Abstract:

Diabetes mellitus is a chronic metabolic disorder marked by persistent high blood glucose levels, termed hyperglycemia. Prolonged hyperglycemia can cause significant harm to the body, impairing function and potentially leading to organ and tissue dysfunction. Insufficiency of insulin production (Type 1 diabetes) and diminished cellular sensitivity to insulin (Type 2 and gestational diabetes) are the causes of prolonged hyperglycemia.The polyphenolicphytoconstitutentcurcumin and resveratrol, both drugs have many common therapeutic activities against different diseases with their individual enormous therapeutic activity. However, due their inadequate aqueous solubility, rapid hydrolytic degradation and hence low bioavailability, clinical application has been greatly declined.To overcome solubility and bioavailability problems; and simultaneously to achieve synergistic therapeutic effects against diabetes, we have developed nanomicelles loaded with drugs Curcumin and Resveratrol.Our study focused on the synthesis of chitosan-succinyl-curcumin amphipathic prodrug, formation of nanomicelle from amphipathic prodrug, characterization and study of type-II antidiabetic activity of nanomicelle for bio-medical applications.To construct an amphipathic molecule, here hydrophilic polymer Chitosan is conjugated with lipophilic compound curcumin via succinyl linker and free form of CCMN and RSV loaded in the nanomicelle core.It was observed that the solubility of curcumin increased manyfold upon conjugation with polymer chitosan through a succinate linker and solubility of resveratrol increased many fold upon entrapment in the nanomicelle core.The nanomicelles were characterized by FTIR, 1H-NMR, ZetaSizer and SEM, TEM and AFM which reveal that spherical micelles were 50-150 nm in size.

Here resveratrol exists in nanomicelle core as free form and curcumin with nanomicelle backbone as conjugated form. So it required to estimate conjugated drug and free drug simultaneously from nano-micelle. We developed a RP-HPLC method, utilized C18 column followisosbestic detection of both drugs which was at 254 nm. The retention time of RSV and CCMN were at 8.15 min and 11.41 min respectively, completely distinguished sharp peak of CCMN and RSV developed with resolution 7.360±0.117, wide range of linearity with correlation coefficient value (R^2) of CCMN and RSV were 0.99987 and 0.99992 respectively and recovery value of CCMN and RSV were 100.041±0.22 % and 100.041±0.21 % respectively. The relative

standard deviation for accuracy, precision and robustness of the method was found to be less than 2%.

In vitro release studies revealed 97% curcumin release at pH 5 in 7 days. A 21-day experiment on diabetic mice compared curcumin and resveratrol containing nanomicelles, standard drugs, and free curcumin’s impact on fasting blood glucose. The study showcased, increased solubility and stability of curcumin and resveratrol; controlled release of curcumin and resveratrol from nanomicelles and significant lowering efficacy of fasting blood glucose level in compare to standard drug, suggesting their potential use in type II diabetes treatment.

Keywords: Curcumin, Resveratrol, Chitosan Nanomicelles, Bioavailability, Diabetes mellitus