COMPUTATIONAL FORMULATION AND EVALUATION OF NANO-PARTICULATE SYSTEMS FOR PULMONARY ARTERIAL HYPERTENSION TREATMENT: QUALITY BY DESIGN AND PHYSIOLOGICAL MODELLING

[1]AMANY K. ELZOGHBY, [2]NADA M. EL HOFFY, [3]REHAB N. SHAMMA, [4]AZZA A. MAHMOUD

[1]Egypt children hospital, Cairo, Egypt
[2, 4]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Future University in Egypt, Cairo, Egypt
[3]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, Egypt
E-mail: nadahoffi@hotmail.com

Pulmonary arterial hypertension (PAH) is a disease characterized by elevated blood pressure in the pulmonary arteries.Although endothelin receptor antagonists (ERA) as bosentan, ambrisentan and macitentanrepresent a cornerstone in the treatment protocols of PAH, yet their oral formspose many drawbacks including potential liver toxicity and teratogenicity.The aim of this work is the computational development, characterization and optimizationofnanoparticulate systems encapsulating ERA for pulmonary delivery utilizing Quality-by-design approach using Design® Expert. A 3^3 full factorial experimental designwas constructed,wherethe independent variables were the ERApercentage, leucine% and solubilizer amount. The targeted systems were prepared using nano-spray drying technique and the obtained formulations were characterized for their particle size (PS), zeta potential (ZP), polydispersity index (PDI), yield percentage (Y%), drug loading percentage (DL%) and drug content percentage (DC%). Results revealed the significance of all the constructed models except the ZP model. All obtained nanoparticulate systems exhibited PS ranging from 90.35±2.05 to 157.30±51.70nm with PDI values ranging from 0.19±0.01 to 0.86±0.17. The observed values for Y%, DL% andDC%ranged from 1.70±0.09 to 33.00±3.00, 0.11±0.01 to 16.44±00.05and 3.29±0.04 to 38.10±0.02, respectively.The optimized formulation exhibited a sustained in-vitrorelease profile compared to the drug solution evidenced by its prolonged release parameters. Moreover, the inhalation profile of the optimized formulation investigated using the cascade impactor revealed the agreable aerosilization profile of the optimized formulation for the deep delivery of the drug into the lungs. Finally, a PBPK model was constructed to predict the clinical behavior of the optimized formulation upon inhahalion. Results of the physsiological modelling alligned with the obtained results from the cascade impactor in terms of penetrability and deposition of the prepared nanosystems. In conclusion, the prepared ERA loaded nanparticulate systemsproved their potentiality for the effective deep pulmonary delivery of the drug.