J Develop Drugs 2016, 5:2(Suppl)
http://dx.doi.org/10.4172/2329-6631.C1.015

Bottlenecks in innovative and translational approach with natural product research

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Studying safety and efficacy of natural product and traditonal medicine formulations using modern medicine methodology is difficult in general. There are several reasons for this. First of all, the underlying principle for treating diseases in major traditional medical systems (TCM, Ayurveda etc.) is fundamentally different from modern medicine. Treatment is often personalized and holistic in traditional medical systems. Therefore, conventional pre-clinical and clinical studies may not be ideal to study safety and efficacy of natural product/traditional medicine modalities. Another major issue is that the natural product drug formulations often contain several ingredients which are mostly herbals. This poses problems with the quality control and standardization of these formulations, which is a requirement for drugs tested using conventional methods. Despite these challenges, several advances have been made in this area in recent years. Major issues facing innovative and translational research in natural product/traditional medicine area, and potential solutions will be discussed in the presentation.

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Oral delivery for amphotericin B: Fact or fiction!

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Amphotericin B (AMB) is the gold standard treatment of systemic fungal infections. However, the only available dosage form of AMB is the parenteral formulations. Oral delivery for AMB is the utmost invention to overcome its adverse effects and nephrotoxicity for better patient adherence and minimal hospitalization time. Therefore, a novel delivery for AMB loaded to PEGylated polylactic-polyglycolic (PLGA-PEG) nanoparticles (NPs) was developed. The feasibility of the developed system in rats with and without an absorption enhancer, glycyrrhizic acid (GA) as well as the *in vitro* efficacy and *in vivo* toxicity of these formulations were the aim of this investigation. The absolute and relative bioavailabilities of AMB selected formulations (F1 and F2) were conducted in nine groups of rats (n=6), using Fungizone® as reference standard. Plasma concentrations were measured using a developed sensitive and precise LC/MS/MS assay. The toxicity of AMB in these formulations was examined by *in vitro* blood hemolysis test and the *in vivo* nephrotoxicity was carried out in five groups of rats (n=3) dosed daily as 5.0 mg/kg via iv after single and multiple dosing for a week by measuring the blood urea nitrogen (BUN) and plasma creatinine (PCr). The *in vitro* AMB antifungal activity of these formulations on *C. albicans* was also assessed. Oral administration of AMB loaded to PLGA-PEG NPs to rats resulted in considerable oral absorption compared to Fungizone® administered orally (63.8%). The addition of GA significantly ($P<0.05$) increases AmB Cmax (2 - 3 folds). There was no significant change ($P=0.09$) in adding GA during formulation or just before administration. The addition of 2% of GA to AMB formulation significantly ($P<0.05$) improved its bioavailability by 10.5% and the relative bioavailability was >790%. The developed AMB formulations show minimal toxicity and better efficacy compared to Fungizone®. No nephrotoxicity, in rats, was developed after a week of multiple dosing of AMB NPs as the BUN and PCr were within the normal levels.

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