# Ethosome-Derived Invasomes as a Potential Transdermal Delivery System for Vardenafil Hydrochloride: Development, Optimization and Application of Physiologically Based Pharmacokinetic Modeling in Adults and Geriatrics

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**Abstract**

Aim: The aim of the current work was to develop vardenafil hydrochloride (VRD)-loaded ethosome-derived invasomes as a possible transdermal system which could be used for patients suffering from pulmonary arterial hypertension. Methods: VRD-loaded ethosomes were developed at three concentrations of phosphatidylcholine (5, 10 and 15 mg/mL) and three percentages of ethanol (20%, 30% and 40%, v/v). The best achieved VRD-loaded ethosomes (ETH9) were optimized to invasomes via incorporation of terpenes (limonene, cineole and a 1:1 mixture) at three concentrations (0.5%, 1% and 2%, v/v). All systems were evaluated for vesicle size, zeta potential, drug entrapment efficiency (EE%), cumulative drug permeated percentages after 0.5hrs (Q0.5h) and 12hrs (Q12h) and steady-state flux (Jss). The optimized system (ETH9-INV8) was further characterized for morphology, histopathology and confocal laser scanning microscopy (CLSM). Physiologically based pharmacokinetic (PBPK) modeling was employed to estimate VRD pharmacokinetic parameters from the optimized transdermal system and an oral aqueous drug dispersion, in adults and geriatrics. Results: The optimized invasomal system (ETH9-INV8) was characterized with spherical vesicles (159.9 nm) possessing negative zeta potential (ī20.3 mV), promising EE% (81.3%), low Q0.5h (25.4%), high Q12h (85.3%) and the largest steady-state flux (6.4 Õg.cmī2 hī1 ). Following a leave-on period of 12hrs in rats, it showed minor histopathologic changes. CLSM studies proved its ability to deeply permeate rat skin. Lower Cmax values, delayed Tmax estimates and greater AUC0-24h folds in adults and geriatrics (å 2.18 and 1.69, respectively) were estimated following the transdermal application of ETH9-INV8 system. Conclusion: ETH9-INV8 is a promising transdermal system for VRD

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