figure 2: Liposome drug delivery system.

is maintained at room temperature for solidification of the lipid[10].

Liposomes

Liposomes are vesicles constituted by a concentric phospholipid bilayer (Figure 2), which involves an aqueous central compartment of 50–100 nm[11].

Due to its larger size, when compared to most particles, liposomes can carry larger amounts of drugs[8].

The organisation of this system is based on the presence of water, since the orientation of the bilayer may be determined by the nature of the polar groups and carbonic chains. The amphipathic nature of liposomes allows transportation of hydrophobic compounds bounded to the carbonic chains of their phospholipids and also of hydrophilic molecules in the interior aqueous cavity. The maintenance of the drug inside the liposome is dependent on the concentration, chemical nature, electric charge of the phospholipid, ionic strength of the media and the size of the drug[12].

Liposomes are non-toxic and biodegradable, have high circulation time and have the possibility of high-scale production. However, like other DDS, liposomes have the disadvantage of leaking the encapsulated agent[4].

Some liposome systems recognise some characteristics of tumour microenvironment, such as hypoxia and low pH, releasing the therapeutic agent only inside the tumour[4]. Some structures are formulated to suffer an acid-catalysed hydrolysis of the vinyl ether group with polyethylene glycol (PEG) removal leading to liposome destabilisation and drug release[13]. Liposomes are also widely used in cosmetic formulations due to their structural similarity with cell membranes, which allows an easy interaction with the skin[11].

Dendrimers

Dendrimers are macromolecules (1–12 nm) with high molecular weight and many well-defined ramifications (Figure 3). They are formed by monomeric or oligomeric units of polyamidoamine (PAMAM), polypropylenimine (PPI) or poly-L-lysine (PLL), for example. These particles are formed by a central nucleus surrounded by several concentric layers, called generations, where therapeutic or diagnostic substances can be stored[5,11,14].

Ramifications on the dendrimers' surface can be modified allowing other molecules to connect to its structure[14]. Dendrimers can be designed to have a hydrophilic surface and still carry hydrophobic molecules in their hydrophobic nuclei[11].

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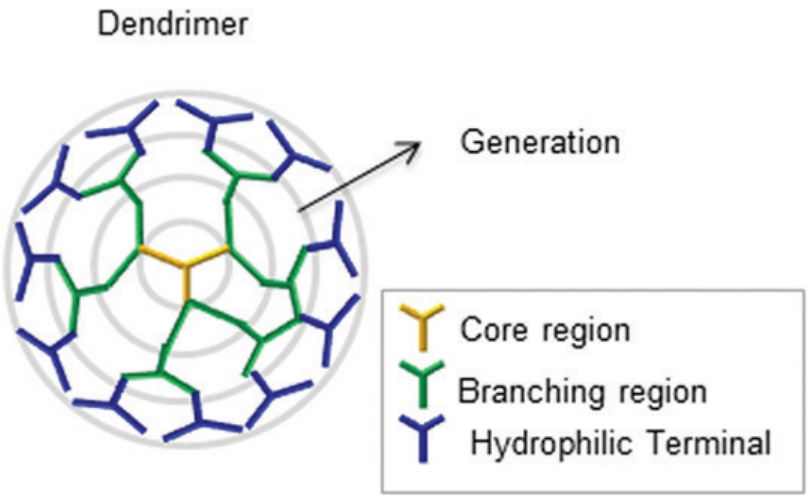

Figure 3: Structure of dendrimer.

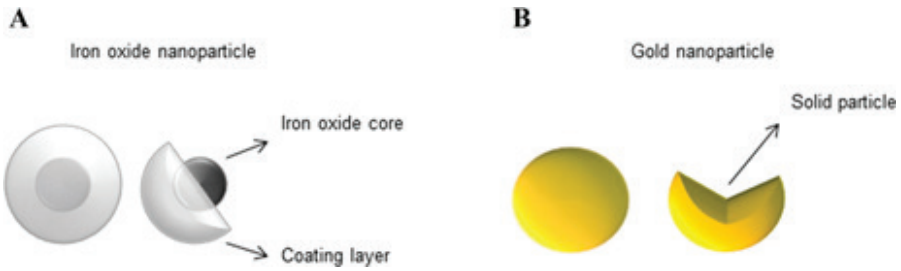

Figure 4: Iron oxide and gold nanoparticles.

There are three key factors for dendrimers' toxicity: number of generations, composition and charge of the surface[14]. For example, cationic dendrimers are more toxic than anionic or neutral dendrimers because they can induce apoptosis through pore formation on cell and organelle membranes, including the mitochondria[15,16].

Dendrimers' surface composition also affects their distribution, since dendrimers lacking hydrophilic groups concentrate on the liver, while negative or neutral dendrimers stay longer in the circulation[11]. Dendrimers are an excellent DDS because of their mouldable structure that enables control of size and ramifications density.

At the beginning, the approach to synthesise the two major dendrimer designs, the PPI and PAMAM, used the divergent strategy (from core to periphery). Briefly, the monomer end group is deprotected to create a new reactive surface functionality and then coupling with a new monomer. This process should be repeated several times depending on the number of generations desired. In contrast, the convergent method constructs a dendrimer from the surface to the centre[17].

Superparamagnetic iron oxides

Iron oxide nanoparticles are formed by a crystalline core of iron oxide (iron oxide I, II or III) and a coating layer (Figure 4A)[5]. The size of these particles varies from 3 to 100 nm and these particles can be synthesised either by sonochemical reaction of iron pentacarbonyl that uses sound/ultrasound radiation or by thermal treatment and oxidation[11].

Superparamagnetic iron oxides (SPIONs) present two important advantages: magnetic property and easy biodegradation, since they are incorporated into the iron metabolism pathway[5].

Starch, PEG, silica and dextran are commonly used as the outer layer. It is important to point out that dextran, compared with other materials, presents higher biocompatibility and lower molecular weight, and can remain in the circulation without triggering immune responses or impairing liver function for long periods of time. However, dextran can suffer opsonisation by plasma proteins. The addition of polyethylene glycol in the coating layer decreases the opsonisation process and coating with silica seems to have low toxicity[5,11,18].

Nowadays, SPIONs have already been approved as a contrast agent for magnetic resonance diagnosis and cancer treatment[11]. In addition, a study has already been developed in mice using SPION aerosol to deliver drugs to the lungs with a target-direct magnetic gradient[19].

Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNs) have a solid structure filled with pores that form channels of nanometric dimensions (2–50 nm)[20]. Such channels can store therapeutic or diagnostic substances (Figure 5).

MSNs are synthesised using a process called supramolecular self-assembly, which consists of hydrolysis and condensation of a silica precursor in the presence of surfactant micelle templates, followed by removal of the surfactant templates to recover mesoporous silica particles. The production method of silica nanoparticles provides different size, morphology, pore size, number of pores, crystallinity and surface topography of the particles, which can cause a large range of biological responses difficult to predict.

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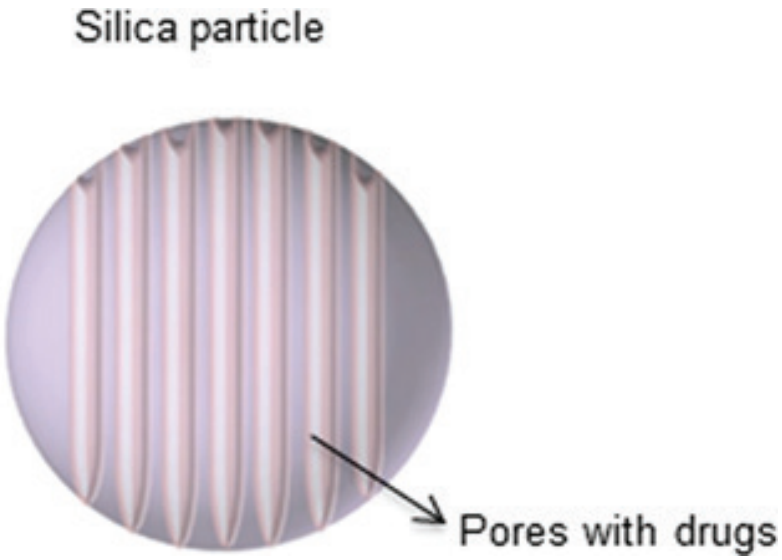

Figure 5: Silica particle.

This array of features can be achieved by changing the parameters of synthesis, such as silica precursor or co-surfactants, size of the surfactant template or concentration of surfactants[21].

Silica nanoparticles are absorbed by endocytosis usually facilitated by clathrin protein, which forms a polymeric net around the endocytosis vesicle[21]. It has been shown that adding polyethyleneimine (positively charged) to MSN reduces toxicity and increases absorption and the speed to reach the site of action[5]. Moreover, silica nanoparticles can be conjugated with SPIONs that generate a magnetic nucleus to orientate the particle to the site of action or for image diagnosis[22].

Silica nanoparticles seem very promising due to easy synthesis, capacity of storage and controlled release of large amounts of substances at a specific target. However, there is a lack of information about their bioelimination, kinetics and toxicity. Thus, many studies are still required to make safe use of these particles[21].

Gold nanoparticles

Gold nanoparticles are solid particles of size 50 nm or less (Figure 4B). This type of nanomaterial can be functionalised with DNA, RNA and antibodies. Gold nanoparticles can be synthesised by reduction with citrate in water. Additionally, gold nanoparticles present unique optical-electronic property: electromagnetic frequency induces a resonant coherent oscillation of free electrons, called surface plasmon resonance. Thus, gold nanoparticles can absorb radiation and emit a rich red light[5,11,14,23].

This type of nanomaterial has been researched for many applications such as organic photovoltaic that converts electromagnetic energy into electric energy; sensory probes; therapeutic agents; drug delivery in biological and medical applications as autoimmune diseases, allergy and cancer; electronic conductors and catalysis.

A study in humans has already been performed using gold nanoparticles to diagnose lung cancer. A gold nanoparticles' sensor can distinguish healthy individuals from patients with lung cancer by their breath. The sensor detects organic volatile substances which are elevated in lung cancer patients[24].

Graphene

Graphene is composed of a carbon sheet. Carbon atoms are attached with each other by an sp2 bond, forming a hexagonal structure (Figure 6). This material presents a high mechanical strength, absorbs in the infrared region and conducts electricity and heat[5,25].

In 2004, graphene was first exfoliated mechanically from graphite. Later, the graphitisation of hexagonal silicon carbide crystals during annealing at vacuum and high temperatures was reported. Under such annealing conditions, the top layers of silicon carbide crystals undergo thermal decomposition; the carbon atoms remain on the surface and form graphene layers. Many different methods of synthesis are being researched. Nowadays, the most common techniques of synthesis are as follows:

- arc discharge—electrons with high pressure, produced by arc discharge, collide on the surface of graphite[25]
- laser ablation—laser beam hits on the graphite, and this reaction uses a transition metal as catalyst and chemical vapour deposition[25].

Polyethylene glycol can be associated with graphene oxide to decrease toxicity and to allow targeting of ligands[5,25].

Carbon nanotubes

Carbon nanotube is the graphene in a cylindrical form. This type of nanomaterial presents a unidimensional cavity of size 50–200 nm; it can be formed by a single wall or multiple walls (Figure 7)[5,14].

Since 2004, carbon nanotubes have been studied with the aim to transport chemotherapeutic agents into cancer cells. In addition, carbon nanotubes can be applied to the photothermal ablation of tumours. Both these uses seem to be effective in the treatment of cancer[5,26].

Until now, there is little information about the toxicity of carbon nanotubes, because of which it cannot be used in vivo. Dermal reactions, alteration of immune system and increase in oxidative stress have already been

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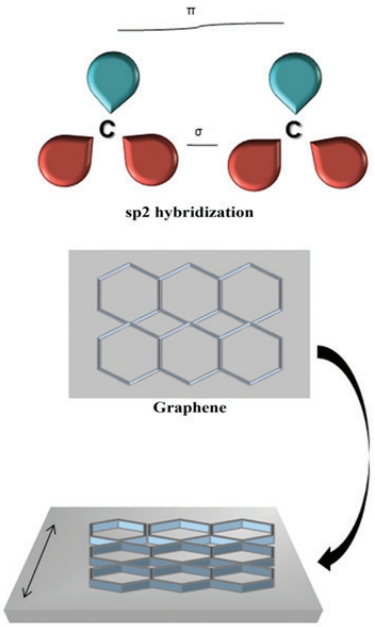

Figure 6: Graphene structure.

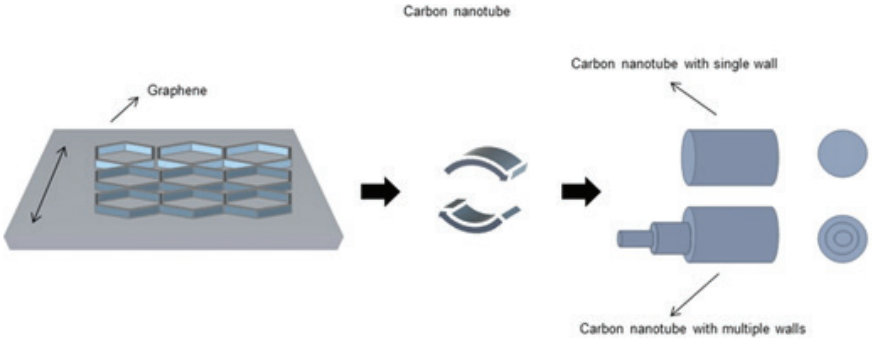

Figure 7: Carbon nanotube.

reported during studies with carbon nanotubes. Also, graphene seems to be toxic to the lung[26].

Efficacy, biodegradation and elimination of nanoparticles

The shape of nanoparticles is important in determining the system efficacy. Spherical particles have better efficacy, while discoid nanoparticles tend to migrate laterally in the circulation (margination), decreasing extravasation to tissue. However, elongated particles are able to overcome phagocytosis[27].

Biodegradation and excretion are important factors to determine the efficacy of the nanoparticles avoiding adverse effects. A good biodistribution and half-life time are important to determine the efficacy of the therapeutic agent carried out by the particle[4]. PEG has been applied at the surface of some nanoparticles in order to increase the circulation time, decreasing toxicity[3]. Nevertheless, unnatural PEG is not biodegradable and may suffer decomposition by oxidation. Some adverse effects, such as vacuolisation of the renal epithelia, are common after chronic treatment with PEGylated particles[28]. In order to overcome PEG issues, a peptide constituted by proline, alanine and serine was developed showing low cost of production, water absorption retarding glomerular filtration without accumulation, maintenance of bioactivity of the compound and biodegradability presenting low toxic effects[29].

Specific molecules or modifications in the nanoparticles' surface that drive it to a specific cell target are also crucial to a good performance. The most common are specific ligands such as antibodies and peptides developed against cell targets, but some polymers can also be used[27]. Some molecules may also be applied to evade the immune system avoiding rejection[5].

Conclusion

Nanoparticles present a very promising perspective to improve the diagnosis and efficacy of pharmacotherapy with specific treatments in which the nanoparticle carries the therapeutic agent dissolved, encapsulated, adsorbed or dispersed with the aim to protect the drug, and increase its solubility or improve its biodistribution and action over a specific target, minimising adverse effects. Some systems such as dendrimers and liposomes are very versatile, allowing incorporation of hydrophobic and hydrophilic agents, but have some specific disadvantages of low biodegradation and leaking of the agents, respectively. Micelles are suitable for hydrophobic molecules, but may use toxic materials in their compositions. SPIONs are efficient agents in magnetic resonance and easily biodegradable; however, at high doses they promote intense oxidative stress. Gold particles are very useful as sensors, but they are immunogenic. Silica particles are easy to synthesise and functionalise; however, very less information about their biodegradation is available. The graphene structures, such as carbon nanotubes, are interesting strategies due to the photothermal, mechanical, electrical and optical properties; however, they are very toxic and accumulative. The exocytosis of undissolved particles and time-consuming synthesis are also limitations of some nanoparticles. The disadvantages of these nanoparticles must be overcome in order to find completely safe and efficient systems. However, the importance of nanoparticles has been growing nowadays, presenting a very promising perspective to improve the diagnosis and efficacy of pharmacotherapy.

Abbreviations list

DDS, drug delivery systems; MSN, mesoporous silica nanoparticle; PAMAM, polyamidoamine; PEG, polyethylene glycol; PLL, poly-L-lysine; PPI, polypropylenimine; SPION, superparamagnetic iron oxide.

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