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RESEARCH ARTICLE

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# *In vitro* and *in vivo* characterization of Entacapone-loaded nanostructured lipid carriers developed by quality-by-design approach

Yogeeta Agrawal[a], Kiran Patil[a], Hitendra Mahajan[b], Mrugendra Potdar[a], Pratiksha Joshi[b], Kartik Nakhate[c], Charu Sharma[d], Sameer N. Goyal[c] and Shreesh Ojha[e]

[a]Department of Pharmaceutics, Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule, India; [b]Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, India; [c]Department of Pharmacology, Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule, India; [d]Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates; [e]Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, Abu Dhabi, United Arab Emirates

**ABSTRACT**

Entacapone, a reversible catechol-o-methyl transferase inhibitor, is used to enhance the action of dopamine agonists by reducing their metabolism and the 'Wearing-off' effects associated with long-term use in the treatment of Parkinson's disease. It is used as an adjunct to levodopa/Carbidopa therapy. Due to limited dissolution and first-pass clearance, it suffers low and variable bioavailability issues. To overcome this problem, the present study aims to explore the potential of nanostructured lipid carriers (NLCs) for the delivery of Entacapone. The Quality by Design (QbD) approach was used for the systematic development of NLCs. The $2^3$ full factorial designs were investigated using Design-Expert®11 software. The three independent variables namely content of total lipid (X1), surfactant (X2), and sonication time (X3) were optimized against two responses namely particle size and entrapment efficiency. The optimized NLCs were characterized for their size, surface morphology, entrapment efficiency, drug release, thermal and crystallographic studies. In-vivo pharmacokinetic studies in Entacapone-loaded NLCs showed an increase in $t_{1/2}$, $AUC_{0-\infty}$, MRT compared to free drug. The reduction in elimination (Kel) depicts the prolonged action of Entacapone by loading in NLCs. The results displayed Entacapone-loaded NLCs have promising potential for oral delivery and enhanced therapeutic effect which otherwise was a major issue.

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Parkinson's disease; Entacapone; quality by design; nanostructured lipid carriers

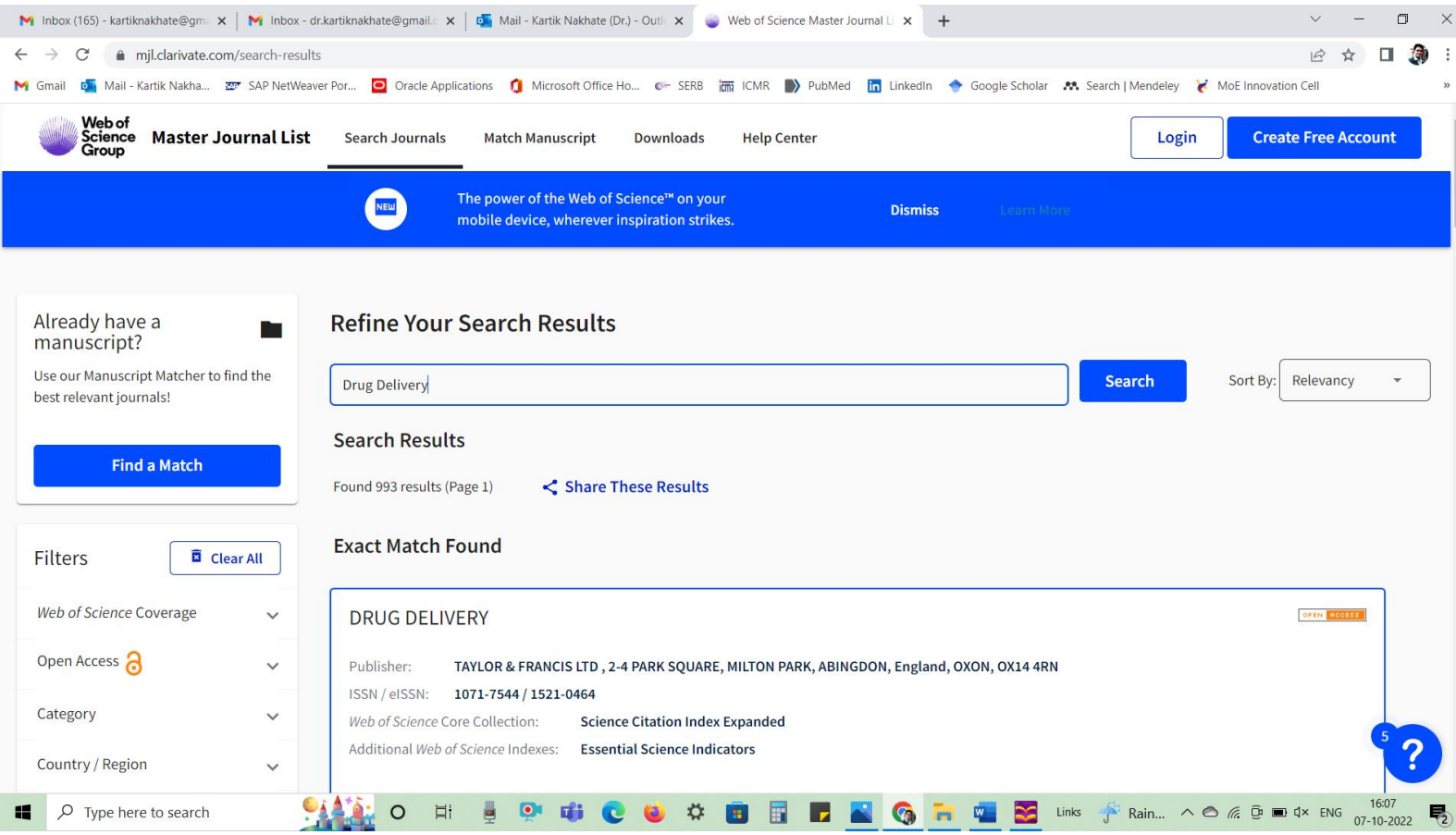
## Introduction

Parkinson's disease (PD) is a neurodegenerative disorder affecting 7–10 million people worldwide. It is caused due to the impairment of small areas in the brain that control posture, balance, and movement (DeMaagd & Philip, 2015; Dorsey et al., 2018). There is no perfect treatment available for PD; however, therapy aims to minimize the impact of symptoms. The symptomatic treatment involves dopamine agonists like levodopa and MAO-B inhibitors. However, conventional treatment becomes less effective as the disease worsens and produces end-of-dose adverse effects known as 'wear off' symptoms. These symptoms are characterized by the reappearance of both motor and non-motor movements of PD as a result of previous carbidopa-levodopa therapy (Chahine et al., 2020).

Entacapone, a nitro catechol compound (Figure 1), has been approved for clinical use in patients with PD. It inhibits the degradation of dopamine and levodopa by blocking the enzyme Catechol-O-Methyl Transferase (COMT) (Najib, 2001). It enhances the action of dopamine and reduces the onset of motor complications to a certain extent. It is used along with carbidopa-levodopa therapy to overcome the 'wear-off' symptoms (Antonini et al., 2018; Müller, 2020). But Entacapone is a BCS class IV drug with low aqueous solubility and low permeability (Bommaka et al., 2018). Moreover, the bioavailability may also be affected by high lipophilicity, pre-systemic clearance in the gastrointestinal mucosa, and the P-GP efflux mechanism (Garg et al., 2020). Therefore, the major challenge is to formulate the drug delivery system that possibly tackles all these problems and increases the bioavailability and residence of the drug.

Several technologies can be used to enhance the dissolution characteristic of such low solubility and low permeability drugs. A lipid-based formulation is an alternative approach for developing a product from laboratory scale to commercial level successfully (Wen et al., 2015). Lipid-based gallows are potential drug carriers due to their propensity to improve the solubility of lipophilic drugs and ultimately augment oral bioavailability (Ashkar et al., 2021).

CONTACT Yogeeta Agrawal goyalyogita@rediffmail.com Department of Pharmaceutics, Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule 424001, India; Shreesh Ojha shreeshojha@uaeu.ac.ae Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, Abu Dhabi, United Arab Emirates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