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Development of Tacrolimus-loaded renal homing HGC nanomicelles as a prospective therapeutic for renal diseases

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Objectives: The growing rate of renal diseases and the limited therapeutic index of the available renal therapeutic drugs highlights the importance of developing new strategies for enhanced drug delivery to kidney. Targeting of drugs to kidney reduces the difficulties triggered by off-target toxicity, narrow therapeutic index and metabolic inactivation of drugs before attaining the target. The narrow therapeutic index and toxicity of the drugs such as tacrolimus (TAC) limits its clinical applications.

Methods: Taking advantage of the kidney targeting property of glycol chitosan polymer, we efficiently loaded the hydrophobic TAC drug into a glycol chitosan based polymeric micelles (HGC), thus developing a renal targeted drug delivery vehicle. The TAC loaded HGC nanoparticle (HGC-TAC) displayed a spherical morphology, average particle size distribution less than 200 nm, with superior drug loading and encapsulation efficiency. The effect of treatment with HGC-TAC and bare TAC on kidneys was compared by immunoblotting and immunohistochemistry, and by changes of body weight and serum creatinine level.

Results: The *in vitro* release study of HGC-TAC nanoparticle exhibited a biphasic drug release profile and biocompatibility when treated in human renal proximal tubular epithelial cells. Following intravenous injection into BALB/c mice, the HGC nanomicelles showed enhanced accumulation in kidney compared to the other organs and the time dependent *in vivo* biodistribution of TAC demonstrated reduced systemic level and enhanced local concentration in kidney tissues. A single administration of HGC-TAC achieved the delivery of comparable amount of TAC to kidney as compared to daily intraperitoneal injections of TAC for 14 days.

Conclusions:

HGC-TAC can be effectively used for the delivery of TAC to kidneys as a safe modality for the renal-targeted delivery of therapeutics. This approach helps in an enhanced renal distribution of TAC and simultaneous reduction in nephrotoxicity.