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Development, delivery strategies, cell uptake and efficacy of nanoparticles and their role for leishmaniasis - a review

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Abstract: Nanoparticles (NPs) have been considered one of the most promising strategies for the treatment of several diseases. There are different types of nanoparticles available, designed to perform specific functions according to the disease model, the type of tissue or target cell and the response you want to achieve. It is known that to synthesize a nanoparticle, there are many protocols developed by researchers according to the area of interest. After the synthesis process, this material needs to undergo different types of physical-chemical characterization to attest its properties, such as surface charge, diameter, chemical composition, electrical conductivity, and stability. The literature has already provided us with a lot of information about how these parameters bring us the "ideal nanoparticle" for each test, informing the appropriate size and the interference of the surface charge for cell uptake, for example. In this review, we will show what is most recent about these parameters, the processes of cell uptake and some NPs that have been tested against leishmaniasis and its main role in target tissues and cells.

Keyword: nanoparticles,zeta potential, diameter,cell uptake, macrophages, leishmaniasis.

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INTRODUCTION

The production of NPs is based on the size and shape of the structures, where optical, electronic, or magnetic properties can be tuned during chemical synthesis process. There is a great interest in investigate NPs in different biomedical applications since their size scale is similar to that of biological molecules(Devika Chithrani et al., 2006).

The physicochemical characteristics of NPs such as surface charge, size, composition and surface hydrophobicity may affect their interaction with plasma proteins and blood components, their uptake and clearance by macrophages, and thus influence their biodistribution and targeted delivery of to the destine target sites(Alexis et al., 2008).

Though, these drug delivery nanosystems have revealed some limitations about the toxicity of the nanoscale materials in the body(Soo Choi et al., 2007)(Park et al., 2009). In order to reduce their toxicity, itis crucial to study endocytosis, exocytosis, and clearance mechanisms for NPs released from the nanoparticle–drug conjugates(Oh & Park, 2014).

Nanoparticle association with the host mononuclear phagocytic system (MPS) is a role of particle opsonization upon contact with blood and recognition of these opsonins through the MPS(Mortimer et al., 2014)(Jenkin and Rowley, 1961). Nanoparticle delivery vehicles designed to any avoid or specifically use this host recognition system could improve delivery, reduce inflammatory effects,and enhance imaging and drug efficacy. Still, to rationally design these better systems, improved understanding is crucial of nanoparticle-macrophage interactions both at cellular and system-wide levels in physiological(Gustafson et al., 2015).

Leishmaniasis is a disease caused by the protozoan Leishmania and affects a many country in the world. The current treatment is ever more unsatisfactory and there is currently a search for more effective drugs with minor collective effects. NPs have been inserted in this context and in the literature, there are already several types available showing different approaches. In this article, we will review the main physicochemical characteristics for ideal

nanoparticles, the mechanisms of entry into cells, and the role of the macrophage in the uptake of these nanoparticles. Besides that, we will present here some types of NPs for leishmaniasis, their main physicochemical characteristics, and their interactions with the cells that place them as possible substitutes for conventional treatment.

ZETA POTENTIAL, PARTICLE SIZE AND COLLOIDAL STABILITY

The surface charge of a nanoparticle is frequently described by measuring the zeta potential, which is the electrokinetic potential at the slipping plane. The ideal sample for zeta potential analysis is amonodisperse in size and with high light scattering properties; dispersed at low salt concentration (conductivities< 1 mS/cm); and in a particulate-free, polar dispersant (purity water) (Gehr, 2019).

The negatively charged cell membrane enhances the uptake of positively charged NPs. Positively charged NPs have higher internalization than neutral and negatively charged NPs (Panariti et al., 2012)(Marano et al., 2011). Neutrally charged NPs will lower the cellular uptake as compared to negatively charged NPs (He et al., 2010)(Allen et al., 1990)(Raz et al., 1981)(Patil et al, 2008). However, the uptake of positively charged NPs may disrupt the integrity of the cell membrane and lead to an increase in toxicity inducing cell death(Hoffmann et al., 1997)(Goodman et al., 2004)(Lovri et al., 2005)(Dawson et al., 2009).

The role of NPs size in cellular uptake is critical to design effective and safe NPs for medical applications. The efficiency of cellular uptake depends on NPs size. NPs with the size range of 120–150 nm are internalized via clathrin- or caveolin-mediated endocytosis, and the maximum size of NPs described to be of 200 nm, although NPs in the size range of 250 nm to 3 μm have been demonstrated to get an optimal in vitro phagocytosis(Rejman et al., 2004)(Panariti et al., 2012).

NPs used in the drug delivery should be not eliminated by the reticuloendothelial system. In this regard, increasing the size of NPs will lead to an increase in the clearance rate and to prolong its circulation time in the blood, thus enhancing the bioavailability at the target(Bruno et al., 2013)(Biswas et al., 2014)(Gendelman et al., 2015)(Behzadi et al., 2017)(Ventola, 2017).

However, in the in vitro and in vivo studies, the sizes of NPs measured after synthesis may change due to agglomeration and aggregation which in turn could affect the cellular internalization pathways(He et al., 2010)(Verma & Stellacci, 2010).

The colloids are the particles in the dispersed phase in the range of 1 nm–1 μm or 1 nm–500 nm (Hofmann, 2004) and its electronic, catalytic, optical, and biological properties must be suitable. However, after the preparation, nanoparticles are often exposed to a liquid phase before processing into a final formulation, thus the long-term stability of colloids must be determined(Gehr P and Zellner, 2019).

To test the stability of colloids, there are methods such as steric and electrostatic stabilization. A steric stabilization can be realized by surfactant (polymer) adsorption or attachment onto the particle surface(Trados, 2007). Electrostatic stabilization can be controlled by variation of the chemical environment (e.g. pH, salt concentration, ion type) or by introducing a surface charge from adsorbing molecules or ions. The basic mechanisms are ion adsorption, ionization of surface groups, ion dissolution, and ion substitution. Particles can be functionalized with appropriate chemical compounds that carry a positive or negative charge(Gehr P and Zellner, 2019).

TYPES OF CELULAR UPTAKE

Clathrin-mediated endocytosis (CME) occurs either via receptor-specific uptake an area of the plasma membrane that is rich in clathrin, whereby is engulfed through the formation of clathrin-coated vesicles(Behzadia et al.,2017)(Foroozandeh & Aziz, 2018).

Adaptor proteins are recognition sites for different cargoes and classification signals. They are used in docking sites on the cytoplasmic face of the plasma membrane and are responsible for the coordination of clathrin nucleation at the sites of internalization in the membrane. (Brown & Petersen, 1999)(Conner & Schmid, 2003)(Schmid et al., 2006). Once inside the cell, clathrin coatings on the exterior of the vesicles are expelled prior to fusing with early endosomes(Xiang et al., 2012)(Rappoport, 2008)(Soldati & Schliwa, 2006)(Praefcke & Mcmahon, 2004)(Cocucci et al., 2012). Particles entering the cell by this route frequently finish in the lysosome and may not be suitable for coating NPs made of materials susceptible to degradation vialysosomal enzymes(Behzadia et al., 2017)(Doherty & Mcmahon, 2009)(Ehrlich et al., 2004).

Caveolae-mediated endocytosis is the route of cellular entry which involves flask-shaped membrane invaginations called caveolae (little caves) present in epithelial and non-epithelial cells, interspersed among regions of dense bodies anchoring the cytoskeleton(Taggart, 2001).

Once caveolae are detached from the plasma membrane, they fuse with a cell compartment called caveosomes that exists at neutral pH. Caveosomes can bypass lysosomes and therefore protect the contents from hydrolytic enzyme and lysosomal degradation.(Conner & Schmid, 2003)(Sandvig et al., 2011)(Oh et al., 2007).

Since the particles infiltrate the cell by caveolin-dependent mechanisms can sometimes escape lysosomal degradation, this entry route is used by some pathogens such as viruses and this emerges to be convenient for the delivery of genes and proteins. However, trafficking into

acidic lysosomes could be the basis for engineering nanotherapeutics with acid- triggered release characteristics.(Carver & Schnitzer, 2003)(Rejman et al., 2006)(Karimi et al., 2016).

Phagocytosis is achieved by specialized cells of the immune system (ie, macrophages, monocytes, neutrophils, and dendritic cells), to remove particles larger than 500 nm from the organism, in a receptor-mediated process.(Aderem & Underhill, 1999)(Hillaireau and Couvreur, 2009).

Phagocytosis of NPs is frequently initiated by opsonization: opsonins such as immunoglobulins, complement proteins, or other blood proteins are adsorbed onto the NPs' surface (Swanson, 2008)(Aderem & Underhill, 1999). Opsonized NPs are recognized by and attached to phagocytes via specific ligand-receptor interactions (Fc receptors, complement receptors, mannose/fructose receptors, or scavenger receptors). This initializes a signaling cascade that can generate actin assembly, the formation of cell surface extensions, engulfing and internalization of particles, forming a "phagosome"(Hervé Hillaireau and Patrick Couvreur, 2009). These vesiclesmature by somefission and fusion events with late endosomes and lysosomes, ensuing in the formation ofphagolysosomes. Internalized particles are then degraded, and the receptors are cycled back to the cell surface. The rate of these successive events depends significantly on the ingested particle and typically lasts from 30 minutes to several hours(Dobrovolskaia & Neil, 2007).The precise mechanism of phagocytosis, and subsequent events, also depend on the type of receptors involved.

MACROPHAGES

Mature macrophages are differentiated forms of circulating hematopoietic premature precursor monocytes or obtained from the tissue precursors in which they reside(Shepard & Zon, 2000)(Wynn et al., 2013). They are leukocytic cells capable of phagocytizing or taking up bacteria, cellular debris, and particles through energy-consuming membrane-engulfing as a

characteristic phenotype (Burke and Lewis, 2002)(Shi, 2011)(Murray, 2012)and are specialized because can preserve biological hemostatic detoxification, or have neurological function (Epelman et al., 2015). As avid phagocytes, they display a spectrum of phenotypes, spanning pro-inflammatory to prohealing, and show to be able of reversible transformations between different distinct functional forms (Locati, 2013).Thus, represent a major defense against invasion of the host by a wide variety of microorganisms, including bacteria, viruses, fungi, and protozoa.

Macrophages move toward the microbial particles guided by a gradient of chemotactic molecules emanating from them (Metchnikoff, 1905). Engulfment then occurs, beginning with the macrophage advancing pseudopodia over regions of the microorganism that are linked to recognition molecules, the opsonins, which bind to specific sites on both invading microorganisms and macrophages. Opsonins are of various types, but those most studied are IgG and fragments of the third component of complement. Receptors that bind specifically to the Fc domain of various subclasses of IgG and several isotypes of C3 are present on the macrophage surface (Adams and Hamilton, 1988). After binding with the appropriate ligand, initiation of the process of internalization and microbial destruction occur (Nathan et al., 1980). Although many microorganisms are phagocytosed and destroyed with comparable ease by macrophages, there are certain pathogens that parasitize macrophages and replicate within them.

The production and intracellular release of ROIs are a major microbicidal mechanism employed by monocytes and macrophages. In addition to oxygen-dependent cytotoxic systems, phagocytes are equipped with oxygen-independent means of killing microorganisms. A variety of granule-associated proteins of macrophages have been shown to possess antimicrobial activity. These include elastase, collagenases, lipases, deoxyribonucleases, polysaccharidases, sulfatases, phosphatases, and the defensins (Elsbach and Weiss, 1988).

Macrophages have evolved distinct pathogenic and foreign material recognition mechanisms(Gordon, 2002)(Janeway & Medzhitov, 2002)(Boller & Felix, 2009). These endogenous processes and patterns are likely important to nanomaterial host recognition as well. Many nanomaterial uptake and cellular processing mechanisms parallel normal immunological pathogenic processing, suggesting conservation in cellular recognition and pathway regulation(Gustafson et al., 2015).

Comparative phagocytosis studies have measured rates of uptake between scavenger, mannose, and Fc receptors. Nanoparticles targeted to mannose and Fc receptors seem to be internalized rapidly, whereas scavenger receptors require significantly longer times (Taylor et al., 2005). This suggests that Fc and mannose receptors are better sustainedto efficiently internalize nanoparticles(Gustafson et al., 2015).

Control and manipulation of particle morphological and surface physicochemical properties to interact in foreseeable ways with physiological components must allow the exploitation of rational particle engineering strategies to select specific cell types, transport routes, internal cell compartments, and more control over dosing, biodistributions, therapeutic action and toxicity (Deretic et al., 2013).

Extracellular particle recognition and processing defines intra-cellular uptake and particle trafficking, where three processing events are possible for nanomaterials in phagocytes: (1) cell-autonomous antimicrobial defense mechanisms, (2) native pathogenic or foreign material cellular process mechanisms, and (3) opsonization recognition events due to specific structural surface similarities with pathogens and foreign materials(Deretic et al., 2013), however, the mechanisms involved for the nanoparticles in each of these pathways are not yet known(Gustafson et al., 2015).

NANOPARTICLES CARACTERISTICS OF LEISHMANIASIS TREATMENT

Leishmaniasis is an infection caused by the protozoan Leishmania sp, transmitted by the straw mosquito, *Lutzomyia longipalpis*, in Brazil(Maingon et al., 2008). The treatment involves the use of compounds containing SbV, such as Glucantime and Pentostam, but there are reports of severe side effects, causing the abandonment of the treatment or resistance of the strain(Berman, 2005)(Singh & Sivakumar, 2004). Numerous studies are indicating new approaches using drugs extracted from plants, new drugs, or nanoparticles. Nanoparticles are promising for the treatment of various diseases, and for leishmaniasis there are already many tests with different types of nanoparticles(Tiwari et al., 2016)(Alvarenga et al., 2015) (Kumar et al., 2017)(Afzal et al., 2019)(Das et al., 2018)(Kumar et al., 2015)(Fanti et al., 2018)(Varshosaz et al., 2018)(Ullah et al., 2018)(Kharaji et al, 2016)(Halder et al., 2018) (Ghadi et al., 2018)(Ovais et al., 2018)(Want et al, 2017)(do Nascimento et al., 2016)(Barazesh et al., 2018)(Halder et al., 2017) (Khatami et al., 2018)(Gupta et al., 2015)(Ammar et al., 2019).

In the table below, some recent studies that used tests with nanoparticles and evaluated their physical-chemical characteristics, toxicity to macrophages, tests with free promastigotes or intracellular amastigotes, and*in vivo* tests were summarized. The articles, in general, present the same approaches concerning the physical and chemical characterizations, mainly indicating the zeta potential and the diameter of their formulations. Some do other tests like TEM, SEM and XRD. But about tests involving cells and the parasite itself, in the articles there is a certain discrepancy, since some do not do tests on macrophages to assess cell uptake and the viability of these cells. *In vitro* tests involving *Leishmania* generally use intracellular promastigotes and amastigotes and check the IC50 of the nanoparticle after contact with the parasite. Few studies have shown *in vivo* tests using nanoparticles in mice or hamsters. Usually, parasitic load, histopathological changes in target organs of the parasite, such as liver, pancreas, bone marrow, and skin are evaluated. As you can see, there is no standard test type using nanoparticles for

leishmaniasis, but most articles show the entire process of synthesis and characterization and, at least, a biological test to show how your drug works.

Table 1: Nanoparticles for leishmaniasis - main characteristics and effectiveness.

Nanoparticle	Zeta	Size	Cell viability	Amastigotes	*In vivo*	Reference
AmB NPs with PLGA	- 27 mV	90 nm	0.08 µ g/mL	IC 50: 0.083 ± 0.005 µg/mL	decrease the lesions	Ammar et al, 2019
Glycine + Fe3 O4 + AmB = GlNPs AmB	pH 6: -25.5 mV;	8–10 nm	-	IC50: 4 ng/mL	94.53% inibition	Kumar et al 2017
PLGA-PEG encapsulated amphotericin B	-	30-35nm	-	-	93.2 ± 6.7% inibition	Kumar et al, 2015
Terpenoid andrographolide engineered gold nanoparticle (AGAunps)	- 21.3 mV	83.25 nm	-	IC50: 12 ± 3 um	-	Das et al, 2018
Curcumin PLGA nanoparticles (CNP)	- 12.7 mV	182.3 nm	-	IC50: 1.61 ug/mL	25-mg/kg dose yielded 70.26% parasitic inibicion	Tiwari et al, 2017
AgNp-bio biogenic silver nanoparticle	-14.3 mV	57.6 nm	Non toxic	25.83% inibition	-	Fanti et al, 2018
TiO2 NPs	42.8 to 78.1mV	170.6 to 853.4nm	-	166.5 ug/mL	-	Varshosaz et al 2018
AgNPs		424 to 431nm	IC50: 100.02 µg/ml (Leaves-AgNPs); 116.81 µg/ml (Stem-AgNPs) and 62.99 µg/ml (Chem-AgNPs)	-	-	Ullah et al, 2018

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PM-SLN (paramomicina in solid lipids)	507 to 572mV	120 to 1500nm	toxic only in high concentrations	390 µg/ml of PM-SLN 15% (120 nm) and 800 µ g/ml of PM-SLN 12.5% are toxic to cells, but also inhibit the propagation of L. major amastigotes; L. tropica showed 400 and 750 µ g/ml of PM loaded in SLN (15 and 12.5%) can also inhibit L. tropica amastigotes while being non-toxic to the cells.	-	Kharaji et al, 2016
LfBANPs (Lactoferrin-modified Betulinic Acid-loaded PLGA)	+27.41 mV	187.5 nm	-	reduced infection significantly	-	Halder et al, 2018
Fusarium silver nanoparticles	-	94 nm	-	Control 4.583 ± 0.41; AgNPs (2.5 µg/ml) 1.308 ± 0.27; Pentostam (100 mg/ml) 2.141 ± 0.47; LSD value 0.538	-	Ghadi et al, 2018
Mannosylated thiolated paromomycin-loaded PLGA nanoparticles	- 8.93; +20.45; +18.84; +16.27	228 to 391nm	-	IC50: 4.73; 3.05; 1.7; 0.38 and 0.13 µg/ml	-	Afzal et al, 2019
Olax nana Wall. ex Benth. (family: Olacaceae) + (ON-AgNPs) ou (ON-AuNPs)	ON-AgNPs 28mV; ON-AuNPs 32 mV	ON-AgNPs 31 nm; ON-AuNPs 65nm	-	ON-AgNPs (17.44 µ g/mL); ON-AuNPs (42.20 µ g/mL	-	Ovais et al, 2018
Nanoliposomal artemisinin	-22 to -37 mV	72 to 138 nm	-	-	NLA: 82.4%, 77.6% (liver and spleen); free artemisinin: 68.3%, 62.7%(liver and spleen)	Want et al, 2017

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Polymeric Nanoparticles of Brazilian Red Propolis Extract	-20 to -26mV	200 to 280nm	-	EEP IC50: 37.9ug/mL and NRPE 31.34 ug/mL	-	do Nascimento et al, 2016
Meglumine antimonate loaded albumin nanoparticles	-	44.58 to 351.9nm	Cytotoxicity less than 40% at the highest concentration	-	-	Barazesh et al, 2018
Monodispersed gold nanoparticles in kaempferol	-21.2mV	120 nm	-	several parameters were analyzed and the nanoparticles showed satisfactory results.	-	Halder et al, 2017
Zinc oxide nanoparticles (green synthesis by Stevia)	-25.1 mV	10 to 90nm	-	-	-	Khatami et al, 2018
Self Assembled Ionically Sodium Alginate Cross-LinkedAmphotericin B Encapsulated Glycol Chitosan StearateNanoparticles	-	196 to 684.7nm	-	-	-	Gupta et al, 2015
NPC - phosphate nanoparticles	-15.5 to -19.5mV	173.1 to 193.5nm	Non toxicity	reduction of infection	-	Alvarenga et al, 2015

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CONCLUSION

Therapies using nanoparticles are increasingly promising. To ensure greater efficiency and safety in its use, several tests are necessary to ensure that they are of adequate size and other characteristics for stability. The evaluation of the methods of entry into the target cells must be careful to obtain the necessary responses. As candidates for the treatment of leishmaniasis, there are several nanoparticles, but due to problems such as production cost, stability, or adequacy to treatment, they are not yet available on the market. Additional studies are being carried out to modify this dynamic and offer a modern and safe treatment for this disease.

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