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Encapsulation of Venlafaxine-Dowex® Resinate: A Once Daily Multiple Unit Formulation

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Abstract : Introduction: Major depressive disorder affects high proportion of the world's population presenting cost load in health care. Extended release venlafaxine is more convenient and could reduce discontinuation syndrome. The once daily dosing also reduces the potential for adverse events such as nausea due to reduced Cmax. Venlafaxine is an effective first-line agent in the treatment of depression. A once daily formulation was designed to enhance patient compliance. Complexing with a resin was suggested to improve loading of the water soluble drug. The formulated systems were thoroughly evaluated in vitro to prove superiority to previous trials and were compared to the commercial extended release product in experimental animals. Materials and Methods: Venlafaxine-resinates were prepared using Dowex®50WX4-400 and Dowex®50WX8-100 at drug to resin weight ratio of 1: 1. The prepared resinates were evaluated for their drug content, particle shape and surface properties and in vitro release profile in gradient pH. The release kinetics and mechanism were evaluated. Venlafaxine-Dowex® resinates were encapsulated using O/W solvent evaporation technique. Poly-ε-caprolactone, Poly(D, L-lactide-co-glycolide) ester, Poly(D, L-lactide) ester and Eudragit®RS100 were used as coating polymers alone and in combination. Drug-resinate microcapsules were evaluated for morphology, entrapment efficiency and in-vitro release profile. The selected formula was tested in rabbits using a randomized, single-dose, 2-way crossover study against Effexor-XR tablets under fasting condition. Results and Discussion: The equilibrium time was 30 min for Dowex®50WX4-400 and 90 min for Dowex®50WX8-100. The percentage drug loaded was 93.96 and 83.56% for both resins, respectively. Both drug-Dowex® resintes were efficient in sustaining venlafaxine release in comparison to the free drug (up to 8h.). Dowex®50WX4-400 based venlafaxine-resinate was selected for further encapsulation to optimize the release profile for once daily dosing and to lower the burst effect. The selected formula (coated with a mixture of Eudragit RS and PLGA in a ratio of 50/50) was chosen by applying a group of mathematical equations according to targeted values. It recorded the minimum burst effect, the maximum MDT (Mean dissolution time) and a Q24h (percentage drug released after 24 hours) between 95 and 100%. The 90% confidence intervals for the test/reference mean ratio of the log-transformed data of AUC0–24 and AUC0−∞ are within (0.8–1.25), which satisfies the bioequivalence criteria. Conclusion: The optimized formula could be a promising extended release form of the water soluble, short half lived venlafaxine. Being a multiple unit formulation, it lowers the probability of dose dumping and reduces the inter-subject variability in absorption.

Keywords : biodegradable polymers, cation-exchange resin, microencapsulation, venlafaxine hcl
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