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Nanoemulsion formulations for anti-cancer agent piplartine—Characterization, toxicological, pharmacokinetics and efficacy studies

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ABSTRACT

Piplartine (PL) is an alkaloid found in black-pepper and known for its anticancer activity, however, due to poor solubility and lack of proper formulation, its use for oral administration is a challenge. The objective of this study was to formulate PL into nanoemulsion drug delivery system for oral delivery and thereafter evaluate toxicity, pharmacokinetics and therapeutic efficacy. Optimized nanoemulsions were formulated by self-emulsification as well as by homogenization–sonication method. Two nanoemulsions enhanced the solubility of PL with low polydispersity index and high stability. Both PL loaded nanoemulsions exhibited enhanced dissolution, cellular permeability and cytotoxic effects as compared to pure PL. Formulation of PL into nanoemulsions did not obstruct its cellular uptake in cancer cells. Blank or PL loaded nanoemulsions did not exhibited toxicity in mice upon daily oral administration for 60 days. Pharmacokinetics of PL followed a two-compartment model after intravenous administration. PL loaded nanoemulsions showed 1.5-fold increase in oral bioavailability as compared to free PL. Finally, PL loaded nanoemulsions showed marked anti-tumor activity at a dose of 10 mg/kg in melanoma tumor bearing mice. In conclusion, for the first time we have developed a stable nanoemulsion delivery system for oral administration of PL, which enhanced its solubility, oral bioavailability and anti-tumor efficacy.

1. Introduction

Piplartine (PL), also known as piperlongumine, is an alkaloid derived from black pepper (*Piper nigrum)* and long pepper (*P. longum)* (Chatterjee and Dutta, 1967; Lin et al., 2007). Recent studies have shown that piplartine is selectively toxic to cancer cells (Raj et al., 2011). Piplartine has been effective in suppressing tumor growth in vivo (Roh et al., 2014). PL exerts anti-cancer activity by elevation of ROS levels leading to induction of apoptosis in cancer cells (Adams et al., 2012). ROS independent mechanism of anti-cancer activity of PL has also been reported (Bharadwaj et al., 2015). Recent studies from our lab have shown that PL induced anoikis in melanoma and pancreatic cancer cells through inhibition of STAT3 (Fofaria and Srivastava, 2014a,b). In all of the above-mentioned studies, PL has only been administered by intraperitoneal route and therefore, its anti-cancer activity by oral administration has never been tested. Due to poor water solubility, oral administration of PL is problematic as it will limit its bioavailability. Hence, it is important to formulate piplartine in a suitable drug delivery system in order to test the oral efficacy in vivo.

Nanoemulsions are colloidal sized droplets of either oil dispersed in aqueous medium or water dispersed in oil medium (McClements and Rao, 2011; Rao and McClements, 2011). Nanoemulsions have been effectively utilized to formulate hydrophobic drug (Sarker, 2005). A recent article has differentiated nanoemulsion (droplet size <300 nm) and microemulsion with respect to stability (12). Although nanoemulsions may be thermodynamically unstable, they are kinetically stable unlike microemulsions (Anton and Vandamme, 2011). Due to high colloidal stability, small droplet size and large surface area, nanoemulsions eliminate several problems like coalescence, sedimentation and flocculation that are associated with conventional emulsions (Sadurni et al., 2005). Nanoemulsions can either be prepared by high-energy dispersion technique or by spontaneous emulsification method such as a self-nanoemulsifying drug delivery system (SNEDDS). Poorly soluble drugs formulated into nanoemulsion have exhibited better in vitro dissolution and in vivo bioavailability (Rajpoot et al., 2011). Therefore, nanoemulsions have emerged as promising drug

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