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Formulation of Lipid-Based Tableted Spray-Congealed Microparticles for Zero Order Release of Vildagliptin

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Abstract : Introduction: Vildagliptin (VG), a dipeptidyl peptidase-4 inhibitor (DPP-4), was proven to be an active agent for the treatment of type 2 diabetes. VG works by enhancing and prolonging the activity of incretins which improves insulin secretion and decreases glucagon release, therefore lowering blood glucose level. It is usually used with various classes, such as insulin sensitizers or metformin. VG is currently only marketed as an immediate-release tablet that is administered twice daily. In this project, we aim to formulate an extended-release with a zero-order profile tableted lipid microparticles of VG that could be administered once daily ensuring the patient's convenience. Method: The spray-congealing technique was used to prepare VG microparticles. Compritol® was heated at 10 oC above its melting point and VG was dispersed in the molten carrier using a homogenizer (IKA T25- USA) set at 13000 rpm. VG dispersed in the molten Compritol® was added dropwise to the molten Gelucire® 50/13 and PEG® (400, 6000, and 35000) in different ratios under manual stirring. The molten mixture was homogenized and Carbomer® amount was added. The melt was pumped through the two-fluid nozzle of the Buchi® Spray-Congealer (Buchi B-290, Switzerland) using a Pump drive (Master flex, USA) connected to a silicone tubing wrapped with silicone heating tape heated at the same temperature of the pumped mix. The physicochemical properties of the produced VG-loaded microparticles were characterized using Mastersizer, Scanning Electron Microscope (SEM), Differential Scanning Calorimeter (DSC) and X-Ray Diffractometer (XRD). VG microparticles were then pressed into tablets using a single punch tablet machine (YDP-12, Minhua pharmaceutical Co. China) and in vitro dissolution study was investigated using Agilent Dissolution Tester (Agilent, USA). The dissolution test was carried out at 37±0.5 °C for 24 hours in three different dissolution media and time phases. The quantitative analysis of VG in samples was realized using a validated High-Pressure Liquid Chromatography (HPLC-UV) method. Results: The microparticles were spherical in shape with narrow distribution and smooth surface. DSC and XRD analyses confirmed the crystallinity of VG that was lost after being incorporated into the amorphous polymers. The total yields of the different formulas were between 70% and 80%. The VG content in the microparticles was found to be between 99% and 106%. The in vitro dissolution study showed that VG was released from the tableted particles in a controlled fashion. The adjustment of the hydrophilic/hydrophobic ratio of excipients, their concentration and the molecular weight of the used carriers resulted in tablets with zero-order kinetics. The Gelucire 50/13®, a hydrophilic polymer was characterized by a time-dependent profile with an important burst effect that was decreased by adding Compritol® as a lipophilic carrier to retard the release of VG which is highly soluble in water. PEG® (400,6000 and 35 000) were used for their gelling effect that led to a constant rate delivery and achieving a zero-order profile. Conclusion: Tableted spray-congealed lipid microparticles for extended-release of VG were successfully prepared and a zero-order profile was achieved.

Keywords : vildagliptin, spray congealing, microparticles, controlled release
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