NANOCRYSTALS AS VERSATILE PLATFORM FOR ENHANCING THE DISSOLUTION PROFILE OF RISPERIDONE FOR THE TREATMENT OF SCHIZOPHRENIA

Rand Ghanma [1], Alejandro J. Paredes[1], Yara A. Naser[1], Akmal Bin Sabri[1], Ryan F. Donnelly[1]

[1] School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, Northern Ireland, U.K.

Background: Schizophrenia is a brain disorder characterized by mental-related symptoms such as delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability. These symptoms occur due to an imbalance in neurotransmitters including dopamine and serotonin. Antipsychotics are a class of drugs that used to treat schizophrenia. These drugs can be categorized into typical and atypical antipsychotics. Risperidone is an atypical antipsychotic that is used for the treatment of schizophrenia and related disorders as it has antagonistic effect on the serotonin-5HT2 and dopamine-D2 receptors. It is a hydrophobic drug that falls under class II according to the Biopharmaceutical Classification System (BCS). It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol. In order to circumvent this limitation, the preparation of nanosuspension may be utilised as a strategy to facilitate solubilisation of lipophilic drugs, such as risperidone. Nanosuspensions can be defined as a biphasic system consisting of poorly water-soluble drug dispersed as nanocrystals (NCs) in aqueous vehicle. Nanosuspensions can be prepared *via* a bottom-up approach where the NCs are prepared by precipitating dissolved drug molecules in an aqueous vehicele. In contrast, the top-down strategy involves applying forces to decrease the size of a coarse drug particle. In the current work, a top-down approach was employed *via* media milling to prepare risperidone nanosupension as this strategy obviates the use of any organic solvent while improving the overall solubility the dissolution profile of the antipsychotic.

Methods: NCs were prepared by wet media milling technique. 300 mg of risperidone, 30% beads (0.1-0.2 mm), 6ml of 2% PVA 9-10 KDa and 4 magnetic bars were placed in a 10 ml vial. The drug was milled at 1250 rpm under room temperature and pressure. The prepared nanosuspension was converted into a powder by lypholisation. The developed NCs were characterized for particle size, polydispersity index (PDI) and the release of the drug was evaluated using an *in vitro* dissolution studies. The release of pure risperidone and the prepared NCs was conducted over a period of 28 days in a water bath set at 37^{o}C. Formulation of pure drug and NC containing 24.2 mg risperidone, were suspended in 1ml PBS (pH 7.4) and pipetted into a Spectra/Por®7 Dialysis Membrane. The loaded dialysis membrane was then placed in a bottle containing 100 mL of PBS spiked with 1% w/w of SLS. At predetermined time points, 1 ml aliquot of the medium was sampled and replaced immediately with the same volume of fresh release medium. The concentration of risperidone in the withdrawn samples was determined by reverse phase HPLC-UV.

Results: The prepared nanosuspension showed a particle size of 298.52 ± 3.72 nm and a PDI of 0.166 ± 0.03. After lyophilization the NCs displayed a particle size of 303.9 ± 3.67 and a PDI of 0.162 ± 0.021. Due to the intrinsic hydrophobicity of risperidone, the dissolution rate of the pure drug was very slow. However, the NCs exhibited significant enhancement in dissolution rate and cumulative release in comparison to the pure drug ($p= 0.0203$). After 28 days, the NCs achieved a cumulative release of 79.59 ± 2.92% relative to the pure drug which only showed a cumulative release of 34.97 ± 7.27% ($p< 0.0001$).

Conclusions: The preparation of risperidone NCs showed an enhancement in the dissolution profile of the drug. Such improvement in the dissolution profile of the drug may lead to enhancement the overall bioavailability of risperidone.