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Journal of Controlled Release xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Current applications of nanoparticles in infectious diseases

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ARTICLE INFO

Article history:
Received 24 October 2015
Received in revised form 3 January 2016
Accepted 5 January 2016
Available online xxxx

Chemical compounds studied in this article:
Amphotericin B (PubChem CID: 5280965)
Chloroquine (PubChem CID: 2719)
Fluconazole (PubChem CID: 3365)
Gentamicin (PubChem CID: 3467)
Penicillin (PubChem CID: 5904)
Rifampicin (PubChem CID: 5381226)
Saquinavir (PubChem CID: 60934)
Streptomycin (PubChem CID: 5999)
Vancomycin (PubChem CID: 14969)
Zidovudine (PubChem CID: 35370)

Keywords:
Nanoparticles
Infections
Drug delivery
Antimicrobial

ABSTRACT

For decades infections have been treated easily with drugs. However, in the 21st century, they may become lethal again owing to the development of antimicrobial resistance. Pathogens can become resistant by means of different mechanisms, such as increasing the time they spend in the intracellular environment, where drugs are unable to reach therapeutic levels. Moreover, drugs are also subject to certain problems that decrease their efficacy. This requires the use of high doses, and frequent administrations must be implemented, causing adverse side effects or toxicity. The use of nanoparticle systems can help to overcome such problems and increase drug efficacy. Accordingly, there is considerable current interest in their use as antimicrobial agents against different pathogens like bacteria, virus, fungi or parasites, multidrug-resistant strains and biofilms; as targeting vectors towards specific tissues, as vaccines and as theranostic systems. This review begins with an overview of the different types and characteristics of nanoparticles used to deliver drugs to the target, followed by a review of current research and clinical trials addressing the use of nanoparticles within the field of infectious diseases.

Contents

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http://dx.doi.org/10.1016/j.jconrel.2016.01.008
0168-3659/

1. Introduction

According to the FDA and IUPAC, "nano" is any product with properties or phenomena attributable to its dimensions, even if these dimensions fall outside the nanoscale range of 1–100 nm [1,2]. Applications in medicine extend from the use of nanomaterials for medical devices, to the use of nanoparticles (NPs) as therapeutic agents, drug delivery systems, and diagnostic imaging systems.

In recent years, many billions of dollars have been invested in the global market for NPs in the life sciences [3], especially in the area of drug delivery systems, which accounts for 76% of nanotechnology research publications in 2014 [4]. The advantage of NP formulations *vs.* conventional systems is that they can increase the efficacy of treatment and reduce side effects thanks to their specific targeting action. This targeting depends on the composition of the NPs themselves as well as their physical and chemical characteristics. The first NP system developed as a drug carrier was a liposome in 1978 [5] and since then a large number of nanoparticles have been developed as delivery systems.

Currently, oncology is the main area of NP applications and the second area corresponds to infectious diseases, although research is also being carried out in other therapeutic areas such as CNS diseases, cardiovascular diseases, ocular pathologies, and Alzheimer's disease, among others [4,6,7]. In particular, the use of NPs for infections is interesting because of treatment failures caused by antimicrobial resistances and the lack of novel drugs under development. Moreover, many pathogens are located intracellularly in an active or latent state, which hinders drug access [8–10].

NPs offer an alternative for overcoming these problems. Thus, current attention is being focused on their use as antimicrobial agents against different pathogens (bacteria, virus, fungi and parasites), multidrug-resistant strains and biofilms; as systems for targeting drugs to infected bones, lungs and the gastric tract; as vaccines and as theranostic systems. This review aims to highlight these current uses and applications of NPs in infectious diseases.

2. Therapeutic interest of nanoparticles in infectious diseases

For decades, infections have been treated effortlessly with anti-infective drugs. However, in the 21st century, infections and minor injuries may become lethal again owing to the development of antimicrobial resistance. According to the WHO definition, a strain is considered resistant when it no longer responds to standard treatments and hence the infection is very difficult to treat and stop its spreading [11]. Some bacteria responsible for common healthcare-associated and community-acquired infections are multidrug-resistant bacteria, like *Mycobacterium tuberculosis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Stapylococcus aureus*, *Enterococci* sp., *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Streptococcus pneumoniae*, nontyphoidal *Salmonella*, *Shigella* sp. and *Neisseria gonorrhoeae* [11,12]. Such resistance means that infections must be treated with second-line drugs. These treatments are not always available, may cause numerous and severe side effects and must be administered through the i.v. route, which is expensive [11]. Nonetheless, the real problem is that bacteria are becoming resistant even to second-line treatments, such as methicillin-resistant *S. aureus* (MRSA) to vancomycin or *K. pneumoniae* to carbapenems, and even to 3rd generation drugs. In fact, in the case of tuberculosis and HIV infections nearly 20% of cases are estimated to be resistant to the currently available treatments [11].

Pathogens can become resistant through different mechanisms such as DNA alterations, modifications in membrane permeability, development of multidrug efflux pumps, activation of enzymes responsible for drug degradation or increase of their intracellular lifecycle [13]. The latter one is becoming so common that some pathogens are now considered to be *de facto* intracellular organisms, such as *Mycoplasma pneumoniae* or *Chlamydophila pneumonia* [14]. They not only reside in the cytosol, but also in endosome, nucleus, and they may even be associated with Golgi apparatus or endoplasmic reticulum of host cells, as shown in Fig. 1A. This mechanism is especially relevant because most drugs remain in the extracellular space. Moreover, the few compounds with the ability to penetrate host cells, once inside the cell, are rapidly degraded or their concentration does not reach therapeutic levels [15]. But the main problem is that intracellular pathogenic microorganisms can also survive and reproduce inside phagocytic cells. Accordingly, these kinds of cells are the first to be "infected" and they act as a reservoir that drugs cannot reach. They protect pathogens from the treatment, favouring their intracellular replication and the spread of infection [15,16].

Regarding the development of new antibacterial molecules, it is slower than in the past [27]. Moreover, new molecules have problems even in phase I trials, due to drug degradation or inactivation at the site of infection [28]. Some drugs also have physicochemical limitations, such as low bioavailability, short half-life or variable absorption. To overcome these problems, high doses and frequent administrations have been established as conventional treatments. Such high antibiotic concentrations can cause severe side effects and even toxicity. This complicates compliance, thus increasing the likelihood of the development of drug-resistance [15,29]. Therefore, current research should focus on solving these problems and increasing the efficacy of available drugs by the use of targeting drug delivery systems.

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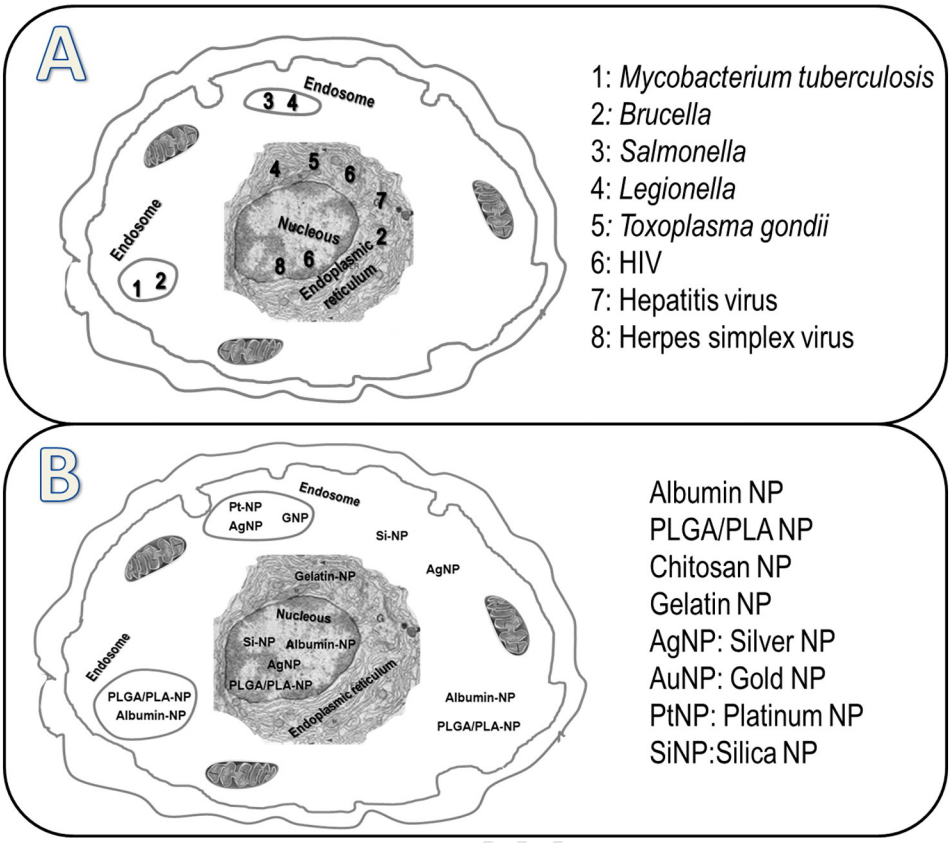

Fig. 1. A. Intracellular localization of different pathogens: 1: *Mycobacterium tuberculosis* [17,18]; 2: *Brucella* [17]; 3: *Salmonella* [17,19]; 4: *Legionella* [17]; 5: *Toxoplasma gondii* [17]; 6: VIH [17,20]; 7: Hepatitis C virus [17]; 8: Herpes simplex virus [17]. B. Intracellular distribution of different kinds of nanoparticles: Albumin NP [21]; PLGA/PLA NP [9,18,22,23]; Gelatin NP [20]; AgNP: Silver NP [24]; AuNP: Gold NP [25]; PtNP: Platinum NP [24]; SiNP: Silica NP [26].

According to the definition of the Paul Erlich "magic bullet" concept, the aim of drug targeting is to deliver drugs to the right place, at the right concentration, and for the proper length of time [30]. NPs allow drugs to be targeted specifically and to reach therapeutic intracellular levels, due to their sustained release depending on environmental conditions. They prevent unwanted interactions and drug degradation prior to reaching the target tissue or cell. At the same time, they optimize the physicochemical characteristics of drugs, allowing their clinical use or administration through more patient-friendly routes. In addition, they can carry different drugs in a single formulation, which is extremely useful in combating infections due to HIV or *Helicobacter pylori*, whose treatment is based on combinations of drugs [31,32].

3. Classification of nanoparticles

NPs can be classified either by the way in which they carry substances or by the characteristics of the matrix. Below, they are classified based on the type of material from which the matrix is made.

3.1. Organic nanoparticles

Organic NPs are the most studied type and they include liposomes, polymeric NPs, polymeric micelles and solid lipid NPs (SLNs). They account for more than two-thirds of the systems approved for therapeutic use in humans [33]. Their main advantage is that they are usually biodegradable and exhibit good compatibility. The compounds they are made of are broken down into biologically tolerated molecules, which are easily metabolized *via* the Krebs cycle. Hence they have minimal associated systemic toxicity [34,35], there are even some studies reporting cell viability outside the cytotoxic threshold [36]. Another advantage is that they can carry either hydrophilic or hydrophobic drugs.

However, they also have disadvantages such as low loading efficacy and drug loss during storage [35]. Although polymeric NPs and SLNs have better chemical and physical stability, they are unstable. Besides, their hydrophilic/hydrophobic characteristics favours their uptake by opsonization and rapid degradation [15,37–39].

Regarding toxicity, it is mainly due to the surface charge and presence of volatile organic solvents. Both *in vitro* and *in vivo* studies of organic NPs report only slight or no toxicity and when some alterations have been detected no important negative effects on the cells have been reported [36,40–43].

3.1.1. Liposomes

Liposomes are formed by a bilayer of phospholipids and their size varies from 20 nm, in the case of small unilamellar vesicles, to more than 100 nm for large and multilamellar vesicles [44]. They are classified based on their composition as niosomes, made from non-ionic surfactants; ethosomes, made from ethanol; bilosomes, from bile salts; or virosomes, from virus-derived molecules [45].

In basic research, the most common synthesis method is the dehydration–rehydration technique. This has a relative high loading efficiency in comparison with other methods such as reverse-phase evaporation or detergent depletion, all with lower encapsulation efficiency [46]. There are a large number of techniques optimized for industrial-scale production and also without the use of organic solvents [46,47].

Liposomes are the most widely developed NPs. In the field of antimicrobials there are formulation in preclinical studies, in clinical trials and even commercial applications like Ambisome® [35].

3.1.2. Polymeric nanoparticles

Polymeric NPs are composed of a polymeric matrix, which can be made of synthetic or natural polymers. They are prepared by several methods, such as solvent evaporation, spontaneous emulsification, solvent diffusion or polymerization [3,29,48]. It is crucial to define and control the synthesis conditions because these also affect the characteristics of the NPs obtained. The type of solvent used and their proportion have influence on the size [49] and the pH of the synthesis medium has influence on the release rate [50]. Likewise, there are different mechanisms for coupling them to lipophilic and hydrophilic drugs: covalent chemistry, hydrophobic interactions or entrapment [3].

The synthetic polymers most widely used are polyesters such as polylactide (PLA), polylactide–polyglycolide copolymers (PLGA) and polycaprolactones (PCL), and polyacrylates (PCA). The most common one is PLGA and several PLGA–drug delivery systems have been approved by the FDA [51]. Natural polymers such as alginate, albumin or chitosan are also used. In general, these polymers exhibit lower immunogenicity than synthetic ones [52]. Chitosan is the substance most commonly used because of its mucoadhesive and antimicrobial properties and the ease with which it can be modified chemically [48].

In the antimicrobial field they have been used to improve both efficacy [53] and pharmacokinetic parameters, such as half-life [54,55] or bioavailability [56,57] allowing better dosage schedules [49,50,53,57,58].

3.1.3. Polymeric micelles

Polymeric micelles are colloidal structures of block copolymers with polymers such as poly(butyl methacrylate) (PBMA), polystyrene (PLS), poly(lactic acid) (PLA) or poly(ethylene oxide)–poly(propylene oxide) (PEO–PPO). Polymers form a micellar structure spontaneously beyond the critical micelle concentration and the critical micellization temperature. Below them, they act as an inert material, however above them the chains become hydrophobic resulting in aggregation and precipitation [29,59,60]. The hydrophobic fragments form the spherical inner core and the hydrophilic ones the outer shell. The inner core must be in a solid state to incorporate drugs, if not the result will be an instant drug release [61]. Besides, a suitable polymeric micelle depends on the drug charge density and the polymer chain length in order to be a good drug delivery system [29,60,61].

The particle diameter is usually comprised within 5–100 nm particle size range. Size control depends on polymers chemical structure and is not dependent on preparation process which can be an advantage *vs.* other type of NPs [29,61]. Like other organic NPs polymeric micelles exhibit low toxicity risk because they disassemble in single polymer chains which can be easily excreted and exhibit no toxicity [59,61].

These nanoparticles are simpler in comparison to liposomes and polymeric NPs. These show greater stability and biocompatibility and are low-cost systems [29,60,62]. Thus, they are mainly used to improve aqueous solubility, intestinal permeability and site targeting [29] of antiviral [20,63] and antibacterial drugs [64].

3.1.4. Solid lipid nanoparticles (SLNs)

SLNs are made of lipids that are solid at body temperature, such as cetyl palmitate or salts of myristic acid. The method of synthesis usually involves heating to liquefy the lipids and allow them to undergo emulsification. Upon cooling, NPs separate out and can be filtered and dried readily. They are stabilized with emulsifiers and co-emulsifiers, such as polysorbates, poloxamers, fatty acid co-esters, lecithin and bile salts [39]. The amount of stabilizer used must be enough to prevent aggregation without reducing drug uptake [65].

SLNs are less toxic, more stable, easier to scale up, and more widely available than synthetic polymer NPs. Furthermore, the state of the lipids depends on the characteristics of the medium (temperature, pH, *etc.*), which allows better controlled release, safety, and efficacy [35,38,39].

There are many systems in preclinical studies in order to achieve increased target concentrations or sustained release of antimicrobial drugs [38,66–68].

3.2. Inorganic nanoparticles

Metallic NPs have been used in India for more than 2000 years, although the first scientific study was done by Faraday in 1857 [24]. They are made of different inorganic oxides and have different sizes, shapes, solubility, and long-term stability [69]. They are usually synthesized by chemical reduction of the metallic salt (gold/silver/silica/aluminium/titanium) with a reducing agent [70] and, depending on the reaction conditions — such as temperature, pH, reduction time or reducing agent concentration — their characteristics can be modified [24,71,72]. Choice of the reducing agent is very important in drug delivery because it acts as a link between the NP surface and the drug or biomolecule of interest [25]. Furthermore, it influences the loading capacity, the release, the aggregation, and the antimicrobial properties of drugs [24,73]. Inorganic nanoparticles can also be synthesized by "green" methods, using biological agents. The microorganism used can be bacteria, actinomycetes, yeast, fungi or algae, although the most common one is bacteria. Depending on the agent used, the mechanism of synthesis may be intra- or extracellular and this can also determine the characteristics of NPs, such as size, capacity to aggregate, or other properties [74,75]. Most methods developed for gold or silver nanoparticles employ *Pseudomonas* sp., *Bacillus* sp. and *E. coli*. Whereas to synthesize semiconductor NPs, yeasts, especially *Sacharomyces cerevisiae*, are more widely used. Fungi are also commonly used. They are easy to handle and they synthesize higher amounts of NPs than bacteria. These "green" methods are cleaner and more eco-friendly than chemical ones. However, they suffer from the problem of the extraction and purification of NPs because unwanted residue may produce adverse reactions [74,75].

Compared with organic NPs, metallic NPs can be smaller, with a size range between 1 and 100 nm, and their loading efficacy is much higher [69]. They are mainly distributed in the liver, spleen and lymph nodes [76]. Therefore they are very useful for treating illnesses whose target is the reticuloendothelial system (RES). However, they are not homogeneous, and they exhibit problems of aggregation, metabolization and accumulation [47,76–78]. Excretion is generally through the bile, which involves a slow and saturable pathway, so they may accumulate for long periods of time in the body [20,69,77]. Nevertheless, this depends on the type of metal used, because some metals have well-established physiological routes of absorption and elimination [79]. Also, they can induce toxic reactions. Their interaction with proteins can produce liver or skin damage, increased spleen weight, inflammation and alterations in RBCs [24,80–84]. The release of toxic ions and the stimulations of ROS and inflammatory cytokines intracellularly can produce immunotoxicity, cytotoxicity and genotoxicity both in healthy and infected cells [83,85]. Moreover, chronic toxicity such as nephrotoxicity, hepatotoxicity or pulmonary toxicity, can be produced by the accumulation of metallic NPs in these tissues [24,80–84].

Despite this, different *in vivo* studies have reported no apparent toxicity [79,81,83,86,87]. In any case, some toxicity problems could be decreased by chemical transformations or with lower NP concentrations. Changes on the surface of NPs, such as electrostatic surface charge or sulfidation as well as modifications in size help to decrease some interactions with proteins [83,88–90]. Nonetheless, although some knowledge about acute toxicity is available, issues such as metabolic processing, clearance, bioaccumulation and long-term effects remain to be elucidated.

3.2.1. Gold nanoparticles (AuNPs)

Some important advantages of these NPs are their large surface area, which allows a great number of drug molecules to be coupled, and the

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ease to quantify very low concentrations of both Au and the drug using different analytical techniques [91].

They have been used to target both drugs [76,91] and genetic material such as iRNA or DNA [92,93], which have been linked to AuNPs through Au–S or Au–amino bonds [76].

3.2.2. Silver nanoparticles (AgNPs)

AgNPs have antimicrobial properties themselves, which support the efficacy of antimicrobial treatments when they are used as carriers. Thus, their main therapeutic application is in the antimicrobial field [81].

Moreover, these NPs are also useful for the design of medical devices with a view to preventing infections. They have been used in trauma and dental implants, prostheses and bone cement, among other applications, as has been reviewed in depth recently [94].

3.2.3. Other inorganic nanoparticles

Other metallic NPs made of platinum, aluminium, zinc, titanium, palladium, iron or copper have also been developed. They have been used as carriers and can improve the therapeutic effect owing to their antimicrobial and/or magnetic properties.

NPs made of porous inorganic compounds, such as silica, aluminium and titanium, are grouped as ceramic nanoparticles. Silica is the most widely used material because of its biocompatibility and the ease of synthesis and modification [3]. Silica NPs have a large surface area with variable pore structures, sizes and shapes that can be synthesized easily [95]. The main advantage of these NPs is that they can carry large amounts of drug [96].

Copper NPs are currently attracting attention owing to their antibacterial and antifungal properties and their low price. Like other metals, the accumulation of copper can be toxic. But unlike silver or gold, there are copper-transporters in the body that help to control copper homeostasis. Notwithstanding, these NPs have problems of agglomeration and rapid oxidation, and hence require the use of a stabilizer. Anyway, the stabilizer concentration must be low because it can modify the shape and size of NPs [97].

Iron oxide NPs (SPION) have been developed mainly for diagnostic and theranostic purposes owing to their magnetic properties [25,98]. They have been used to detect microbial infection in a fast and sensitive manner [98] and to target and release drugs *via* external magnetic stimulation [59].

Quantum dots are metallic NPs with a core or shell made of semiconductor materials, such as cadmium or zinc. They have unique optical properties that increase the possibilities of detecting and tracking them. In this sense, they can be observed by fluorescence resonance over extended periods of time [84]. They have good perspectives for future biomedical applications, although with the problem of toxicity due to the presence of heavy metals. Thus, their success will depend on the dose required to reach efficacy or allow signal detection without damage to cells [30,69,84,99,100].

3.3. Other nanocarriers

Currently, new nano-systems are being developed. One of the most popular technologies involves carbon nanostructures, such as nanotubes. Their geometry and their electrochemical, thermal and spectroscopic properties, together with the wide variety of structures and surface modifications, make them a good choice for use in nanomedicine [84]. Their small size enables them to interact with the microbial cell surface, disrupting its membrane integrity, metabolic processes and morphology [101]. In order to increase the efficacy of antimicrobial drugs, these nanocarriers have been used with drugs such as amphotericin B and pyrazinamide, among others [101–103].

Other recently developed nanocarriers are nanobubbles. These are gas-filled colloids wrapped by a polymer, protein and/or surfactant. The composition of the shell has a strong influence on their stiffness and resistance to rupture, as well as on recognition and clearance by the RES. Their size ranges from 200 to 500 nm. Release is activated by ultrasound so they can be optimal systems for theranostics or for targeting drugs to specific sites [104]. Although they are mainly used in the fields of oncology or gene delivery [104–106], they also have antimicrobial properties due to the mechanical impact of their explosive expansion [106]. However, studies addressing the toxicity of nanobubbles have revealed considerable liver and kidney toxicity and cytotoxicity [107,108], though the use of oil components helps to decrease it [108].

4. Pharmacokinetic behaviour of nanoparticles

The pharmacokinetic behaviour of NPs depends on many aspects. The administration route determines whether the action will be systemic or local. Also, the physicochemical characteristics of NPs and the ligands used affect uptake. Finally, it should be also taken into account that their chronic toxicity is influenced by the elimination pathway.

4.1. Route of administration

If the target is the liver or spleen, i.v. route is the best choice [109]. Thus, the biodistribution of the antiretroviral lamivudine was modified using chitosan-NPs. They mainly targeted the liver and spleen, and in addition lamivudine concentrations were higher in the lungs and lower in the kidneys, where the drug is cleared [52].

The local administration route chosen depends on the target region. In the case of muscle or skin targeting, the route used can be topical, intramuscular, intradermal or subcutaneous, whereas oral or intranasal administration is used in the case of targeting the mucosa. The advantage of these routes is that they reduce systemic toxicity [110]. In this case, mucoadhesive NPs are more useful because they increase the residence time at the absorption site [65]. Taking into account this characteristic, different NP systems, such as liposomes and polymeric NPs, have been designed for treatment of pulmonary infections through inhalation [111].

4.2. Distribution of NPs

4.2.1. Passive targeting: physicochemical NP characteristics

Passive vectoring is related to the inherent capacity of phagocytic cells when they recognize substances foreign to the organism. Uptake may occur through different mechanisms: phagocytosis, macropinocytosis or endocytosis. The pathway mainly depends on size, so the most common one is by endocytosis, owing to the typical small size of NPs [8,29,37,47].

The physico-chemical characteristics of the NP surface also play a decisive role in uptake and other important processes like biodistribution or clearance.

Size may affect clearance, biodistribution and uptake. The smaller the NPs, the slower the uptake rate by phagocytic cells, and faster biodistribution due to rapid dissolution [24,38,112]. Small size is better for reaching the lymphatic system [113], preventing uptake by the RES [114] and guiding distribution inside the cell [26]. Moreover, small size is sometimes necessary for NPs to circulate through capillaries, sinusoids, tissue structures and membrane or mucosa pores in order to reach extra- and intracellular compartments [26,77,86,115]. The size influences different parameters; thus smaller sizes increase the drug loading efficiency and the antimicrobial effect, lowering MIC [116–118]. It also affects the NP biodistribution [119], so the election of size used depends on disease targets and drug characteristics.

The zeta (ζ)-potential affects both biodistribution and uptake by cells. Interactions with the proteins of the blood, tissues or mucosa, and with the cellular membrane depend on the charge. Regardless on the kind of NPs, these interactions will be responsible for the amount and type of proteins adsorbed; the adhesion or not to the mucosa and

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for how long; the endocytosis mechanisms; and biodistribution [24,77, 84,109,115,119–121]. Macrophages and other cells display a negatively charged surface, so cationic NPs undergo better uptake than zero or negatively charged NPs [62,120]. In HIV infection, infected cells express positively-charged proteins (viral protein gp120), and hence anionic NPs provide better interaction [114]. The ζ-potential also influences the antimicrobial effect. NP interactions with the cell membrane modify its permeability and cytoplasmic flows, killing the pathogens or infected cells [122]. Moreover, in fungal infections, cationic NPs change the ζ-potential of the cell surface, which results in fungal cell death [38].

Regarding other properties, the increment of hydrophobicity decreases the diffusion kinetic in mucus [115]; favours cellular uptake, owing to interactions with the lipids of the cell membrane [120]; and influence output from endosome and drug release [29,123]. Moreover, this characteristic plays an important role in clearance. Hydrophilic NPs show fewer interactions with opsonins and the complement system, and hence undergo slower clearance from the blood than hydrophobic ones [47,77].

4.2.2. Active targeting: ligands for specific uptake

Distribution and uptake can also be driven by active vectoring. This involves the addition of specific compounds (ligands) to the NP surface. Such ligands favour interactions with the cell membrane, thus enhancing the recognition of NPs by cells [15,22]. They can be attached *via* a spacer, such as polyethylene glycol (PEG), or directly on the surface. Different studies have shown that ligands such as saccharides, cell penetrating peptides or transferrin among others, are useful for targeting to specific tissues (Table 1). So, the ligand is chosen depending on its stability and selectivity as regards the target cells. Other factors such as availability and interactions with immunologic cells or with membranes are also taken into account.

If the target cells are macrophages or phagocytic cells, the best ligands are saccharides because they interact with lectin receptors on the surface of phagocytic cells. Thus, mannose-NPs have been reported to target isoniazid to alveolar macrophages [124] and zidovudine to lymph nodes [125]. In the case of zidovudine, the use of NPs led to lymph node concentrations 28-fold higher than with the free drug [125]. By contrast, in order to prevent the clearance of NPs by the RES, ligands such as PEG or cell-penetrating peptides (CCPs) reduce the interactions with opsonins [69,77,109,126]. However, if the target is infected cells, the ligand should be chosen according to the main element of the microbial or viral surface. For example, in the case of the influenza A virus the main glycoprotein is haemagglutinin [113, 127]. Accordingly, this compound or other similar ligands, such as sialic acid, interact with viral receptors present on the infected cells. This theory has already been applied in vaccines, such as Inflexal® V [44] and in virosomes developed to treat hepatitis B intranasally [112].

To target other cells, such as hepatocytes or non-parenchymal liver cells, glycosylation of the surface is also useful [128]. However, the most common ligands for specific cell targeting are CPPs or antimicrobial peptides (AMPs) [129,130]. These are relatively short cationic peptides (10–40 amino acids) that facilitate interaction with phospholipid membranes and depending on the nature and composition of the primary sequence, their activity may vary [130]. The most common are TAT, penetratin, transportan, polyarginine and MPG [69].

If the target is the central nervous system, different methods can be used to favour passage across the BBB. The use of apolipoproteins (apo A1, B, or E) or compounds in which these are adsorbed like polysorbate 80, helps drugs to reach the brain through lipoprotein receptors [132]. Thus, it was found that polysorbate 80-polymeric NPs reach the brain faster and the uptake is 35% higher than uncoated NPs [133,134]. Other receptors that also help NPs to cross the BBB are insulin or transferrin receptors [132].

The use of transferrin or insulin receptor alpha monoclonal antibody (83-14 MAb) enhances the uptake as much as 10 times higher than the free drug or uncoated NPs [135,137].

All these ligands also play an important role in intracellular NP biodistribution. Depending on the ligand, the carrier may remain within the endosome or escape from it to reach other organelles in the cytoplasm, such as the nucleus [21]. Fig. 1B shows some examples of NPs intracellular distribution.

4.3. Elimination of nanoparticles

Following complete drug release, NPs must exit the cell if they have not been degraded. The exocytosis rate depends mainly on NP composition, ligands and surface properties. Cationic NPs have a slow rate of exocytosis from macrophages because they agglomerate intracellularly [88]. By contrast, PEG NPs have the highest exocytosis rate because they have very few interactions with intracellular proteins [138].

Eventually, NPs are excreted from the body. This rarely occurs by urine and only in the case of NPs smaller than 5 nm. Bigger NPs are reabsorbed and trapped in the collagen network of the glomerular basal membrane, where they are taken up by macrophages [47,77]. NPs smaller than 200 nm are mainly excreted in the bile. This process is slow and saturable, and hence NPs may accumulate. However, some studies have addressed clearance sensitization after an initial dose, called accelerated clearance. This features a first phase of induction and decreases between 2 and 4 weeks later. The reaction mainly occurs with naked NPs. But according to some clinical trial results, when these NPs are coupled with ligands or drugs, this effect is reduced or even disappears [77,139].

5. Drug release

Once at the target site, NPs must release the drug. Some polymers are able to modify their structure in a reversible way, depending on specific stimulus. Thus, they control and self-regulate drug delivery, which may occur immediately or be sustained over a period of time [59]. The stimulus may involve physiological conditions such as pH, hydrophilic/hydrophobic equilibrium, ionic strength or presence of specific molecules. The medium pH can modify release kinetic, that may occur rapidly or very slowly, thus protecting the drug from degradation in unwanted conditions [28,50,59]. By contrast, in only slightly acid environments NPs can be destroyed because of the hydrophilic/hydrophobic equilibrium and the whole amount of the drug is released [140]. Similarly, ionisable polymers can modify their size, solubility and fluorescence due to changes in ionic strength [59].Other stimuli may involve the presence of proteins such as blood proteins, pancreatic esterases, proteolytic enzymes or even the virulence factors of bacteria [61,77, 141–143].

Table 1
Most promising ligands for targeting of anti-infective drugs.

Ligand	Target	Reference
Saccharides	Macrophages or phagocytic cells	[124,125]
Polyethylene glycol (PEG)	Avoid RES	[69,77,109,126]
Haemagglutinin or similar	Cells infected by influenza A virus	[113,127]
Glycosylation	Hepatocytes or non-parenchymal liver cells	[128]
Cell-penetrating peptides (CPPs)	Specific cells with this peptides	[69,129–131]
Antimicrobial peptides (AMPs)		
Apolipoproteins	Central nervous system	[132]
Compounds that adsorb apolipoproteins	Central nervous system	[133,134]
Transferrin	Central nervous system	[135,136]
Insulin	Central nervous system	[137]

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The stimuli may also be external, such as electricity, magnetic fields, ultrasound or light which strengthen the drug release [59,144]. Moreover, the stimulus can be used at the same time as treatment. Stimulation of metallic NPs by light is used as photothermal antimicrobial treatment to avoid the use of drugs against *Staphylococcus aureus*, *E. coli* and *Bacillus anthracis* [145,146].

6. Special applications

6.1. Nanoparticles against pathogens

In general, drugs present better efficacy when they are carried by NPs, regardless of the type of drug and pathogen. Both metallic NPs and organic ones have raised the antimicrobial activity of different kinds of drugs (antimicrobial, antiviral, antifungal and antiparasites) [49,91,147–149] as well as other agents [150], encouraging the development of new therapeutic systems against pathogens.

This is a consequence of the targeting effect of NPs that increase intracellular drug concentrations until even 10-fold [35,53,150]. Thus, drugs reach specific infected organelles or tissues [19] targeted by naked NPs or NPs with ligands [131,135,136]. By using NPs, problematic tissues such as deeper fungi infected skin layers [151,152] or infected brain by bacteria, virus or leishmania [67,99,137,153,154] have been reached easily. Besides, NPs can reach these tissues by more patient-friendly routes like intranasal [155]. The lower drug accumulation in non-targeted tissues also allows for a decrease in side effects and toxicity at the same time. In this way, drugs like acyclovir, lamivudine, amphotericin B, primaquine or artemeter have reduced their haematological problems and nephrotoxicity by coupling with organic NPs [43,52,56,150,156,157].

Besides improvement of drug efficacy, the use of NPs also allows more patient-friendly regimens. The dose can be lowered, as in the case of antifilarial drugs or chloroquine liposomes [153,158]. The dosage intervals can be increased until 24 h or even 10 days with NPs like liposome [158], polymeric NP [58], polymeric micelles [159] and SLN [68]. This increment of the interval can be due to a longer half-life or longer residence time. The half-life of antiviral [55], antifungi or antiparasite drugs [54] can be increased even more than two-fold because NPs protect them from degradation. In fact, detectable concentrations of antiretroviral drugs have been found 28 days after a single intraperitoneal dose [31]. Regarding the residence time, this is also influenced by the mucoadhesive properties of NPs. For that reason, chitosan NPs can increase three-fold precorneal residence time of amphotericin-B [160]. Finally, different administration routes can be used, such as oral [20,38,66,153], ocular [160], subcutaneous or transdermal [151,152] due to the better drug bioavailability after NP formulation.

6.2. Nanoparticles against drug-resistant pathogens

The antimicrobial resistance to anti-infective drugs is currently increasing, not only in bacterial infections but also in viral and fungal ones, such as HIV and systemic candidiasis [11]. The use of NPs as carriers allows recovering drug efficacy by overcoming some resistance mechanisms, such as drug degradation by β-lactamase [76,161], efflux pumps [122,162] or wide cell walls [122,163], as it is reflected in Table 2.

Besides increasing the efficacy of drugs, different studies have shown lower probabilities of inducing resistance after treatment with drug-NPs [12,58,76]. NPs have multifunctional mechanisms to attack bacteria and for this reason, resistance after treatment with free drug is significantly more common than after treatment with drug-NPs [58].

6.2.1. Nanoparticles against bacterial biofilms

Biofilms are compact bacterial clusters that adhere to inert or biological surfaces. They rapidly produce an extracellular polymeric matrix that is hard to penetrate, thus increasing the likelihood of drug resistance. Moreover, they are usually localized at sites difficult to reach, so current treatments are rarely successful. Today, they are responsible for most microbial infections and the best option, besides prevention, is to remove the colonized tissue or implant [34,173–175].

Some kinds of drug-NPs are able to cross the barrier and eliminate biofilms. For example, only one dose of ciprofloxacin-PLGA NPs reduced the *P. aeruginosa* biofilm mass, size and live cell density by more than 80%, and repeated administrations prevented new formations [176]. Table 3 shows different kinds of drug-NPs with efficacy against bacteria and fungi biofilms. Recently, this theme has been reviewed focusing on liposome and polymeric NPs [34].

6.2.2. Nanoparticles for bone infections

Osteomyelitis is an infection of bones and can cause serious impairment to patient mobility. The most common responsible bacterium is *S. aureus*, which adheres to and persists within osteoblasts [183]. The use of NPs tagged to antibiotics is very helpful to treat this infection. They facilitate the movement of antibiotics such as nafcillin, vancomycin and daptomycin across the osteoblast membrane and ensure better drug delivery to the intracellular bacteria [183,184]. Moreover, they favour drug targeting by the use of ligands like alendronate or calcium with high affinity by the bone tissue [185]. Another advantage of NPs is sustained release which can last years [186], improving the therapeutic regimen in this chronic illness.

6.2.3. Nanoparticles for pulmonary infections

Infections by *P. aeruginosa* and its resistant strains are common in cystic fibrosis patients, causing 90% of deaths [187]. Tuberculosis is

Table 2
Drug-NPs effective against resistant strains.

Pathogen	Resistant to	Drug coupled	Nanoparticle	Ref.
Fluconazole resistant *C. albicans*	Fluconazole	Fluconazole	AgNP	[164]
Resistant strains of *Plasmodium* sp.	Chloroquine	Chloroquine	Liposome	[150]
HIV-infected cells with drug efflux pumps	Multiple drug resistances	Nelfinavir and saquinavir	Polymeric micelles	[162]
Methicillin-resistant *S. aureus*	Multiple drug resistances, mainly to beta-lactam, including penicillins and cephalosporins	Penicillin	Silica NP	[165]
		Streptomycin	Chitosan NP	[166]
		β-Lactam, and penicillin	Liposome	[167]
		Penicillin	PLA NP	[168]
		Ampicillin	AuNP and AgNP	[76,161]
Ampicillin-resistant forms of *E. coli*	Ampicillin	Ampicillin	AuNP	[76]
Ampicillin-resistant forms of *P. aeruginosa*			AuNP and AgNP	[161]
Vancomycin-sensitive and -resistant *S. aureus* strains	Vancomycin	Vancomycin	Chitosan NP	[163]
			AuNP	[76]
Vancomycin-resistant enterococci	Vancomycin	Vancomycin	Liposome	[169]
			AuNP	[170]
Resistant strains of *P. aeruginosa*	Polycationic antibiotics	Polymyxin B	Liposome	[171]
Tetracycline-resistant *E. coli*	Tetracycline	Tetracycline	ZnO-PEI NP	[172]

Please cite this article as: H. Zazo, et al., Current applications of nanoparticles in infectious diseases, J. Control. Release (2015), http://dx.doi.org/10.1016/j.jconrel.2016.01.008

Table 3
Nanoparticle systems used for prevention and treatment of biofilms.

Bacterial biofilm	Drug coupled	Nanoparticles	Ref.
C. albicans	Terpinen-4-ol	SLNs	[177]
C. glabrata	Nystatin or Chlorhexidine	AgNPs	[178]
E. coli	Ciprofloxacin and levofloxacin	PLGA/PLC NPs	[179]
	Nafcillin and levofloxacin	PLGA NPs	[180]
S. aureus	Penicillin	Liposome	[181]
	Vancomycin	Chitosan NPs	[163]
P. aeruginosa	Ciprofloxacin	PLGA NPs	[176]
P. fluorescens	Ceftriaxone	AgNPs	[148]
S. mutans, *F. nucleatum*, *A. actinomycetemcomitans* and *P. gingivalis*			
S. mutans, *S. sobrinus*, *F. nucleatum*, *A. actinomycetemcomitans*, *E. faecalis*	Chlorhexidine	SiNPs	[182]

SLN: solid lipid nanoparticles; AgNP: silver nanoparticles; PLGA/PLC NP: polymeric nanoparticles; SiNP: silica nanoparticles

also becoming a frequent pulmonary infection because of resistant strains and the infection of immunosuppressed and HIV patients [188]. In order to enhance current treatment, researchers are now focusing on the use of different kinds of NPs to improve efficacy and at the same time provide more comfortable administration routes and better dosage schedules [67,159,187,189].

Inhalation is the best route to target drugs to the lungs. The efficiency of inhaled therapies depends on the characteristics of both the aerosol and the patient. The inhalation technique and the air flow capacity of the patient are important in this respect; in fact, the latter is normally limited in obstructive and restrictive ventilation disorders [111,187]. Efficiency also depends on the region of sedimentation, which is determined by physiological structures and aerosol characteristics. Particles between 1 and 5 μm deposit in the primary and secondary bronchi and particles smaller than 1 μm reach the tertiary bronchi and bronchioles. Particles smaller than 0.5 μm are deposited in the alveoli, but if they have very low mass they may be exhaled during administration. Particles with a low density of ~0.4 g/cm^3 and diameters >5 μm have been shown to be more efficiently aerosolized than smaller nonporous particles and avoid phagocytic clearance [187]. Both aerosol and NPs characteristics are important to prevent exhalation and to ensure that NPs will be deposited in the region of interest. Important aerosol parameters are temperature, the type of nebulization, and the presence and type of diluents, such as the mannitol, leucine or lactose used in some NP formulations. Relevant NP characteristics are size, density and geometry [111, 159,187,190]. Inhaled nanoparticles could be exhaled during administration due to their extremely low mass. This problem has been solved by formulating nanoparticles into inhalable microaggregates that have been prepared for amikacin, ciprofloxacin, tobramycin, vancomycin and rifampicin. These aggregates persist for longer in the lungs and show better lung deposition than unaggregated nanoparticles [191, 192].

The NPs administered must also be able to avoid mucociliary clearance from the airways. One way to increase the residence time is by using mucoadhesive NPs, such as chitosan NPs, but also by functionalization with lectin, wheat germ agglutinin (WGA) or saccharides such as mannitol, trehalose or bovine serum albumin (BSA). Both techniques help to deepen and increase the deposition, at the same time favouring the uptake of alveolar macrophages due to the interaction with mannitol and lectin receptors in the alveolar epithelium [111,159,193]. The greater deposition and the sustained release of drug nebulized as NPs allow pharmacokinetic parameters, such as the half-life or bioavailability, to be enhanced and thus the time between administrations to be increased [159]. However, many *in vitro* studies have been carried out in the absence of a mucus barrier, taking into account only the characteristics of NPs as sustained release and interaction with biological membranes. Accordingly, in some *in vivo* studies the improvement is not observed or may even be increased or decreased due to the different affinities and interactions of the free antibiotic and the NPs with the mucosae [143].

Moreover, in pulmonary infections the mucus is sometimes altered, forming plugs that may obstruct airways, inhibiting drug deposition in peripheral regions and favouring the formation of biofilms. On the other hand, this alteration has the advantage of a slow and defective clearance, which increases the residence time of drugs used in the treatments [143,187]. Many antibiotics have been formulated for nebulization either as drug solution or coupled to NPs [190]. Drug-NPs present greater extent of deposition and better antimicrobial and antibiofilm efficacy. This has been reported by many authors, regardless of the drug used and the type of NP [159,171,190]. An example of this is the inhaled liposomal formulation of amikacin Arikace®. It is now in Phase II and III clinical trials to treat different lung infections [194]. Similarly, a nebulised liposomal formulation of ciprofloxacin has been patented as Lipoquin™ [195].

In the case of immunocompromised patients, both bacterial and fungal infections increase mortality and morbidity rates by more than 50% [190]. Current treatments administered through oral and/or intravenous routes, may lead to systemic toxicity. In order to decrease drug toxicity, studies are also focusing on the development of inhaled formulations of the current treatments or new ones such as NPs [190]. The advantage of the use of NPs is that they achieve better antimicrobial and antifungal activity but elicit lower toxicity [111].

6.2.4. Nanoparticles for gastric infections (*H. pylori* infection)

H. pylori is the most important and common infection in the GI tract. Since 1994 it has been recognized as a carcinogen, hence the huge importance of its eradication. The problem is the difficulty encountered by drugs to cross the gastric surface and reach the bacterium [196]. The use of NPs as carriers helps to circumvent these problems. NPs with mucoadhesive properties interact with mucin and infiltrate better through cell–cell junctions to the intercellular spaces where *H. pylori* infection resides [28,48,196]. Thus, they increase the residence time in the stomach and allow sustained release of drugs, increasing efficacy and the time required between administrations [197–199]. Moreover, the affinity of the bacterium to specific carbohydrate receptors can be used to design ligands, like fucose, for better bacteria targeting. By this way, the drug is released directly into the site of infection increasing their efficacy and decreasing side effects like gastrin inflammation [200].

Another problem for *H. pylori* eradication is the two bacterial forms that it can adopt, and therefore the possibility of the emergence of drug resistance [196]. Formulations such as linoleic liposomes have been developed to kill both the spiral and coccoid forms of the bacterium, and even metronidazole-resistant strains [201].

Currently, the treatment against *H. pylori* involves the concomitant use of a proton pump inhibitor, clarithromycin and amoxicillin, for 7 to 14 days, twice a day [202]. All these drugs together can be included in a single NP formulation, which also offers better dosing schedules and efficacy than current treatment.

6.3. Naked nanoparticles as anti-infective agents

In the last 10 years, publications addressing the use of nanoparticles as anti-infective delivery systems or as antimicrobial agents themselves have increased more than four-fold (Fig. 2A). In fact, there are more researches about NP as antimicrobial agents themselves, primarily as treatment of drug-resistant bacteria (Fig. 2B). When an antibiotic is coupled to antimicrobial NPs, in most cases the efficacy against sensitive bacteria is higher than with the free drug or the NPs alone. However, for the treatment of resistant bacteria, naked antimicrobial NPs have the

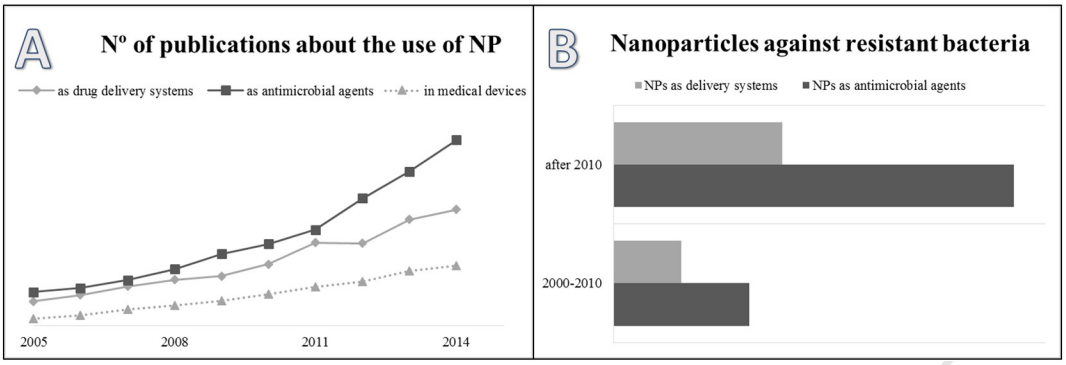

Fig. 2. A. Publications about the uses of nanoparticles. B. Publications about the use of nanoparticles against resistant bacteria. Source: Medline.

same or greater efficacy than the free drug or the drug-NPs. Thus, it has been reported that the combination drug-AgNPs against sensitive bacteria improved efficacy of the drug in 90% of cases, but only in 15% of the cases against resistant bacteria [203]. Moreover, naked NPs can also eliminate biofilms. AgNPs, ZnONPs or SPIONs are able to eradicate the bacterial cluster and also inhibit the formation of new ones [122].

The antimicrobial properties of some types of NPs, mainly metallic ones, have been demonstrated in both *in vitro* and *in vivo* studies against Gram-negative and -positive bacteria, as well as resistant strains. Their antimicrobial mechanism and efficacy depends on the size, shape, ζ-potential, ligands, and kind of material used [73,78,98,101,204]. AgNPs are the most widely studied, but there are other ones with antimicrobial properties such as copper NPs, carbon NPs or chitosan NPs (Table 4).

AgNPs exhibit good antimicrobial properties against bacteria and other microorganisms with a broad spectrum of action [12,78,98,217]. They are not substrate for multidrug efflux pumps, so they can overcome this mechanism of resistance [207]. They kill bacteria through various mechanisms which inhibit or prevent the development of resistance. These NPs attach to the cell membrane, damaging it and increasing its porosity. In addition, once inside the cell the release of silver ions generates free radicals and increases reactive oxygen species (ROS) level. These alterations inhibit respiratory enzymes and evoke inflammatory responses, which finally induce apoptosis [12,175,210]. In this way, AgNPs can exhibit even higher antimicrobial activity than antibiotics such as gentamicin or vancomycin against *P. aeruginosa*, *S. aureus* or MRSA [218].

They also exhibit antiviral activity against: tacaribe virus, poxviruses, respiratory syncytial virus, herpes simplex virus, influenza virus, rotavirus, feline calicivirus and even hepatitis B virus (HBV) and human immunodeficiency virus (HIV) [78,219,220]. The mechanisms of inhibition depend on the virus, but they can be summed up in two types: inhibition of binding with the host cell and destruction of the viral membrane [219].

Metal NPs made of copper, zinc or titanium also show good antimicrobial properties and they are more cost-effective, more stable and have less virulent effects on human and animal cells than AgNPs [12,98]. Their antimicrobial mechanism is based on the peroxidation of lipids in the membrane and the release of ions. This modifies cell homeostasis and increases ROS production, damaging amino acids and DNA, which causes the death of the bacteria [98,175]. Copper and zinc oxide NPs have better efficacy against Gram-positive bacteria. By contrast, titanium oxide NPs have better efficacy against Gram-negative bacteria [98,175].

Finally, other kinds of NPs with antimicrobial properties are those made of carbon or chitosan. Carbon NPs have shown antimicrobial activity in *in vitro* studies, but there are few studies addressing their toxicity and activity *in vivo* [101]. Chitosan is a natural polymer with a broad spectrum of antimicrobial activity, mainly against viruses and fungi but also against bacteria. Their efficacy depends strongly on the molecular weight of the chitosan used. Chitosan NPs have many advantages over metallic NPs, such as their low toxicity and broad spectrum of activity. The antimicrobial mechanism involves binding to the surface and modifying the membrane. However, they also inhibit the activity of enzymes by penetrating the nucleus and inhibiting RNA and protein synthesis [12,48,98].

An emerging problem is that despite their multiple antimicrobial mechanisms, there are some bacteria that are becoming resistant to NPs [76,149]. Some studies have addressed the resistance of some kinds of bacteria to NPs made of silver, copper and gold [76,175,221], even after only one dose [222].

Table 4
Metallic NPs with antimicrobial properties.

Metallic NP	Microorganism target		Ref.
	Bacteria	Other	
Copper NP	*S. aureus*/*S. epidermidis*/*MRSA*	*C. albicans*/*C. parapsilosis*	[205]
AuNP		*Candida* clinical isolated strains	[117]
		C. albicans/*C. glabrata*/biofilms	[206,207]
	S. enterica		[73]
	S. flexneri		[73,208]
	L. monocytogenes		[73]
	S. aureus	MRSA	[73,208–211]
	S. typhimurium		
Silver NP	*S. typhi*		[73]
	S. flexneri		
	L. monocytogenes		
	E. coli		[208–211]
	K. pneumoniae		[210,211]
	MDR strains of *P. aeruginosa.*	Biofilms	[211,212]
	B. subtilis		
	M. luteus		[208]
	V. cholerae		
ZnO NP	MDR strains		[172]
SPION		MRSA biofilm	[213,214]
	Staphylococcus strains		[215]
Al_2O_3 NPs	MRD clinical isolates of *E. coli*		[216]

NP: Nanoparticles; SPION: Superparamagnetic iron oxide nanoparticles; MRSA: Methicillin resistant *S. aureus* strains; MDR: Multi-drug resistant.

6.3.1. Medical devices with nanoparticles

Microorganisms such as *S. aureus*, *Enterococcus faecalis*, *E. coli*, *P. aeruginosa* or *K. pneumoniae* grow on the surface of medical devices such as catheters, dental or orthopaedic materials, and wound dressings. The antimicrobial properties of nanoparticles against them are

very useful to prevent these infections and the development of biofilms. The impregnation of these devices with NPs prevents the growth of microorganisms for at least 30 days, even after they have been washed [223]. Many types of NPs are used such as magnesium fluoride NPs [224], Ag-hydroxyapatite (HA) NPs [225], chitosan NPs [226], ZnO NPs [227], and mesoporous silica NPs [228], although the most widely used are AgNPs.

The first impregnated medical devices were prosthetic heart valves coated with AgNPs, but this caused haematological side effects [78]. Accordingly, they have been coated with chitosan NPs which also have antimicrobial properties but not haematological toxicity [226]. AgNPs have also been used to coat other catheters, such as venous, external ventricular drain or urinary ones [223,229,230]. According to the preclinical studies, NPs can reduce bacteriuria and biofilm formation [225] and prevent problems such as catheter-associated ventriculitis (CAV) or infections (CRI) [231–233]. However, in a clinical trial, the use of AgNP impregnated central venous catheters (CVCs) did not show reduction in rates of infection or colonization in comparison with conventional ones [234]. This controversy in clinical trials, together with conflictive results about toxic alterations, supports the need for further research [235,236].

Odontology is another field where the most common complications are due to infections. The incorporation of metallic NPs in endodontic fillings or composite resins increases the antibacterial effect [227,237]. NPs are also impregnated in adhesives [78,227] and titanium implants [237] to prevent biofilm formation. Titanium implants are also common in orthopaedic surgery, with the same problems. To avoid infection and biofilm adherence, naked NPs [238–242] or antibiotic-NPs [243] are added to the titanium oxide surface. The antibacterial efficacy, even against biofilms, and the successful biointegration of this kind of material have been demonstrated in *in vitro* and *in vivo* studies [238,240,241,243]. Also, with a view to decreasing post-operative infections in orthopaedic surgeries, bone cements have added NPs to their composition, with no modifications of their mechanical properties [244]. Different kinds of NPs have been used, ranging from polymeric [184,245] to silica NPs and AgNPs [246]. For the latter ones, it has been pointed out that their concentration must be as low as 0.1% w/w in order not to modify the mechanical properties [247] and to prevent cytotoxicity in osteoblasts and osteoclasts [248].

Other impregnated medical devices are dressings used to treat wounds such as chronic ulcers, toxic epidermal necrolysis, and burns [236]. In fact, there are several commercial products impregnated with silver NPs available: Acticoat™ (Smith & Nephew Inc., Hull, UK), Aquacel® Ag (Convatec Inc.), PolyMem Silver® (Ferris MFG Corp., Burr Ridge, IL, US) and SilvaSorb™ (Medline Industries and Acry Med). These systems have antimicrobial and anti-inflammatory properties, and they also help to accelerate re-epithelialization thanks to the AgNPs included [78,236,249]. The problem is that resistant bacteria have already been isolated [221], so the research about these systems should continue.

6.4. Nanoparticles as vaccines

Prophylactic vaccination is one of the most successful medical interventions to prevent and treat infectious diseases [44,113]. Modern vaccines are recombinant or purified proteins or peptides of the corresponding pathogen, essential to the stimulation of the immune response [45]. However, they have poor immunogenicity and little effectiveness in the long-term. The immune response can be improved by using NPs that can themselves be adjuvants [44]. The CAF01 liposomal system has been used as adjuvant in both tuberculosis (TB) and HIV-1 vaccine inducing a long-lasting memory response (clinical trials respectively: NCT00922363 and NCT01009762) [250,251]. Similarly, virus-like particles (VLP) can stimulate both innate and adaptive immune responses [252]. So they have been used as adjuvant in vaccines like human papillomavirus vaccine Gardasil® (NCT00157950) [251,253] or HIV vaccine Dermavir® (NCT00712530) [251,254].

NPs can also act as carriers of adjuvants such as viral glycoproteins, toll-like receptor (MPL®) or protein fractions (QS21). This technique has been used in Hepatitis A vaccine Epaxal®, influenza vaccine Inflexal® V, malaria vaccine RTS,S/AS01 and leishmania vaccines. This way, these vaccines are safer and induce strong, long-life and protective immune response [62,255–259]. Furthermore, when antigens are being carried by NPs, they are protected from the aggressive environment. Thus, NPs allow reducing the amount of antigen needed and frequency of booster vaccinations [45].

The time taken by the antigen and adjuvant to enter cells is another important factor in the immune response. The adjuvant has to reach the cell before or at the same time as the antigen in order to have a good response [113]. The use of NPs as both adjuvant and adjuvant carrier ensures that the timing is correct.

Another advantage of the use of NPs is that they increase the possibilities of using more patient-friendly administration routes, such as the oral, intranasal or transcutaneous ones. Mucosa is the first line of defence, so that NP mucosal vaccines protect the host from infections even before the pathogen reaches the systemic circulation. But in case pathogen reaches it, systemic antibody production is also activated by the mucosal immune system [44].

NPs also modulate the immune response achieved or allow achievement of the immune response needed. This way subcutaneous hepatitis B vaccine induces strong humoral but negligible mucosal immunity, while intranasal glycol-chitosan-NPs stimulate both immune responses strongly [260].

Oral vaccination is a comfortable route which can trigger mucosal and systemic immune responses, and the intestine is the mucosa lined with the highest number of immune cells [44,127,261]. The problem is that oral vaccines must avoid degradation in the gastrointestinal tract and fast clearance, so they normally require many large multiple doses [127]. These problems can be circumvented by encapsulating the oral vaccine in NPs. The NPs protect the antigens from degradation and increase the drug residence time. By this way, tetanus toxoid encapsulated in bilosomes (resistant to the GI tract) enhances the efficacy of administration through the oral route and efficacy is even higher than that of the free i.m. vaccine [262].

Intranasal administration is also another comfortable route that in comparison with the oral one requires fewer antigens and elicits better systemic responses. However, it has other problems like fast clearance and poorly reproducible dosing [44]. The use of mucoadhesive NPs helps to overcome these features with higher levels of mucosal, systemic and cell-mediated immunity response, so different systems such as chitosan-PLGA NPs and AuNPs have been developed for human [263,264] and veterinary [265] use.

Another ideal route is through the skin. The skin is the largest organ of the body and has many immunocompetent cells able to stimulate innate and adaptive immune responses. Thus, intradermal administered vaccines may be much more effective than subcutaneous or intramuscular injections [44]. The problem is how to ensure that they will penetrate the stratum corneum in an accurate dose. The penetration capacity of NPs depends on their characteristics (size, composition, hydric properties, *etc.*) and physiological skin state (altered, lesioned or health), but mechanical effects can also modify it [44].

Despite their advantages, NP vaccines also have important problems. On one hand, release may start before the target cell has been reached, which decreases efficacy. Also, any modification in surface composition and structure can change the uptake by different types of cells, causing unwanted effects [113]. Furthermore, the correlation between preclinical studies in rodent models and clinical trials is poor [261]. The extrapolation to humans is better for porcine, bovine or ovine models, but these models are subject to stricter ethical conditions and are more expensive [45,127]. On the other hand, there is a vast gap in our knowledge about the cytotoxicity and pharmacokinetics of vaccines with

Please cite this article as: H. Zazo, et al., Current applications of nanoparticles in infectious diseases, J. Control. Release (2015), http://dx.doi.org/10.1016/j.jconrel.2016.01.008

NPs, which are or will be administered to healthy people and — probably — healthy children. Hence, even the slightest risk or side effect is unacceptable [113,127].

6.5. Theranostic nanoparticles

Theranostic is a combination of therapeutics and diagnostics whose main goal is to diagnose and treat diseases at the earliest stage. It is a very promising strategy, even for fatal diseases such as cancer or AIDS [266]. Diagnostic and therapeutic agents can be combined in several ways. One option involves the coupling or loading of therapeutic agents (drugs) with NPs used for imaging purposes, such as Quantum dots, IONPs or AuNPs. The second option is to reverse the agents, encapsulating the imaging contrast agents or NPs inside therapeutic NPs. Moreover, both agents can be loaded simultaneously on nanoplatforms such as polymeric NPs or porous silica NPs [267]. Currently, there are many systems used in research, mainly in oncology. However, the advancement of theranostic nanoparticles is struggling due to toxicity problems and a lack of knowledge about their pharmacokinetics [267].

In the anti-infective domain there are examples of NPs theranostic systems with very low cytotoxicity and a persistent resonance signal [268,269]. Currently, an AuNP test commercialized for diagnosis is available: Verigene®. It is an *in vitro* test to detect Gram-positive bacteria directly in the blood. By contrast to the minimum of 2 days of conventional tests, about only 3 h are required to identify the specific genus and species of the most important and frequent bacteria and virus including resistant strains [270,271].

These systems can also be used to quantify the level of infection, even with very low concentrations. The techniques used range from fluorescence signals, as vancomycin-FITC-silica NPs [240]; to colorimetric techniques, such as the one used for the detection of hepatitis E virus with AuNP [272]; and spectrophotometric techniques, such as gold nanoparticles for hepatitis B virus [273]. In general, these techniques are fast (around 1 h) and show high repeatability, sensitivity, and specificity [272,273]. Another technique developed involves the use of magnetic iron oxide NPs. It captures and analyses bacteria using matrix-assisted laser desorption/ionization mass spectrometry in less than 1 h. With this technique, the minimum detection limit was 10^4 CFU/mL but it can be reduced to 50 CFU/mL if the bacteria captured are incubated [274]. However, the high cost of this technique is certainly a problem.

Another theranostic system developed is the hemozoin vapour nanobubbles. The nanobubbles expand and collapse after they interact with the hemozoin particles of the malaria parasite. This generates an image and destroys the parasite mechanically, without any harm to uninfected neighbouring cells and with the added advantage that no drugs are used [275].

7. Clinical experience and market success

Since the first development of a liposome as a carrier [5], nearly 20 years passed before the first NP drug delivery system was approved by FDA [276] and currently there are very few nanoparticle systems on the market. One reason can be the problems for a good translation from the lab to the market. First of all, the results of preclinical studies cannot be always compared. The studies might use different cell lines, types of NPs, formulations, methods or units of measurement (mM, mg/kg, $\mu g/m^3$, *etc.*). Some clinically important parameters, such as the safe dose range or the % of targeting compared with the amount found in non-specific target tissues, are not always reported or determined correctly [77]. For a good clinical translation, preclinical studies should primarily consider the therapeutic efficacy parameters used in clinical trials, followed by the safety of the NP system, either due to the material or drug concentration in each tissue.

After that, problems also arise in scaling up [3,77,84] and proper cost-effective characterization of each batch of NPs synthesized [46]. Finally, the financial aspect is another important barrier during the journey of a drug from its inception to the market. Most research addressing this field, as well as the patents filed, has been performed by academic researchers [33,111] with governmental nanotechnology funding programmes, such as those available in the US, Germany or Japan [4]. However, without true support from industry for the development of clinical trials, and without national and international regulation, the real commercial success of nanomedicine is difficult to predict.

This explains why there are only 276 clinical trials exploring the use of NPs in infectious diseases [251], whereas thousands of research papers have been published. These clinical trials have sought approval for new systems, such as ciprofloxacin liposomes (Pulmoquin) (NCT01515007); new applications, such as the use of Arikace™ in bronchiectasis (NCT00775138), cystic fibrosis (NCT00558844) or chronic infection (NCT01315691); and in other populations, such as neonates (NCT00815516) [251]. There are also clinical trials addressing their use as vaccine carriers for Ebola virus (EBOV) (NCT02370589) or as antimicrobial agents in medical devices, such as AgNPs in central venous catheters (NCT00337714) [251]. In the end, there are less than 10 NP systems available on the market. Few of them have therapeutic purposes like the liposomal carrier Ambisome® (Amphotericin B); the SLN Nanobase® to treat hepatitis C; or the virosomal vaccines Inflexal® V and Epaxal®. The others are for diagnostic use or as medical devices (Verigene®, Silverline®, Acticoat™ or Endorem™ SPIONS) [46,270,271,277,278].

Once on the market, they must show a good cost-effectiveness ratio if they want to be included in the common therapeutic arsenal. Currently, the price of nanotechnology systems is very high, so cost-effectiveness studies carried out in different countries support the choice of conventional treatments [279–281]. However, these NP systems can be recommended in certain specific situations, such as the Ambisome® treatment for disseminated histoplasmosis and AIDS patients [46]. In any case, although nanotechnology treatments are considerably more expensive than conventional treatments, they can save resources and improve quality of patients' lives owing to the fewer frequent and less severe adverse effects [282].

8. Conclusions

NPs offer promising treatments for infectious illnesses by targeting the specific and hard-to-reach sites where pathogens are harboured. Moreover, they enhance the effects of drugs, even in the case of resistant bacterial strains. At the same time they optimize physicochemical characteristics, allowing the clinical use of new agents or their administration through more comfortable routes. Furthermore, these actions can enable lower drug dosing, better administration schedules, better bioavailability, and fewer and less severe side and adverse effects. However, they also have drawbacks. We still know very little about the metabolism, clearance and toxicity of NPs, the nature of the optimal targets of certain infections, and the optimum drug levels for therapeutic activity at the target site of pathogens. These problems, together with the difficulty inherent in reproducing and moving preclinical studies up to ensuing steps, decrease the likelihood of successful development of NP systems. Moreover, the lack of financial input, ineffective regulation and in some cases the poor cost–benefit balance hamper progress towards commercial marketing and the addition of NPs to the common therapeutic arsenal.

The best way to ensure the real success of nanomedicine is through interdisciplinary collaboration. Physicists are needed to develop good quantitative techniques; health-care researchers (biologists, pharmacists, physicians, *etc.*) must seek to develop good therapeutic agents; clinical researchers in the health field are needed to translate this knowledge to clinical trials, and funding from industry is crucial for ensuring that these products will end up available on the market. With an interdisciplinary team it is easier to find the primary factors of NP system needed for clinical translation, like safety, big loading capacity,

Please cite this article as: H. Zazo, et al., Current applications of nanoparticles in infectious diseases, J. Control. Release (2015), http://dx.doi.org/10.1016/j.jconrel.2016.01.008

milieu-control release, specific target or biodistribution. The selection of the NPs used depends on disease targets and the characteristics of drug or drugs loaded. In this way these systems should help to design more patient-comfortable dose regimens at the same time that they have more effectiveness.

Acknowledgements

This work was supported by the Spanish Ministry of Education through the National Program FPU (grant number AP2010-5540).

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Please cite this article as: H. Zazo, et al., Current applications of nanoparticles in infectious diseases, J. Control. Release (2015), http://dx.doi.org/10.1016/j.jconrel.2016.01.008

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Please cite this article as: H. Zazo, et al., Current applications of nanoparticles in infectious diseases, J. Control. Release (2015), http://dx.doi.org/10.1016/j.jconrel.2016.01.008

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Please cite this article as: H. Zazo, et al., Current applications of nanoparticles in infectious diseases, J. Control. Release (2015), http://dx.doi.org/10.1016/j.jconrel.2016.01.008