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Review

An Update on Advancements and Challenges in Inhalational Drug Delivery for Pulmonary Arterial Hypertension

Vinit Agnihotri [1], Yogeeta Agrawal [1,*], Sameer Goyal [1], Charu Sharma [2] and Shreesh Ojha [3,*]

[1] Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule 424 001, India; vinit.agnihotri@svkm.ac.in (V.A.); goyal.aiims@gmail.com (S.G.)
[2] Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain P.O. Box 15551, United Arab Emirates; charusharma@uaeu.ac.ae
[3] Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain P.O. Box 15551, United Arab Emirates
* Correspondence: yogeeta.goyal@svkm.ac.in (Y.A.); shreeshojha@uaeu.ac.ae (S.O.); Tel.: +91-2562-297802 or +91-2562-297805 (Y.A.); +971-3-7137524 (S.O.)

Abstract: A lethal condition at the arterial–alveolar juncture caused the exhaustive remodeling of pulmonary arterioles and persistent vasoconstriction, followed by a cumulative augmentation of resistance at the pulmonary vascular and, consequently, right-heart collapse. The selective dilation of the pulmonary endothelium and remodeled vasculature can be achieved by using targeted drug delivery in PAH. Although 12 therapeutics were approved by the FDA for PAH, because of traditional non-specific targeting, they suffered from inconsistent drug release. Despite available inhalation delivery platforms, drug particle deposition into the microenvironment of the pulmonary vasculature and the consequent efficacy of molecules are influenced by pathophysiological conditions, the characteristics of aerosolized mist, and formulations. Uncertainty exists in peripheral hemodynamics outside the pulmonary vasculature and extra-pulmonary side effects, which may be further exacerbated by underlying disease states. The speedy improvement of arterial pressure is possible via the inhalation route because it has direct access to pulmonary arterioles. Additionally, closed particle deposition and accumulation in diseased tissues benefit the restoration of remolded arterioles by reducing fallacious drug deposition in other organs. This review is designed to decipher the pathological changes that should be taken into account when targeting the underlying pulmonary endothelial vasculature, especially with regard to inhaled particle deposition in the alveolar vasculature and characteristic formulations.

Keywords: particles deposition; inhaled drug delivery; lipid nanoparticles; pulmonary arterial hypertension; targeted delivery; endothelial dysfunction

Citation: Agnihotri, V.; Agrawal, Y.; Goyal, S.; Sharma, C.; Ojha, S. An Update on Advancements and Challenges in Inhalational Drug Delivery for Pulmonary Arterial Hypertension. *Molecules* **2022**, *27*, 3490. https://doi.org/10.3390/molecules27113490

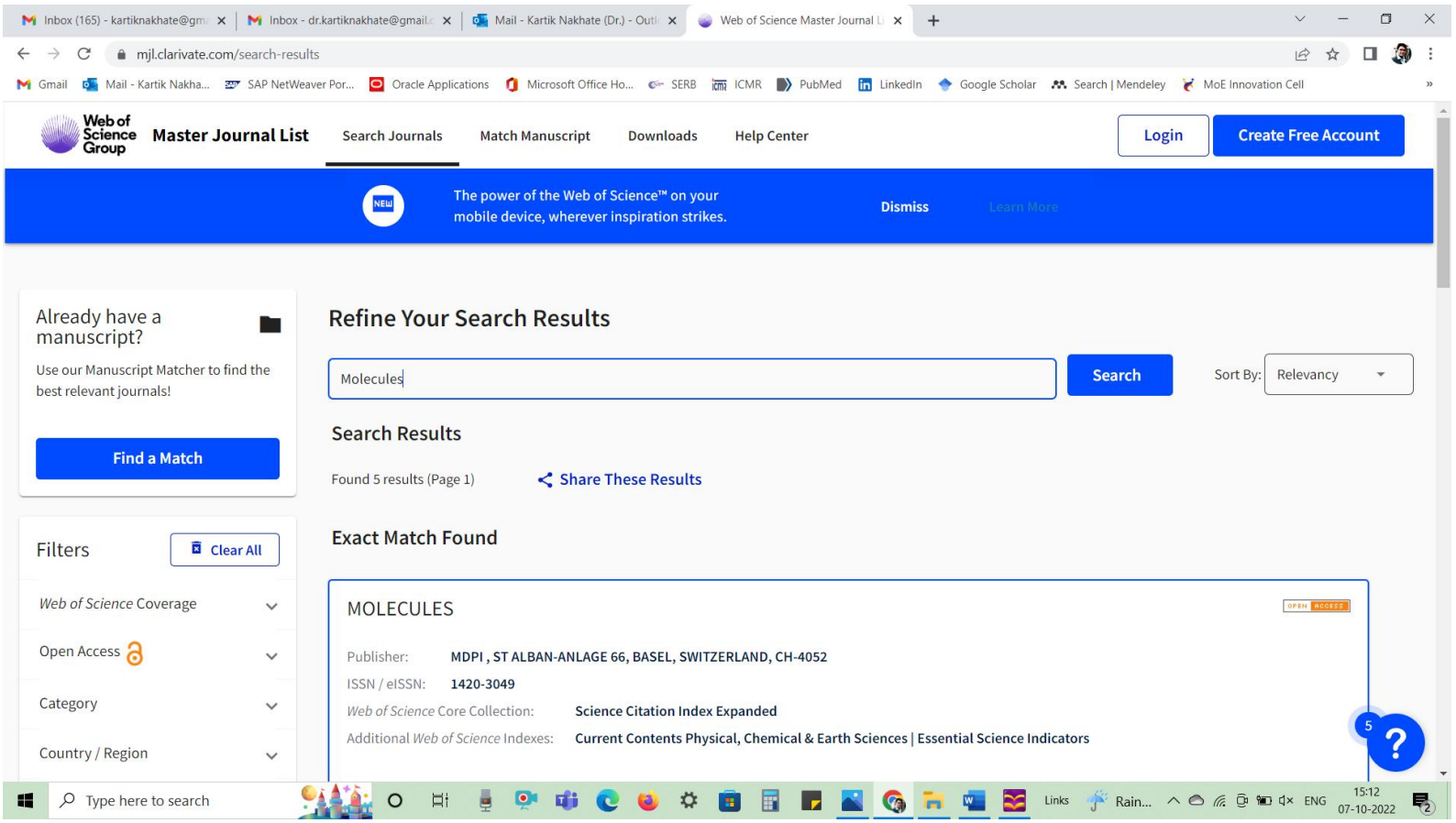
Academic Editors: Makoto Oba and Thomas Mavromoustakos

Received: 12 March 2022
Accepted: 17 May 2022
Published: 29 May 2022

1. Introduction

Cardiopulmonary disarray of arterial pressure that initiates a series of lethal events at the juxtaposition of capillaries and alveoli leads to pulmonary arterial hypertension (PAH). The characteristic vascular remodeling of distal arteries at the alveolus is followed by increased pressure of the arterioles above 25 mmHg, an ailment that is fatal and complex for the vasculature in the lungs, i.e., pulmonary circulation. This increased flow resistance in PAH, as well as the resulting overload at RV [1], causes diastolic dysfunction, which drives the cardiopulmonary vasculature to fibrosis, hypertrophy, and hyperplasia [2,3]. All the above episodes lead to failure of the right heart, which is a significant provenance of mortality in PAH patients [4]. Hemodynamically, there is an elevation in mean pulmonary artery pressure (mPAP) $\geq$ 30 mmHg, while standard left ventricular refilling pressures are retained at normal levels. Nevertheless, the mPAP at rest is $\geq$25 mmHg [5].

Therapeutics for PAH operate in the pursuit of chief pathways such as inhaled NO or Nitric Oxide/cGMP, prostacyclin and its analogs, the endothelin pathway, soluble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Inbox - dr.kartiknakhate@gmail.c
Mail - Kartik Nakhate (Dr.) - Outl
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