Abstract: Design of an oral nano therapeutic drug delivery system for controlled release of an antidepressant drug.

Depression is one of the most prevalent global mental illnesses affecting more than 264 million people of all ages worldwide. Presently, an excess of 4% of the global population is affected by mental depression. A significant number of bioactive agents (drugs) intended for treatment of depressive symptoms, enhance the availability of chemical neurotransmitters at the synapse by inhibiting the reabsorption of the neurotransmitter. Regardless, many antidepressant drugs have reduced efficacy due to their inability to reach the desired brain binding receptors, when administered via traditional routes of administration. Stability, solubility, absorption, bioavailability and site targeting are often challenges experienced by therapeutic agents orally administered. Duloxetine which is a first line treatment drug for depression, has low solubility resulting in low bioavailability when administered orally. The purpose of this study was to synthesize duloxetine (DLX) loaded eudragit-chitosan (Eud-CHT) nanoparticles, enclosed in gelatin capsules and to evaluate their potential for transport of Duloxetine to the CNS via oral delivery path for improved efficacy with reduced side effects. DLX loaded Eud-CHT nanoparticles preparation was by the solvent emulsion evaporation method and synthesis confirmed by physicochemical properties including Scanning Electron Microscopy (SEM), Fourier Transformation Infrared Spectroscopy (FTIR), zetasizer, Ultraviolet (UV) spectroscopy, Thermogravimetric Analysis (TGA) and Differential Scanning Calorimeter (DSC) for thermoanalysis. Scanning electron microscopy clarified the configuration of the surface and shape of the nanoparticles together with pore distribution of the nanoparticles. The synthesized nanoparticles were evaluated utilizing the zeta-sizer and the nanoparticles were found to be in the size range of 100 ± 73,41 nm, with polydispersity index (PDI) of 0,283 and with a zeta potential of 16±2,79 mV. A drug entrapment efficacy (DEE) percentage of 72 was attained by the nanoparticulate formulation. DLX release studies showed a constant release over a 24hour period. The synthesized DLX-Eud-CHT nanoparticles were dissolved in three pH environments simulating the stomach pH 1,2, intestinal pH 6,8 and physiological pH 7,4. At pH of 6,8, 40 % of DLX was released from the copolymeric nanoparticles, whereas only 20 % was released at pH 1,2 and 35 % was released at pH 7,4. This illustrates the shielding effects of the Eud-CHT nanoparticulate formulation on the DLX in an acidic environment of the stomach. FTIR results exhibited the formation of nanoparticulate structure with comparable peaks between the polymers, DLX and the DLX-Eud-CHT nanoparticles. DLX-HCL compared to DLX-Eud-CHT nanoparticles showed peaks at 1281 attributed to -C-O vibration, at 3328 attributed to -N-H stretching and -CH_2 bending at 1324. DSC and TGA thermal studies indicated that the Eud-CHT nanoparticulate structure increased the stability of DLX. In addition, HEK 293 neural cells were treated with DLX loaded Eud-CHT copolymeric nanoparticles and evaluated for cytotoxicity utilising a 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide dye (MTT) assay and absorbance measured at 570 nm employing a Thermo Lab systems Multiskan MK3 microplate reader. From the MTT assay analysis conducted, the results indicated that the DLX-Eud-CHT nanoparticles were less toxic to the HEK cells compared to free DLX. The combined trials and results from the synthesis of DLX-Eud-CHT nanoparticles, showed evidence that these

nanoparticles can be utilized as potential invaluable formulation for oral drug delivery of Duloxetine with improved neuro-availability.