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Review

Nanotechnology as a potential therapeutic alternative for schistosomiasis

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ABSTRACT

Schistosomiasis is a neglected disease that affects millions of people worldwide, recognized as the most important human helminth infection in terms of morbidity and mortality. The treatment of choice presents low bioavailability and water solubility, in addition to the induction of parasite resistance. In this context, researchers have been conducting studies seeking to develop new drugs to ensure safety, quality, and efficacy against this parasitosis. In this scenario, nanotechnology arises including the drug delivery systems in nanoscale: nanoemulsions, liposomes and nanoparticles. These drug delivery systems have been extensively applied for *in vitro* and *in vivo* studies against *Schistosoma* spp. with promising results. This review pointed out the most relevant development scenarios regarding the treatment of schistosomiasis as well as the application of nanotechnology as a vaccine, highlighting the use of nanotechnology as an alternative therapy for both the repositioning of drugs and the use of new pharmaceutical products, with promising results regarding the aforementioned disease.

1. Introduction

Human schistosomiasis, one of the most prevalent neglected tropical diseases, is a major public health problem affecting more than 200 million people in 78 countries and ~800 million people are at risk of infection (Steinmann et al., 2006). Although mortality rates are difficult to assess for schistosomiasis, it has been estimated that this disease causes approximately 280,000 deaths per year and may still cause severe damage to the host (Van-Der-Werf et al., 2003). It is a helminthiasis caused by intravascular trematode of the *Schistosoma* genus, with three main species adapted to human infection: *Schistosoma haematobium*, *S. mansoni* and *S. japonicum*. Poor sanitary conditions as well low economic development are involved in the disease dissemination (King, 2009; Rollinson et al., 2013).

The adult forms of this parasite inhabit in various locations of the mesenteric vessels of the vertebrate host, which at times seem to be specific for each species. For example, *S. japonicum* is most frequently found in the superior mesenteric veins draining the small intestine while *S. mansoni* occurs more frequently in the superior mesenteric veins draining the large intestine. *S. haematobium*, in turn, is more found in the venous plexus of the bladder, but it also occurs in the rectal venules (CDC, 2016).

Intermediate forms develop in the aquatic gastropod snails of the *Biomphalaria* (intermediate host of *S. mansoni*), *Bulinus* (*S. haematobium*) and *Oncomelania* (*S. japonicum*) genus. The life cycle of schistosomes begins with cercariae which break out of the snail into the water and penetrate the human skin when swimming or in contact with contaminated water (Gryseels et al., 2006). After penetrating in the human body, cercariae differentiate into schistosomules which migrate to portal blood in the liver. After lodging in the mesenteric veins, they reach sexual maturity and are considered adult worms, coming into copulation and releasing a high amount of eggs in the small venules of the portal and perivesical systems. The eggs are moved progressively toward the lumen of the intestine (*S. mansoni* and *S. japonicum*) as well as the bladder and ureters (*S. haematobium*) and eliminated through feces or urine, respectively. The eggs excreted reach the water again, miracidia forms hatch from excreted eggs entering in the specific host snails and multiply asexually to form cercariae, restarting the life cycle (CDC, 2016).

Some eggs can get trapped in the vertebrate host: *S. haematobium*

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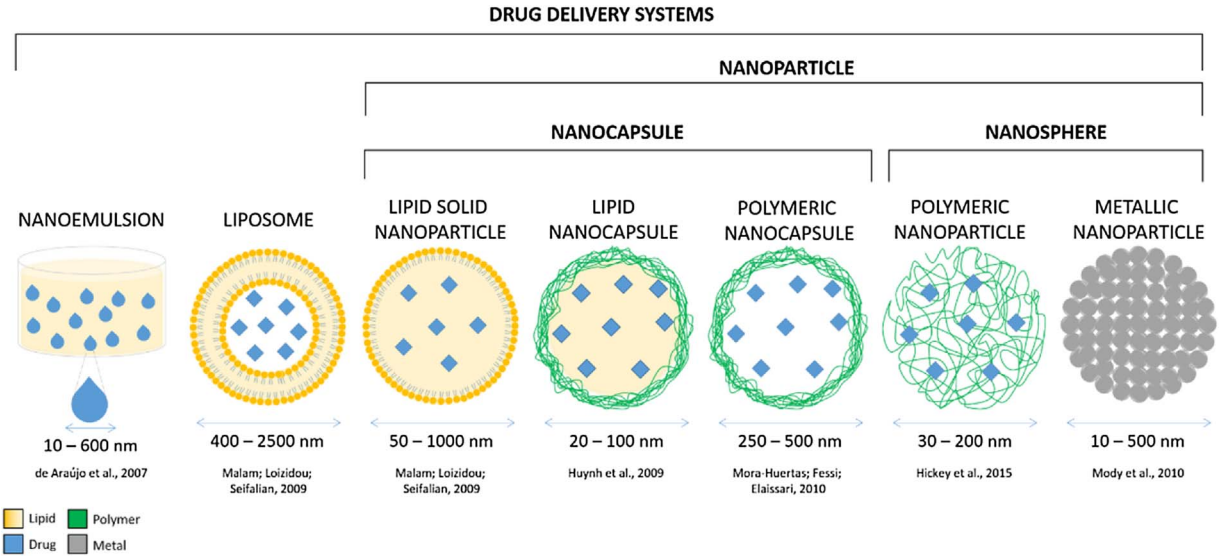

Fig. 1. Scheme showing Drug Delivery System – Types, size and composition. Schemes demonstrating the types of drug delivery system used in Schistosomiasis, as well as relating the types, sizes and composition of each nanostructure. Nanoemulsion, liposome and nanoparticles are separated into two groups: nanocapsule, containing lipid solid nanoparticle, lipid nanocapsule and polymeric nanocapsule; and nanosphere, composed by polymeric nanoparticle and metallic nanoparticle. Nanoparticles presents size about 10–2500 nm and may be composed of lipids, polymers and metal.

eggs cause damage to the urinary tract, bladder cancer is common in advanced cases; eggs of *S. mansoni* and *S. japonicum* cause intestinal schistosomiasis (CDC, 2016). The acute phase of this disease may be either symptomatic (Katayama fever) or asymptomatic with possible progress to chronic infection with progressive enlargement of the liver and spleen as well as damage to the intestine, caused by fibrotic lesions around the schistosome eggs lodged in these tissues and hypertension of the abdominal blood vessels (WHO, 1997). The disease can still result in impairments in cognition, physical aptitude and child development; anemia; hepatosplenomegaly, neurological complications that can lead to death (Gryseels et al., 2006; Rollinson et al., 2013; Zoni et al., 2016).

In 2012, the World Health Assembly adopted the WHA65.21 resolution in Geneva, Switzerland appealing to promote greater investment in the schistosomiasis control and supporting the start elimination programs in endemic countries (Americas, Asia and Africa), since the treatment of this parasitosis is limited due to the small amount of available chemotherapeutic agents that exhibit efficacy, safety and tolerability (WHO, 2012).

Currently, the control of schistosomiasis is based on the monitoring of the host snail, health education, hygiene promotion, access to clean water, and improved sanitation. The first-choice drug for the treatment is praziquantel (Ferrari et al., 2003). Oxamniquine is listed as 'complementary drug' for use when praziquantel treatment against *S. mansoni* fails since it is effective only against this species (Colley et al., 2014). Cases of parasite resistance have been limited since the oxamniquine action spectrum is limited (Fenwick et al., 2006).

The anthelmintic action of praziquantel is uncertain, however authors declare that probably due to the sodium-potassium ATPase (Na^+-K^+) inhibition in adult worms, increasing the membrane permeability of the worm to certain monovalent and divalent cations, mainly calcium, which leads to the intensification muscle activity, followed by contraction and spastic paralysis (Cioli, 1998; Cunha et al., 1988). This drug has the advantage of low cost and wide therapeutic spectrum by operating in the three species adult forms of *Schistosoma*, even though, it is not effective in immature worms because the fast praziquantel metabolism after oral administration converts the drug extensively to an inactive or considerably less potent compound (Liu et al., 2017; Chen et al., 2012). Since the younger forms are found in the systemic circulation, these parasites become less exposed to praziquantel (Andrews, 1985; Xiao et al., 1985; El-Arini and Leuenberger, 1998). Thus, it is necessary that high oral doses overcome the first pass metabolism and achieve sufficient drug concentrations in the larval tissue (Becket et al., 1999).

Furthermore, the praziquantel use is mainly limited by low bioavailability and water solubility, therefore, various studies have described many technological alternatives to improve the oral absorption of this drug and new compounds which may be used in the prevention and treatment of this disease (Mourão et al., 2005; Mainardes et al., 2006; Yang et al., 2009; De Souza et al., 2012).

Nanotechnology has the potential for restoring the use of toxic drugs through the use of complex structures which allow to carry drugs being able to achieve only the pathogen, preserving the host cells and exerting its effect with less toxicity, improved selectivity consequently greater efficacy (Forrest and Kwon, 2008). Regarding the parasitosis, nanotechnology has already been employed as drug delivery systems such as in toxoplasmosis, leishmaniasis, malaria and trypanosomiasis (Date et al., 2016).

Therefore, it is possible that strategies involving nanotechnology are capable to associate drug therapeutic benefits in order to provide infected people with benefits (Kolenyak-Santos et al., 2014). In this sense, this review aims at addressing the current situation of the studies using different nanomaterials as drug delivery systems that allow the vectorization of old drugs, successfully employed in the pharmaceutical field, or new compounds as a therapeutic alternative for the treatment of schistosomiasis.

2. Drug delivery systems

Nanotechnology is the area of science and engineering dedicated to materials with diameter in the range of tens to hundreds nanometers. The nanosize of these particles, named nanomatherials, allows various communications with biomolecules on the cell surfaces and within the cells influencing several biochemical and physiochemical properties of these cells (reviewed in: Salata, 2004).

Nanotechnology represents useful drug delivery systems to improve the pharmacokinetic profile of drugs. This means that bioavailability increases with the enhancement of solubility, stability, dissolution rate and surface area, in addition to modulating the therapeutic action and permeability of the drug through the absorptive membranes leading to the use of lower drug doses (Verma et al., 2003; Joshi et al., 2004).

Nanosize-based drug delivery systems can be classified according to their particular characteristics in nanoemulsions, liposomes or