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NANOTECHNOLOGY VERSUS OVERDOSING ANTIMICROBIAL SUBSTANCES

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Abstract

In the last century, antimicrobial therapy evolved from being one of the most important achievements in the history of medicine to one of the major global health challenges. The overdosing of antimicrobial substances was held responsible for the appearance and the worsening of the antibiotic resistance phenomenon. Thus, scientists were called to design and implement new strategies surmounting the shortcomings of the antibiotic therapy. Nanotechnology has revealed promising solutions to the overdosing problem by use of tailored antibiotic administration schemes, both as dosage and administration route. The aim of this review is to highlight the role of nanotechnology in preventing and controlling antibiotic resistance, also emphasizing its advantages and limitations, for a better understanding of the current trends. The paper is based on scientific articles and systematic reviews identified on the Web of Science database, centralized and classified according to specific keywords. Due to their unique physico-chemical properties, the nano-based delivery systems described could become an important mean of avoiding irrational employment of antibiotics by usage of the minimal clinically active amount.

Key words*: antimicrobial resistance, nanoparticles, drug delivery systems.*

INTRODUCTION

Antimicrobial substances were one of the greatest discovery in modern medicine era and reported as one of the most successful forms of chemotherapy in the history of therapeutics and pharmacology (R. I. Aminov, 2010). The years 1935, 1941 and 1943 marked the discovery of sulphonamides, penicillin and streptomycin but also marked the lowest rate of mortality in infectious diseases (R. Aminov, 2017), highlighting the impact that antimicrobial theraphy had via prophylactic and metaphylactic use both in human and veterinary medicine. Nowadays, more and more antimicrobial substances are starting to lose their curative activity and even to harm by beeing used abusively without results (Gupta, 2018). Estimations are that antimicrobial resistance (AMR) will be held responsible by 2050 for the death of 10 milions of people (Shankar, 2016) and CoVID pandemic seems to be worsening and speeding up the process due to unauthorised prescriptions and high rates of biocides used (Lucien et al., 2021). In what concerns a *One Health* approach, it can be mentioned that the areas involved both in the originate of the AMR and also in finding alternative ways to reduce it are human, animal and environmental sectors (Palma et al., 2020). Regarding the fact that the development of new antimicrobial substances is happening at a relatively slow rate (Chebotar et al., 2021), some alternative methods can be mentioned such as genetical approaches, viral attacks, fecal microbiota transplants and last but not least nanotechnological approach (Gupta, 2018). Nanotechnology has become indispensable in almost every sector and presents an important research interest for biomedical applications (Castro et al., 2020). Defined as the understanding and restructuring of biomaterials to the order of nanometers, it has a remarcable role in responsible but most of all controlled drug administration, aiming to deliver the active compounds at predefined rates and targeting a specific group of cells (Safari & Zarnegar, 2014). The development of antimicrobial therapy through nanoparticle systems allows the achievement of the therapeutic effect with the minimum dosage and it can be applied due to their unique physicochemical properties (Kalhapure et al., 2017). In this framework, the review aims to highlight the main mechanism of AMR, the role of overdosing the antimicrobial substances and also the implications of nanotechnology in combating this phenomenon. Moreover, our main focus is on describing the main drug delivery systems, their advantages and limitations and the medical applications possible for combating the overdosing and overusing antimicrobial substances.

MATERIALS AND METHODS

Succeeding a bibliographic study, scientific articles were selected from the *Web of Science Core Collection* database, they were centralised and classified according to specific key words. An ascendant trend was observed by searching the key words "antibiotic-loaded nanoparticles", and since their first citation (2010) and the current year (2022), an increase of 300% of the number of publication was observed, resulting a growing interest for researchers in varied areas of interest.

THE PHENOMENON OF ANTIMICROBIAL RESISTANCE

Microorganisms that are naturally sensitive to the action of an antibiotic may sometimes develop partial or total resistance either by destroying the antibiotic or by maintaining the bacterial growth even in the presence of the active substance which should inhibit the growth and development (Premlatha, 2019). Microbial resistance to antibiotics is a serious public health problem being largely caused by the inappropriate use of active substances and all aproaches, including the *One Health* principle, in order to analyse this phenomenon, should consider also that deaths are still ocurring in developing countries due to lack of access to appropriate antibiotic treatment (Ma et al., 2016). A rapid increase in the number of antibiotic-resistant microorganisms, together with the relatively slow development and late implementation of the new antimicrobials, poses a serious threat to humanity (Ma et al., 2016). International organizations have launched a series of complex activities aiming to limit the spread of bacterial resistance, including monitoring resistance, managing and analysing data obtained and also approving and inducing relevant administrative and legislative decisions and proposed novel approaches for combatting antimicrobial resistance (Eleraky et al., 2020). Therefore, antibiotic resistance can be defined as the ability of bacteria to reproduce in the presence of a certain concentration of drugs, which exceeds the normal concentration of the antibiotic used. The inherited ability of microorganisms to grow at high concentrations of an antibiotic, regardless of the duration of the treatment is quantified by the minimum (low) inhibitory concentration of that antibiotic, formula that is often used to evaluate the eficacity of an active substance (Brauner et al., 2016).

THE ROLE OF NANOMEDICINE

The appearance of highly pathogenic bacteria together with the limited production of new antibacterial substances have led to the inefficency of current antibiotic therapy with relevant risks in both human and veterinary medicine (Parisi et al., 2017). The availability of new antibacterial drugs is a very complex process, given the ability to produce and apply new effective and safe drugs, in addition to the high production costs and the time required for the approval of new drugs, which can take more than 10-15 years (Eleraky et al., 2020). Nanotechnology plays a vital role in increasing the efficacy of existing antimicrobial substances by increasing their physicochemical properties and stability, prolonging their release, ability to act directly at the site of the infection and improving systemic circulation, with a subsequent reduction of the associated side effects, compared to the classic medications used so far in therapy (Eleraky et al., 2020; Kalhapure et al., 2015). The physicochemical properties of nanosystems as particle size, surface charge and solubility are key factors that control vital processes, such as intracellular absorption or biodistribution. Nanometer-sized substances allow better loading efficiency of both hydrophilic and lipophilic drugs, thus improving the antibacterial effect (Bottaro, Larsen, 2008). In addition, for a better penetration into the cells of nanosystems loaded with antibiotics, the transition to the reticuloendothelial system was performed, therefore improving cell biodistribution and absorbtion. Host cells, such as anionic macrophages, attract positively charged nanosystems compared to uncharged or negatively charged ones (Eleraky et al., 2020).

TYPES OF ANTIBIOTIC-LOADED NANOPARTICLES

Nanosystems can be classified according to the properties of the matrix and the material in which they are loaded, therefore being divided into inorganic and organic nanosystems (Baranwal et al., 2018). It can also be mentioned that certain NMs (nanomaterials) posses antimicrobial ability by themselves, while others require proper biochemical modifications including conjugations or loading with antimicrobial substances, acting as delivery agents (Eleraky et al., 2020; Parisi et al., 2017). Inorganic nanosystems come from inorganic oxides and their synthesis technique depends on the chemical reduction of metal salts with a reducing substance. Environmental parameters (e.g. temperature, pH) play a major role in determining the specificities of these capacity, but rather the improvement, optimization and bioavailability of the material used and also the ability to deliver patient benefits (Mcdonald et al., 2015). Therefore, polymeric nanoparticles are less than 100 nm in size, and are composed of biodegradable and biostable polymers, copolymers and drug molecules that can be entrapped, encapsulated, physically adsorbed on the surface or chemically linked to the surface of the particle (Safari & Zarnegar, 2014).

CONCLUSIONS AND DISCUSSIONS

Following the bibliographic study, the nanotechnology seems to be representing the most promising solution to the phenomenon of antimicrobial resistance caused mainly by overdosing the active substances (Skwarczynski et al., 2022). Therefore, antibiotics like ciprofloxacin (Ibrahim et al., 2015), gentamicin (Huang et al., 2016), enrofloxacin (Paudel et al., 2019) and so many others can be improved in terms of performance by also minimising the dosage and reducing the risk of overdosing. The clinical application of nanomedicine is generally difficult to achieve due to limited time resources and high costs. The main challenges are related to clinical translation regarding the biological properties such as safety, biocompatibility, intellectual property, legal directives and also the release of in vitro drugs and therefore their antibacterial activity (Eleraky et al., 2020). Organic nanosystems, such as liposomes, lipid based nanoparticles, polymer micelles or polymer nanoparticles have better biodegradability and biocompatibility, thus constituting the main choice in clinical use (Parisi et al., 2017; Safari & Zarnegar, 2014). Known and mentioned in scientific literature since 1920, polymer science was able to provide synthetic chemistry options and also to initiate the first clinical applications two decades later (Mcdonald et al., 2015). Polymeric nanoparticles are highly used as nanocarriers due to their high structural integrity, stability during storage, method of synthesis and preparation and controlled release at the desired site (Alonso, 2004; Donelli, 2014). A general agreement has been formed that the size range is not as important, the overall advantages and profitability compared to the traditional way of treatment (Eleraky et al., 2020). These barriers limit the use of nanoparticles in the current protocols of treatment regardless of their effectiveness. Certain aspects need to be considered before the clinical approach of nanomedicine as follows: *the nanopharmaceutical design* (can influence the physical and chemical stability, biodegradability, way of administration and also the possibility of having a comercial product), *the preclinical evaluation* (the need to evaluate *in vitro* the cytotoxicity, the pharmacocinetics and pharmacodynamics and toxical evaluations) and *the clinical evaluation* (clinical trials in order to establish the practical applicabiliy of the antibiotic-loaded nanoparticles) (Eleraky et al., 2020).

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