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Design, development, and characterisation of clofazimine-loaded mannosylated nanostructured lipid carriers: 3^3-Box-Behnken design approach

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ABSTRACT

The *Mycobacterium Tuberculosis* infection can be treated via clofazimine (CLF)-loaded nanostructured lipid carriers (NLCs). Precipitation-hot microemulsification-probe sonication method was employed for formulation of CLF-NLCs and optimised by using 3^3 Box–Behnken design. The surface of CLF-NLCs was modified with mannose ligands. The mannose modified and bare CLF-NLC formulations show highest encapsulation efficiencies greater than 70%. The preliminary evaluations were performed by using analytical techniques like Fourier transform infrared spectroscopy, differential scanning colorimetry, and powder X-ray diffraction studies. *In-vitro* drug release studies showed pH-dependent, sustained drug release profiles and best fitted for first order and Higuchi kinetics. The spherical morphologies of NLCs were confirmed by field-emission scanning electron microscopy. The formulations showed high storage stability at ambient and refrigerated conditions. Thus, present research successfully demonstrated the application of QbD principles in developing CLF-NLCs and improved the performance of CLF.

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Quality by Design (QbD); clofazimine; Nanostructured Lipid Carriers (NLCs); characterisation

Introduction

Tuberculosis (TB), one of the pandemic diseases worldwide killing three individuals per minute, is a disease that occurs due to infection of *Mycobacterium Tuberculosis* (*M Tb*) bacilli [1,2]. As per the World Health Organisation's (WHO's) global TB report 2018, about 10 million people developed TB infection out of which India is accounting for nearly 1/4th of the world's TB population. Also, as per the revised estimates provided by India TB report 2018 (RNTCP annual status report), out of 2,790,000 TB cases (together with HIV), 147,000 cases were found to have the rifampicin resistant TB (RR-TB) and multi-drug resistant TB (MDR-TB) that is caused by the development of resistance to rifampicin and isoniazid [3]. All these evidences depicted the high burden and severity of the TB disease.

WHO's global TB report 2016 suggested two sets of regimens such as conventional and shorter regimens for MDR-TB and RR-TB under which at least five drugs are required to be taken by the patient. Also, the degree of success of the MDR-TB treatment was only 52% that highlighted the limitations of the regimen [4]. Therefore, to minimise these limitations, we are proposing the supplemental therapy of clofazimine (CLF) loaded nanostructured lipid carriers (NLCs) intended for administration via the inhalation route.

A weak pipeline of alternative anti-TB drugs and the low evidence of resistance for CLF has rejuvenated our interest in selecting CLF for TB therapy [5]. As per the WHO global TB report 2019, CLF is currently under testing in phase-III trials as a part of 'endTB' and 'TB-Practecal' regimens for MDR-TB [2].

It is well-known fact that the *M Tb* bacilli are the acid-fast, obligate aerobe and intracellular pathogen which reside inside the oxygen-enriched acidic micro-environment of alveolar macrophages (AMs) [6,7]. Mannose receptors (MRs) are highly expressed on the surface of macrophages [8]. Therefore, for targeting these cells, mannose-coated nanocarrier systems are extensively explored in recent years. Our most recent manuscript highlighted potentials of mannose-coated nanocarriers such as site-specific delivery, improved pharmacokinetic/pharmacodynamic profiles, and enhanced transfection efficiency of the active moieties [9].

Amongst various nanocarriers, NLCs unveiled superiority like high encapsulation efficiency (% EE), good storage stability, controlled release drug profile, and good aerodynamic characteristics. More importantly, the fabrication of NLCs involve the use of biodegradable, biocompatible, and Generally Regarded as Safe (GRAS) listed excipients [10]. In the present attempt, NLCs are intended to develop for administration via inhalation route because of the presence of huge absorptive surface area (~100 m^2), enormously thin mucous membrane (0.1–0.2 μm), and highly vascular system [11]. Also, for

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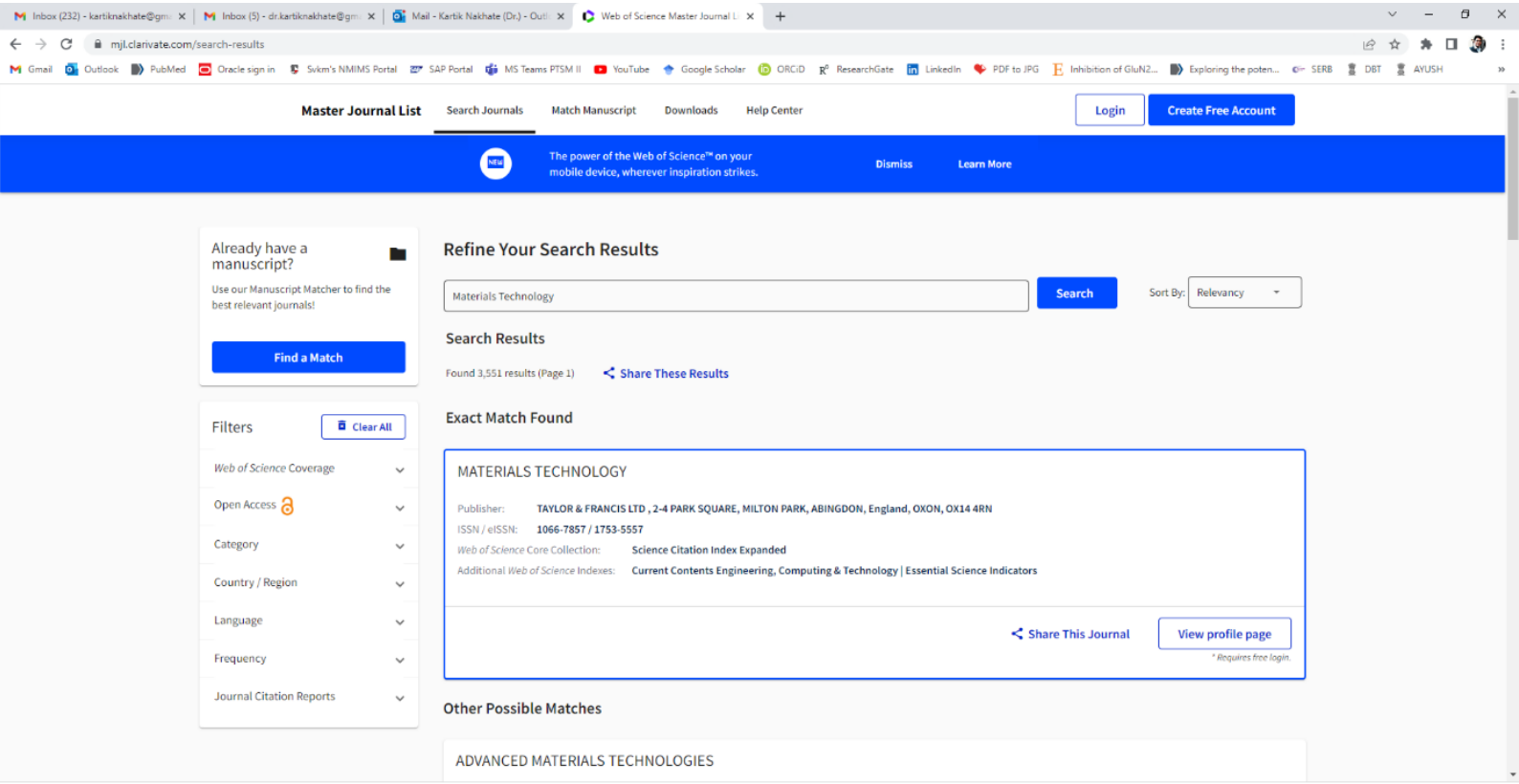
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