DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY
https://doi.org/10.1080/03639045.2021.1892743

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RESEARCH ARTICLE

Nanostructured lipid carrier-mediated lung targeted drug delivery system to enhance the safety and bioavailability of clofazimine

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ABSTRACT

Tuberculosis (TB) disease is caused due to the infection of *Mycobacterium tuberculosis* bacilli which reside in alveolar macrophages (AMs). Clofazimine (CLF) has been reinstated clinically for the treatment of TB. However, major challenge of using CLF is its severe side-effects after oral administration. The present research was aimed to establish the safety and enhance the bioavailability of CLF by loading it into nanostructured lipid carriers (CLF-NLCs) and mannosylated NLCs (M-CLF-NLCs) to selectively target the drug toward AMs. The safety of CLF-NLCs and M-CLF-NLCs was evaluated by *in vitro* hemocompatibility studies, cell viability studies on macrophage J774 cell lines, and *in vivo* acute inhalation toxicity studies. The bioavailability was estimated by single-dose pharmacokinetics and biodistribution studies. Hemocompatibility studies showed normal RBCs count and least hemolysis of 0.23 ± 0.081% for M-CLF-NLCs treated group. Cell viability studies revealed greater safety of NLCs than CLF-drug dispersion in the concentration range of 2.5–25 μg/ml. *In vivo* acute toxicity studies revealed no physiological or behavioral changes and no mortality recorded over 14 days period. In pharmacokinetic studies, a maximum concentration of the drug (C_{max}) of 35.44 ± 0.34 μg/g from M-CLF-NLCs after 48 h and longer residence time in lung tissues observed due to its sustained release and mannose receptor-mediated endocytosis. M-CLF-NLCs showed a maximum $AUC_{0-\infty}$ value of 2691.83 h μg/ml in lungs that indicated twofold greater bioavailability as compared to CLF-drug dispersion. Thus, mannosylated NLCs can be used as promising carriers for the safe and effective delivery of CLF via inhalation route for the management of TB disease.

ARTICLE HISTORY
Received 20 July 2020
Revised 10 November 2020
Accepted 1 February 2021

KEYWORDS
Clofazimine; nanostructured lipid carriers; macrophage J774 cell lines; acute toxicity; pharmacokinetics

Introduction

Tuberculosis (TB) is a common respiratory infectious disease, triggered due to *Mycobacterium tuberculosis* (*M Tb*) bacilli. *M Tb* bacilli are acid-fast, intracellular, and obligate aerobic microorganisms that reside within alveolar macrophages (AMs) internalized by the phagocytosis process. Though TB is a curable disease, it is one of the top 10 reasons for death killing three people per minute [1,2]. As per the current treatment suggested by the World Health Organization (WHO), at least five high-dose antibiotics need to administer over a long period (18–24 months) [3]. High pill burden and severe adverse effects of the antibiotics are responsible for discontinuation of the treatment earlier by the patients that is one of the reasons for the development of multi-drug resistant TB (MDR-TB). Furthermore, in the case of second-line injectable drugs, the presence of a healthcare worker is needed [2].

Hence, for minimizing the above-mentioned limitations of the regimen and for effective targeting toward the site of infection, CLF-loaded, mannosylated nanostructured lipid carriers (M-CLF-NLCs) are proposed. The proposed formulation will not only achieve a high local concentration of drug at the targeted site but also helps in reducing the dose and dosing frequency of the drug and thereby enhances patient compliance. It may also reduce the chances of development of MDR.

NLCs are composed of a mixture of solid and liquid lipids from 70:30 to 99.9:0.1. Therefore, by blending these lipids in different ratios, more space is made available for effective encapsulation of a drug. In recent years, NLCs are emerged as superior carrier systems concerning its high stability, the involvement of biocompatible, biodegradable, and generally regarded as safe (GRAS) listed excipients and sustained release profile [4].

Mannose receptors (MRs) belong to the C-type lectin receptors (CLRs) superfamily expressed in the mice or humans and can bind the mannose moiety. MRs mediate the phagocytosis and endocytosis of carbohydrates bearing microorganisms such as mycobacteria, Gram-positive and negative bacteria, yeasts, parasites, and mannosylated compounds. These receptors are highly expressed on the surface of antigen-presenting cells (APCs) like macrophages and dendritic cells. In our recent publication, we have highlighted the advantages of mannosylated nanocarriers like increased targeting efficiency and enhanced pharmacokinetic and pharmacodynamic profiles of active ingredients [5]. Therefore, the development of mannosylated NLCs can effectively target the *M Tb* bacilli infected AMs.

Clofazimine (CLF, B663) was reported as an antimycobacterial agent for the first-time by Vincent Barry and coworkers. It is highly lipophilic riminophenazine dye synthesized from compounds present in the lichen *Buellia canescens*.

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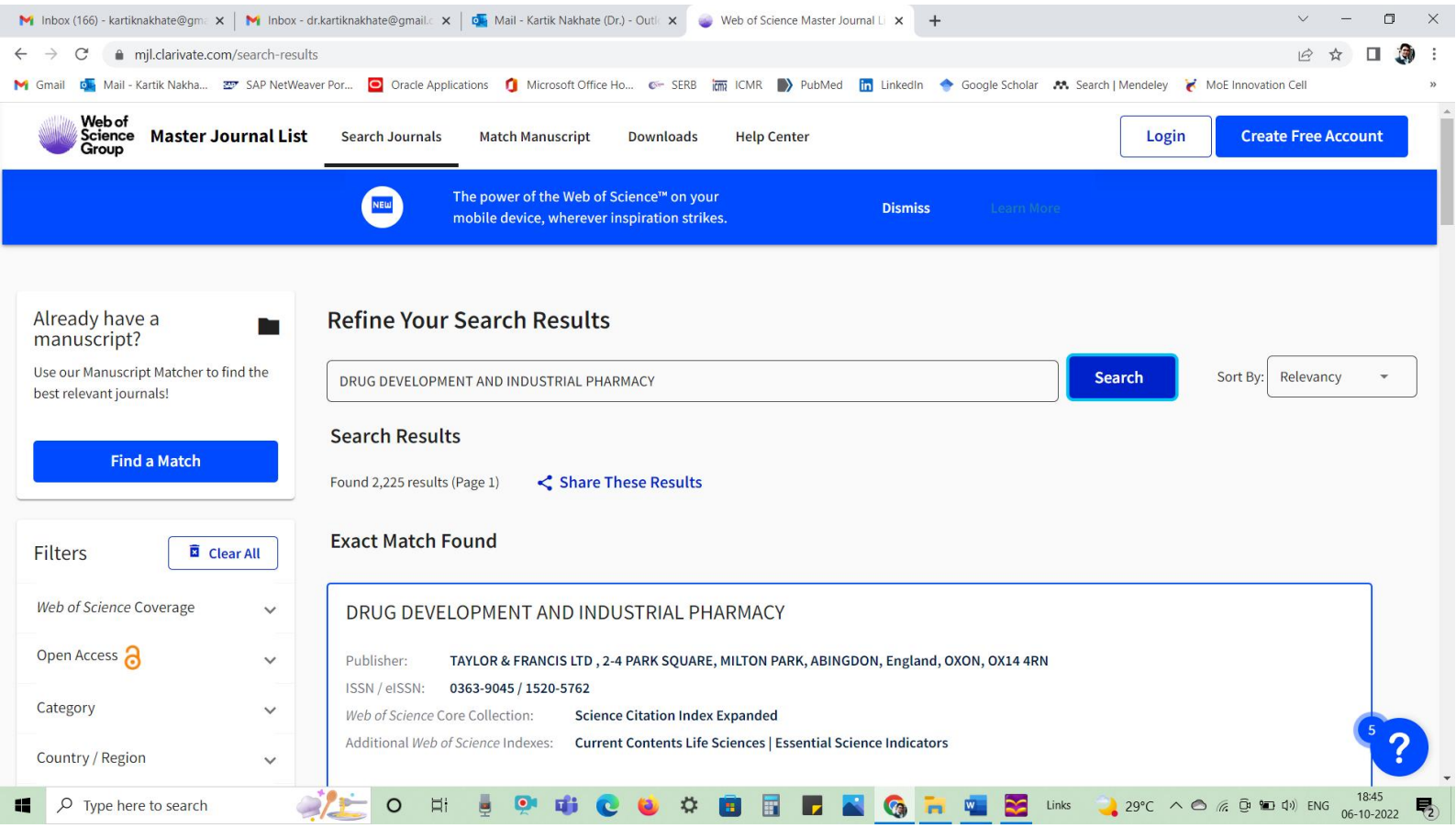
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