# Synthesis and Characterization of Simvastatin-N-succinyl chitosan-citicoline Conjugated Form Intended for Improving Alzheimer's Disease in Long Term Use of Simvastatin

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**Abstract**

**Introduction:** Simvastatin is a semisynthesis statin. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, a key enzyme of cholesterol synthesis, in AMPK (AMP-activated protein kinase) signaling pathway. Simvastatin is able to cross blood brain barrier more than the other statins, due to its lipophilic nature. There is controversy about the effect of simvastatin on Alzheimer's disease (AD). For example, simvastatin can induce AD through insulin signaling pathway but can ameliorate AD *via* MAPK (Mitogen-Activated Protein Kinase) signaling pathway. In this study, we report the synthesis of a conjugated form of simvastatin with citicoline, to block negative effect of simvastatin on insulin signaling pathway and increase positive effect of simvastatin on MAPK signaling pathway and chitosan as a linker between these two drugs.

**Methods and Results:** for simvastatin-n-succinyl chitosan-citicoline synthesis, chitosan reacted with succinic acid to form n-succinyl chitosan. Then simvastatin connected to n-succinyl chitosan *via* acetylation reaction. After 24 hours citicoline was added to reaction media. H-NMR and FT-IR were done to examine whether the conjugation reaction has been done or not. Characterization and morphology tests have been done on reaction result.

H-NMR results approved the synthesis of drug-polymer. FT-IR results showed both amide and ester peaks. Maximum absorptions ($\lambda_{max}$) of all primary chemicals were seen in UV visible spectroscopy results of conjugated form. SEM result showed that the conjugated form has nanoparticulate structure in size range of 100-300 nanometers. X-RD result showed a peak under 25 theta. Another characterization test was RBC hemolysis with six different concentrations, in which normal saline was negative control and Triton was positive control.

**Conclusions:** Conjugation of lipophilic simvastatin with hydrophilic citicoline to improve AD can be done with helping of a polymer which is rich in carboxylic acid.

**Key words:** Alzheimer's disease, simvastatin, chitosan, insulin signaling pathway, MAPK signaling pathway.