World Academy of Science, Engineering and Technology
International Journal of Mathematical and Computational Sciences
Vol:14, No:12, 2020

Studies on Effect of Nano Size and Surface Coating on Enhancement of Bioavailability and Toxicity of Berberine Chloride; A p-gp Substrate

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Abstract : The aim of the present study is study the factual benefit of nano size and surface coating of p-gp efflux inhibitor on enhancement of bioavailability of Berberine chloride (BBR); a p-gp substrate. In addition, 28 days sub acute oral toxicity study was also conducted to assess the toxicity of the formulation on chronic administration. BBR loaded polymeric nanoparticles (BBR-NP) were prepared by nanoprecipitation method. BBR NP were surface coated (BBR-SCNP) with the 1 % w/v of vitamin E TPGS. For bioavailability study, total five groups (n=6) of rat were treated as follows first; pure BBR, second; physical mixture of BBR, carrier and vitamin E TPGS, third; BBR-NP, fourth; BBR-SCNP and fifth; BBR and verapamil (widely used p-gp inhibitor). Blood was withdrawn at pre-set timing points in 24 hrs study and drug was quantified by HPLC method. In oral chronic toxicity study, total four groups (n=6) were treated as follows first (control); water, second; pure BBR, third; BBR surface coated nanoparticles and fourth; placebo BBR surface coated nanoparticles. Biochemical levels of liver (AST, ALP and ALT) and kidney (serum urea and creatinine) along with their histopathological studies were also examined (0-28 days). The AUC of BBR-SCNP was significantly 3.5 folds higher compared to all other groups. The AUC of BBR-NP was 3.23 and 1.52 folds higher compared to BBR solution and BBR with verapamil group, respectively. The physical mixture treated group showed slightly higher AUC than BBR solution treated group but significantly low compared to other groups. It indicates that encapsulation of BBR in nanosize form can circumvent P-gp efflux effect. BBR-NP showed pharmacokinetic parameters (Cmax and AUC) which are near to BBR-SCNP. However, the difference in values of T1/2 and clearance indicate that surface coating with vitamin E TPGS not only avoids the P-gp efflux at its absorption site (intestine) but also at organs which are responsible for metabolism and excretion (kidney and liver). It may be the reason for observed decrease in clearance of BBR-SCNP. No toxicity signs were observed either in biochemical or histopathological examination of liver and kidney during toxicity studies. The results indicate that administration of BBR in surface coated nanoformulation would be beneficial for enhancement of its bioavailability and longer retention in systemic circulation. Further, sub acute oral dose toxicity studies for 28 days such as evaluation of intestine, liver and kidney histopathology and biochemical estimations indicated that BBR-SCNP developed were safe for long use.

Keywords : bioavailability, berberine nanoparticles, p-gp efflux inhibitor, nanoprecipitation method
Conference Title : ICSRD 2020 : International Conference on Scientific Research and Development
Conference Location : Chicago, United States
Conference Dates : December 12-13, 2020