ORAL NANOMEDICINES FOR THE TREATMENT OF PARASITIC DISEASES

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Purpose: Visceral Leishmaniasis (VL) is the second deadliest parasitic disease after malaria managed mainly by parenteral chemotherapeutics. Buparvaquone (BPQ), a hydroxylnaphtoquinone with known antileishmaniasis activity (ED50:0.05μM), has not been translated into an effective therapy due to its low aqueous solubility (<30ngmL^{-1}, BCS Class II). The current project is aimed at enhancing the solubilisation capacity and oral bioavailability of BPQ in the gut by encapsulation in self nanoemulsifying drug delivery systems (SNEDDS) prepared from GRAS excipients towards the development of an oral, thermally stable and ideally solid nanomedicine for the treatment of VL.

Methods: Pseudoternary phase diagrams were constructed to optimize BPQ-SNEDDS (BS) (Capryol:Labrafil M1944:Labrasol:BPQ 3:1:5.99:0.01w/w/w/w). BPQ loading was quantified after centrifugation of BS containing excess BPQ (RP–HPLC). Stability studies of BS were performed at 40 ± 2 ^{o}C and 75 ± 5% relative humidity. BPQ solid SNEDDS (BSS) were prepared by adsorption of BS on acid-degraded glycol chitosan (14 kDa) and mixing with lactose and croscarmellose sodium prior to lyophilisation and characterisation (PXRD, DSC, FT-IR, TEM, SEM). BS filled capsules and BSS compressed tablets underwent dissolution testing. The *in vitro* anti-leishmanial activity against *L. infantum* promastigotes was assessed. RP-HPLC was used to analyse plasma levels achieved after oral administration of BS or BPQ.

Results: The maximum loading of BPQ in SNEDDS was 16.92±1.59mgg^{-1}. BS aqueous dispersions elicited quasispherical nanoparticles (241±49.6nm) that remained stable over 10 weeks (content, size and ζ-potential). The porous BSS elicited similar size nanoparticles upon reconstitution. Near complete release was observed with BS capsules and BSS tablets. BS and BSS possess potent *in vitro* efficacy (nanomolar range) with negligible cytotoxicity. BS significantly enhanced the bioavailability of BPQ after oral administration (55% increase in plasma AUC_{0-24}).

Conclusions: Developed SNEDDS or solid-SNEDDS prepared from GRAS excipients are cost-effective, stable oral alternatives for the delivery of poorly soluble antiparasitic drugs.

Preference: Oral

Scientific session: Drug Resistance and Translational Medicine

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