Study and Characterization of Telmisartan Controlled Release's Devices using Cyclodextrins and Biodegradable Polymers

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Statement of Purpose: Cardiovascular disease remains a leading cause of morbidity and mortality in all world and hypertension is one of the most important risk factor for their development. Unhealthy diet, stress and tobacco increases possibilities of become hypertensive. Pharmacological treatment has been shown efficient to decrease the risk of cardiovascular implication and there are different drug classes to treatment, one of them is Telmisartan, angiotensin II receptor antagonist that is highly specific for AT1 receptor. The solubility of Tel in aqueous solution is strongly pH-dependent and in the range of pH 3-9 it is practically insoluble. To address this problem we have examined the host:guest complexation approach using cyclodextrins to alter solubility and improve the encapsulation and release from polymer microspheres. Cyclodextrins are oligosaccharides that can interact with drugs via non-covalent interactions, doing the inclusion compounds, modifying their physical-chemical and biological properties, mainly solubility and bioavailability. Poly (*dl*-lactic-co-glycolic) acid (PLGA) is biodegradable polyester that can be used to do controlled release devices with lots of molecules.

Methods: Telmisartan (Tel) was acquired from Cipla (India); β-cyclodextrin (β-cd) from Roquette (USA); Polylactic-co-glicolic (PLGA) used was 50/50 proportion and 0.82 (g/dL) for density from Lactel (USA); polyvinyl alcohol (PVA) 80% hydrolyzed was Sigma-Aldrich (USA) and dichloromethane was acquired from Carlo Erba (Brazil). Deionized water was the vehicle for the inclusion compound preparation and all the chemical reagents were analytical grade. The inclusion compound was prepared in an equimolar proportion using freeze-drying method: Tel was resuspended in an aqueous β-CD solution and submitted to freeze-dry. For preparing microspheres, Tel was dispersed in water and this mixture was emulsified with phase containing PLGA and dichloromethane. The emulsion was stabilized in 1% PVA aqueous solution, then the solvent was evaporated and the mixture centrifuged. The inclusion compound was characterized by Fourier Transform Infrared Spectrophotometry (FT-IR), X-ray powder diffractometry (XRPD) and Nuclear Magnetic Resonance (NMR). Physical mixtures Tel/β-cd in the same molar ratio were prepared, which was previously treated separately as in complex separation for all experiments. The microspheres were characterized by dynamic light scattering, scanning electron microscopy (SEM) and kinetic delivery profile. Anti-hypertensive efficacy of inclusion compound Tel-βcd was tested *in vivo* by telemetry using spontaneously hypertensive rats (SHR).

Results: The FT-IR, XRPD and NMR results confirmed the inclusion of Tel in the β-cd cavity by freeze-dried method and it was also observed weak interactions as van der Waals interactions and hydrogen bonds between Tel and β-cd and the bidimensional NMR experiments showed a spatial interaction between both (Fig.I). Physical mixtures presented different behavior of the inclusion compound.

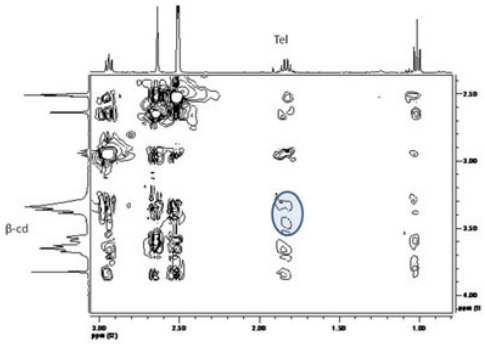

Figure I – Correlation map 2D-Roesy of Tel/β-cd inclusion compound.

The microspheres between Tel/PLGA prepared by emulsified method showed a porous surfaces and diameters about of 15 μm. The *in vitro* delivery kinetics study was carried out and showed a zero order kinetics profile, maintaining Tel concentration constant for 200 hours. The anti-hypertensive efficacy *in vivo* using telemetry in SHR rats demonstrated longer effect and higher decrease of the blood pressure media (PAM) for the inclusion compound Tel/β-cd, when compared with pure Tel, during the entire experiment (Fig.II).

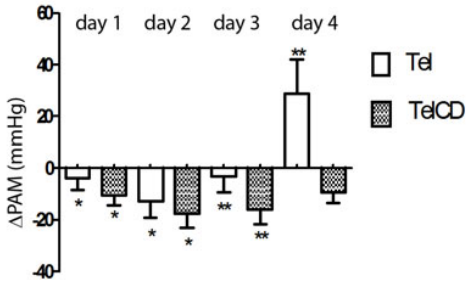

Figure II– Anti-hypertensive efficacy of Tel and Tel/β-cd.

Conclusions: The inclusion compound was obtained and characterized using physico-chemical techniques and *in vivo* experiments demonstrated better effect of the inclusion compound Tel/β-cd. The Tel polymeric delivery system developed exhibits good release characteristics for at least 8 days and may be suitable for delivery of the anti-hypertensive agents in the hypertension treatment.

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