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Review Article

Antibiotic loaded biodegradable polymeric based micro/nanoparticles potentials for multidrug resistant bacteria treatment

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ABSTRACT

The spread of the antibiotic-resistant bacteria has become a serious global concern that demands the implementation of remedial strategies to control this health-threatening problem, different approaches have been investigated, and using nano-materials represents one of the promising strategies, and the biodegradable polymeric micro/nano-particles may be a good candidate owing to its low cytotoxicity, bio-compatibility, selectivity, and the ability to release the loaded antibiotic in a precise sustained and controlled manner, in addition to an alteration of the antibiotic/microbial cell interaction mode. This review will shed light on using antibiotic loaded biodegradable polymeric micro/nanoparticles as a platform for more efficient treatment of antibiotic resistant bacteria.

Keywords: Antibiotic delivery, Biodegradable polymers, Micro-particles, Multi-drug resistance, Nano- particles

INTRODUCTION

In 2019, the World Health Organization included antimicrobial resistance (AMR) as one of the top ten threats to global health,[1] this resistance can occur through several mechanisms including the prevention of the antibiotic from interaction with the target site of action, pumping the antibiotic out of the target cell, and the microbial enzymatic modification or destruction of the antibiotic molecule.[2] The conventional approaches for infectious diseases treatment that are based on oral or systemic administration in a high doses are sometimes unable to give the desired results, above that there is a possibility for the appearing of some side effects in addition to the relatively high cost, and patient discomfort,[3] and one of the most promising tools to overcome these drawbacks is using biodegradable polymeric-based micro/nanoparticles as a carrier for the antibiotics the thing that will have a positive impact on the antibiotic fate within the human body (change the pharmacokinetics, bio-distribution, tissue deposition, and cell penetration),[4] biodegradable polymers are classified according to its origin into natural (sodium alginate, cellulose, chitosan, hyaluronic acid, dextran, etc.), and synthetic (Polyglycolic acid, Poly [lactic-co-glycolic acid] [PLGA] Poly–ε-caprolactone [PCL], Polyvinyl alcohol, etc...) that these polymers have a general characteristics of biocompatibility, low toxicity, flexibility, and controlled and sustain release.[5]

So instead of entering into the typical cycle of new AMR, another proposed strategy should be adopted to avoid resistance, and that can be realized by the appropriate selection of delivery

systems that can achieve a precise delivery in addition to the enhancement of the accessibility of antibiotics to the site of action, which are considered as the key determinants of the clinical outcome.[6]

METHODOLOGY

A number of the most relevant data were collected and screened, and several experimental examples were arranged in such a way to serve the purpose.

DISCUSSION

In an *in vivo* study Zhang *et al*. found that the survival incidence in *Staphylococcus aureus* infected Zibra Larvae fish was higher when treated by gelatin micro-spheres loaded with vancomycin in comparison with that treated by free vancomycin systemically the thing that highlights the role of these vector in increasing the vancomycine antimicrobial effect,[7] furthermore in another *in vitro* study Aksoy *et al*. reported the efficiency of gelatin composite micro-spheres loaded with vancomycine against *S. aureus* and *Staphylococcus epidermidis* and the possibility to be used in Osteomyelitis (bone infection disease) treatment.[8]

Furthermore, Mohd Sabee *et al*., in a study (*in vitro*) to verify the susceptibility of gentamicin when loaded in PLA micro-spheres against *S. aureus* and *Escherichia coli*, found that gentamicin released in a controlled and sustained manners that were able to kill the mentioned microbial strains.[9]

Jiao *et al*., in an *in vivo* study, reported the successful use of PLGA micro-spheres loaded with an antimicrobial peptide (OH-CATH30) for the treatment of keratitis caused by bacteria, and a remarkable antibacterial effects were observed both *in vitro* and *in vivo* in the slow antibiotic release mode.[10] While Le *et al*. in an *in vitro* study revealed that there was an enhancement of the antimicrobial activity against planktonic and biofilm forms of S. aureus when treated by Ciprofloxacin and levofloxacin PLGA loaded nanoparticles.[11] Moreover, regarding the release profile (pharmacokinetics), Filipović *et al*. found in a study (*in vitro*) that PCL Poly (ε-caprolactone) micro-spheres was able to release selenium nanoparticles in a controlled manner with a considerable antibacterial activity against: *S. aureus* (ATCC 25923) and *S. epidermidis* (ATCC 1228).[12] And to demonstrate the micro/nano-particles role in increasing the antimicrobial potency, Cruz *et al*. found in a comparison study that GIBIM-P5S9K (new antimicrobial peptide) loaded PLA, and PLGA nanoparticles were able to inhibit the growth of *E. coli* O157:H7, methicillin-resistant *S. aureus,* and *Pseudomonas aeruginosa* in q concentration of 50% of the free form of the antibiotic.[13]

Within the same context of antibiotic potency enhancement, Piras *et al*. found in a study that temporin B (antimicrobial peptide) loaded in chitosan nanoparticles had an increased anti-microbial activity against *S. epidermidis* with a reduced toxicity.[14] Above that Xiong *et al*. reported the ability of a differential delivery of vancomycin to the *S. aureus* infected cells, by a poly ε-caprolactone (PCL) based Lipas sensitive triple-layered nanogel causing effective killing of the infectious bacteria.[15] Moreover, Baier *et al*. designed an enzymatic responsive hyaluronic acid nanocapsules containing polyhexanide that exploited the enzymatic pathogenicity and invasion factor which is hyaluronidase as a triggering agent (that interact with hyaluronic acid) for the of antimicrobial agent release and consequently an efficient killing of bacteria such as *S. aureus* and *E. coli*.[16] Furthermore, Shaaban *et al*. found in an *in vitro* study that the impenem-loaded PCL nanoparticles caused faster microbial killing of resistant isolates of *Klebsiella pneumoniae* and *P. aeruginosa* within 2–3 h compared with free drug, antibiotic protection against enzymatic degradation, and most importantly preventing the development of resistant colonies.[17] Aboelenin *et al*. reported on a study on fluoroquinolone resistance *Acinetobacter baumannii* from different resistance clinical isolates that ciprofloxacin and levofloxacin-loaded PCL nanoparticles were able to kill these resistant strains within 5–6 h in a 1.5–6 and 6–12-fold decrease in the minimum inhibitory concentration MIC, in addition to the ability of the prepared nanoparticles to overcome the efflux pumps mediated resistance for these antibiotics.[18]

CONCLUSION

It is clear that using biodegradable polymeric micro/nano-particles in the treatment of antibiotics resistant bacteria has always an added value in comparison with the traditional approaches toward the increase of the microbial inhibitory effects of the antibiotics due to the ability of these vectors to alter the whole pharmacokinetics of the antibiotics in addition to the antibiotic-microbial interaction profile, and consequently more selectivity and precise controlled delivery, the thing that makes these tools as a promising strategy in overcoming the bacterial resistance to antibiotics.

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