



Original article

Mannosylated PAMAM G2 dendrimers mediated rate programmed delivery of efavirenz target HIV viral latency at reservoirs

Rohini Kharwade^a, Mohsin Kazi^b, Nilesh Mahajan^{a,*}, Payal Badole^a, Sachin More^c,
Asaad Kayali^d, Md Noushad Javed^e, Mohammed Kaleem^{c,**}

^a Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, MS, India

^b Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

^c Department of Pharmacology, Dadasaheb Balpande College of Pharmacy, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra 440037, India

^d Department of Biomedical Sciences, College of Health Science, Abu Dhabi University, Abu Dhabi P.O. Box 59911, United Arab Emirates

^e NationNanotechnology Center of Excellence, College of Engineering and Computer Science, The University of Texas Rio Grande Valley, Edinburg, TX, USA

ARTICLE INFO

Keywords:

PAMAM G2

Mannose conjugation

Efavirenz

Ritonavir

Viral reservoir

Targeted drug delivery

ABSTRACT

In this current research, we conceptualized a novel nanotechnology-enabled synthesis approach of targeting HIV-harboring tissues via second-generation (G2) polyamidoamine (PAMAM) mannosylated (MPG2) dendrimers for programmed delivery of anti-HIV drugs efavirenz (EFV) and ritonavir (RTV). Briefly, here mannose served purpose of ligand in this EFV and RTV-loaded PAMAM G2 dendrimers, synthesized by divergent techniques, denoted as MPG2ER. The developed nanocarriers were characterized by different analytical tools FTIR, NMR, zeta potential, particle size, and surface morphology. The results of confocal microscopy showed substantial alterations in the morphology of H9 cells, favored by relatively higher drug uptake through the MPG2ER. Interestingly, the drug uptake study and cytotoxicity assay of MPG2ER demonstrated that it showed no significant toxicity up to 12.5 μ M. A typical flow cytometry histogram also revealed that MPG2ER efficiently internalized both drugs, with an increase in drug uptake of up to 81.2 %. It also enhanced the plasma pharmacokinetics of EFV, with C_{max} 7.68 μ g/ml, AUC of 149.19 (μ g/ml) * hr, and MRT of 26.87 hrs. Subsequently, tissue pharmacokinetics further evidence that MPG2ER accumulated more in distant Human immunodeficiency virus (HIV) reservoir tissues, such as the lymph nodes and spleen, but without exhibiting significant toxicity. Abovementioned compelling evidences strongly favored translational roles of MPG2 as a potential therapeutic strategy in the clinical eradication of HIV from viral reservoir tissue.

1. Introduction

Human immunodeficiency virus (HIV) is a single-stranded (ss) RNA enveloped retrovirus; belongs to *lentivirus* family. Among the majority of HIV cases, HIV-1 is primarily responsible for the worldwide AIDS pandemic (Seitz, 2016). HIV propagation requires active CD4 host cells. Once viral gp120 adheres to the host CD4 receptor, it forms a CD4-gp120-chemokine receptor complex (Rojekar et al, 2021a). Through this complex, the viral particle enters the cell and initiates the virus cycle

(Rojekar et al, 2021b).

Several factors are responsible for managing HIV infection, including latent viral reservoir sites. These sites are inaccessible for various drugs and drug delivery systems owing to contribution of several factors, more particularly inadequate perfusion of drugs to the specific tissues and elimination of therapeutic moieties via P-gp efflux pumps. Highly active antiretroviral therapy (HAART) with two or three classes of drugs is also not effective at delivering a sufficient concentration of drugs and is therefore inefficient at controlling infection. Suitable concentrations of

* Corresponding author at: Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, MS 440037, India.

** Corresponding author at: Department of Pharmacology, Dadasaheb Balpande College of Pharmacy, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, 440037, India.

E-mail addresses: rohinismore1@gmail.com (R. Kharwade), mkazi@ksu.edu.sa (M. Kazi), nmmahajan78@gmail.com (N. Mahajan), payalbadole09@gmail.com (P. Badole), sam007more@gmail.com (S. More), asaadkayali@hotmail.com (A. Kayali), rxnoushad@gmail.com (M. Noushad Javed), kaleemmubin88@gmail.com (M. Kaleem).

<https://doi.org/10.1016/j.jsps.2024.102154>

Received 23 March 2024; Accepted 7 August 2024

Available online 13 August 2024

1319-0164/© 2024 The Author(s). Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).