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QbD based development of proliposome of lopinavir for improved oral bioavailability

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Abstract

Aim of present work was to apply quality by design (QbD) principles for the development of proliposome of poorly soluble lopinavir (LPV). The patient-centric quality target product profile (QTPP) was defined and critical quality attributes (CQAs) earmarked. Risk assessment studies were carried out to identify the probable risks affecting the CQAs of the product. On the basis of preliminary study, lipid:drug ratio and amount of carrier were selected as critical material attributes (CMAs) and were optimized by face centered central composite design. Liposome vesicle size, drug entrapment efficiency and % drug release after 60min were selected as CQAs and mathematical relationship between CQAs and CMAs was derived using multiple linear regression analysis. Optimum composition of CMAs, identified using numerical optimization and desirability function, demonstrated excellent entrapment efficiency (>90%), drug release characteristics (>95% in 60min) and had vesicle size of 659.7±23.1nm. Solid state characterization studies (Differential Scanning Calorimetry, scanning electron microscopy and X-ray diffraction) were performed for optimized proliposome, suggested

transformation of crystalline to amorphous form. Oral bioavailability study in Wistar rats revealed that LPV proliposome exhibited 2.24 and 1.16 fold higher bioavailability than pure LPV and available commercial formulation of LPV/RTV (lopinavir+ritonavir), respectively. Stability study of the optimized LPV loaded proliposome was performed as per ICH guideline and was found to be stable for period of 6months. Overall results of the study indicate that the proliposome offers advantages of enhanced oral bioavailability for poorly soluble LPV.

Keywords: Acetonitrile (PubChem CID: 6342); Bioavailability; Design of experiments; Lopinavir; Lopinavir (PubChem CID: 92727); Maltodextrin (PubChem CID: 107526); Mannitol (PubChem CID: 6251); Methanol (PubChem CID: 887); Microcrystalline cellulose (PubChem CID: 14055602); Monobasic disodium phosphate (PubChem CID: 24203); Potassium dihydrogen phosphate (PubChem CID: 516951); Proliposome; Quality by design; Sodium hydroxide (PubChem CID: 14798); Solubility; Sorbitol (PubChem CID: 5780).

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