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) (Figure 1A) 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 (Figure 1C,D). BS and BSS possess potent in vitro efficacy (nanomolar range) with negligible cytotoxicity. Hydrogen bonding between the hydroxyls of glycol chitosan and the quinine carbonyl group of BPQ was indicated (Figure 1G,F). BS significantly enhanced the bioavailability of BPQ after oral administration (55% increase in plasma $AUC_{0\text{-}24}$).

Conclusion

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

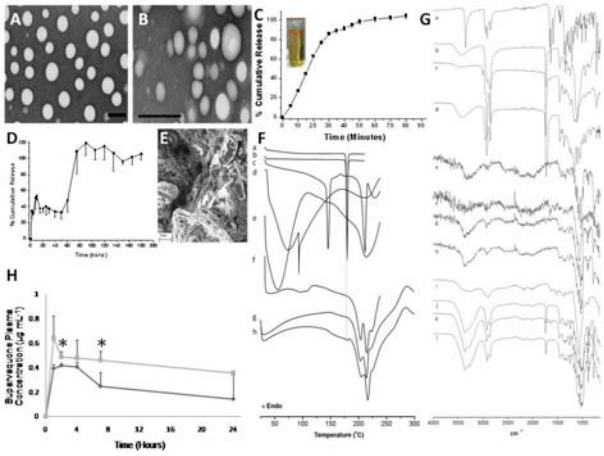

Fig. 1. **A, B**: TEM image of BPQ SNEDDS (Capryol:Labrafil M1944:Labrasol:BPQ 3:1:5.99:0.01 w/w/w/w) and BPQ - Solid SNEDDS after reconstitution (1 in 200 dilution) respectively (Bar: 500 nm), **C**: % Cumulative BPQ release from BPQ-SNEDDs loaded capsules (NP CapsTM, pullulan, Capsugel) was studied in the flow through cell (USP, Apparatus IV) at various pH levels [USP 2013 simulated gastric fluid without enzyme (1.2), acetate buffer (4.5) and phosphate buffer (6.8), flow rate 6ml min·1], **D**: % Cumulative BPQ release from BPQ – Solid SNEDDs (USP, Apparatus I, pH 1.2: 0-60min, pH 6.8: 60-180 min, 50rpm) , **E**: SEM image of BPQ - Solid SNEDDS, **F**: DSC analysis of BPQ (a), BPQ lyophilised (b), lactose (c), Croscarmellose sodium (d), Glycol chitosan 14 kDa (GC24) (e), BPQ - Solid SNEDDs (GC24) (f), Blank Solid SNEDDS (GC24) (g), Physical mixtrure of BPQ (10% w/w) and Blank Solid SNEDDS (GC24) (h), **G**: FT-IR spectra of BPQ (a), Labrasol (b), Labrafil 1944 CS (c), Capryol 90 (d), Lactose (e), Glycol chitosan 200 kDa (GCU) (f), BPQ - Solid SNEDDS (GCU) (g), Blank Solid SNEDDS (GCU) (h), BPQ - Solid SNEDDS (Glycol chitosan 14 kDa) /GC24) (i), (GC24) (j), Blank Solid SNEDDS (GC24) (k), Physical mixture of BPQ (1% w/w (k) or 10% w/w (l) and Blank Solid SNEDDS (GC24). **F**: Buparvaquone plasma concentration after oral administration of BPQ (aqueous suspension – probe sonicated, rhombus) and BPQ-SNEDDs (1.1% w/w, square) formulations to CD-1 mice (n=3, Student t-test: *p<0.05, dose: 6 mg kg^{-1} of BPQ).