Pharmacokinetic Evaluation of Improved Oral Bioavailability of Valsartan

The purpose of this study was to develop proliposomes and self-nanoemulsifying drug delivery system (SNEDDS) for a poorly bioavailable drug, valsartan, and to compare their in vivo pharmacokinetics. Valsartan is used to treat high blood pressure, congestive heart failure, and to reduce death for people with left ventricular dysfunction after having had a heart attack. According to the report of American heart association, cardiovascular disease is the leading global cause of death, accounting for 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. About 85.6 million Americans are living with some form of cardiovascular disease or the after-effects of stroke.

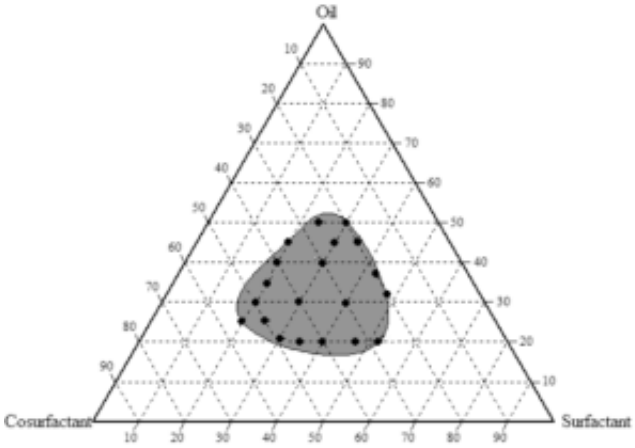

Fig.1. Ternary phase diagram of valsartan SNEDDS

Direct and indirect costs of cardiovascular diseases and stroke total more than $320.1 billion. This includes health expenditures and lost productivity. Valsartan, orally active angiotensin receptor blockers, inhibits the renin angiotensin system by selectively blocking the angiotensin type 1 subtype of angiotensin II receptor. Low permeability of valsartan was reported due its two acidic centers, the carboxylic acid group (COOH–) and tetrazole ring with pKa values of 4.7 and 3.9 respectively. Due to these two close pKa values the drug exhibits poor solubility and low permeability in the gastro-intestinal tract. In adults, the absolute bioavailability of valsartan following oral administration is approximately 23%. Both proliposomes and SNEDDS are emerging platform technologies for improving the oral delivery of drugs with poor bioavailability. Proliposomes were prepared by thin-film hydration method using different lipids such as soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), distearyl phosphatidylcholine (DSPC), dimyristoylphosphatidylcholine (DMPC), and dimyristoyl phosphatidylglycerol sodium (DMPG) and cholesterol in various ratios. SNEDDS formulations were prepared using varying concentrations of

capmul MCM, labrafil M 2125, and Tween 80. Although proliposomes and SNEDDS are well known for bioavailability enhancement, no study was reported till date comparing both the delivery technologies for improved oral delivery. Therefore, in this study, we made an attempt to compare these drug delivery systems for improved in vitro and in vivo performance. SNEDDS is a well-established platform technology with successful products in the market; however, there is no approved proliposomal-based drug product for oral delivery in spite of its extensive utilization in the formulation research in last two decades.

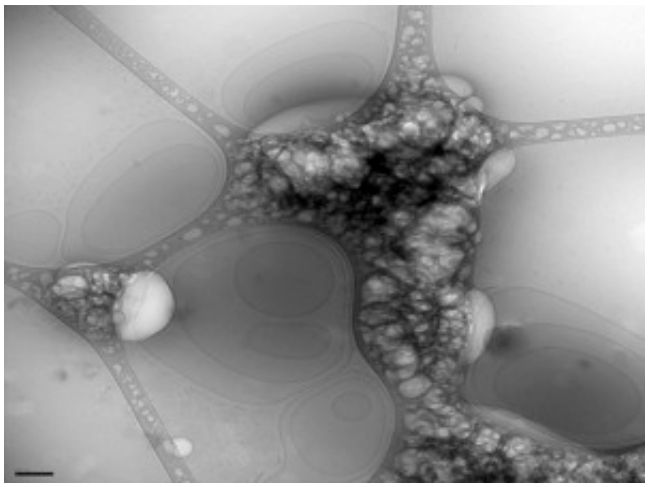

Fig. 2. Cryo-TEM image showing the oligolamellar vesicles of valsartan proliposomal formulation

Both proliposomes and SNEDDS were evaluated for particle size, zeta potential, in vitro drug release, in vitro permeability, and in vivo pharmacokinetics. In vitro drug release was carried out in a discriminating dissolution media(s) using USP type II dissolution apparatus. In vitro drug permeation was studied using parallel artificial membrane permeation assay (PAMPA) and everted rat intestinal permeation techniques. Enhanced drug release was observed with proliposomes and SNEDDS as compared to pure valsartan. Valsartan permeability across PAMPA and everted rat intestinal permeation models was significantly higher with proliposomes and SNEDDS compared to pure valsartan suspension. The study results indicated that both proliposomes and SNEDDS formulations are comparable in improving the oral bioavailability of valsartan. The research contribution may substantially benefit the fight to cure or prevent cardiovascular diseases. Improving the oral delivery of valsartan may significantly enhance the therapeutic response and reduction in the overall dose resulting in reduced toxicity risk.

Publication

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