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New active formulations against *M. tuberculosis*: bedaquiline encapsulation in lipid nanoparticles and chitosan nanocapsules

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In the last years, the increase in antimicrobial resistance, together with a lack of new drugs for the treatment of bacterial infections resistant to classical antibiotics are of growing concern. Moreover, some of current therapies induce severe side effects and are often difficult to administer. In 2012 the FDA approved the use of bedaquiline, as the first new very effective drug against TB in the last 40 years. Despite its effectiveness, unfortunately bedaquiline side effects can be so dangerous that at present it is to be prescribed only when no other treatment options are available. The development of effective and safe nanotechnology-based methods can be particularly relevant to increase antimicrobial concentration at the site of infection, to reduce doses in the general circulation, which in turn reduces adverse effects. In this work bedaquiline was encapsulated in two types of nanocarriers, lipid nanoparticles and chitosan-based nanocapsules with high encapsulation efficiency and drug loading values. The efficacy of the drug-encapsulating nanocarriers has been demonstrated *in vitro* against *Mycobacterium tuberculosis*, together with the excellent compatibility of both carriers with animal cells. The obtained results open the way for further studies on multi-drug resistant strains of *M. tuberculosis* and for *in vivo* studies of the optimized nanocarriers. The promising behaviour of drug-loaded nanocarriers will hopefully lead to a reduction of the administered doses of a quite dangerous drug as bedaquiline, tuning its biodistribution and so decreasing its adverse effects, finally allowing its use in a higher number of patients.

1. Introduction

Novel drug delivery systems based on nanocarriers are a promising strategy to overcome current therapeutic limitations thanks to nanomaterials unique physicochemical properties. These include their small size, which allows them to reach the cellular level, their high surface to volume ratio, which increases interactions with target cells and their ability to be structurally and functionally modified to control their biodistribution. In addition, nanocarriers allow the improvement of aqueous solubility of poorly soluble drugs, the drug protection in order to avoid its degradation before reaching its target, its selective transport to the sites of infection and the controlled release of the medication to decrease the frequency of administration [1].

Many studies have been carried out for different anti-TB drugs, showing the success and usefulness of this technology to improve the treatment of tuberculosis [2].

The increase in antimicrobial resistance observed in last years is of growing concern worldwide and only thirteen new antibacterial agents were approved by the Food and Drug Administration (FDA) between 1999 and 2011 [3]. *Mycobacterium tuberculosis* (TB) have developed a high level of drug resistance to