A Novel Self-nanoemulsifying Lipid Carrier System for the Enhancement of Anticancer Activity of Curcumin

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Purpose
Curcumin, the golden spice from Indian saffron, has shown chemoprotective action against many types of cancer including breast cancer. However, poor oral bioavailability is the major concern in its clinical application. In the recent years, self-nanoemulsifying drug delivery system (SNEDDS) has emerged as a promising tool to improve the oral absorption and enhancing the bioavailability of poorly water soluble drugs. In this context, complexation with lipid carriers like phospholipid has also shown the tremendous potential to improve the solubility and therapeutic efficacy of certain drugs with poor oral bioavailability.

Methods
In the present investigation, a systematic combination of both the approaches was utilized to prepare the phospholipid complex of curcumin and its incorporation into SNEDDS. A series of experiments were carried out in a sequential manner to investigate the objective, i.e. enhancement of oral bioavailability and anticancer activity of curcumin. Therefore, our investigation began with preparation of curcumin-phospholipid complex (CPC). The next step was to select suitable ingredients (oil, surfactant and co-surfactant) on the basis of solubility of CPC. Their concentration ranges were determined with the help of a ternary phase diagram. The Box-Behnken experimental design approach was followed for optimizing the concentration of the formulation ingredients. Then, the intestinal absorption and pharmacokinetics of the curcumin formulation (CPC-SNEDDS) were studied in male Sprague Dawley rats. The cytotoxicity and cell uptake studies in metastatic breast cancer cell line were performed to evaluate the anticancer activity of curcumin from CPC-SNEDDS. Also, the expression of apoptotic proteins like Bcl-2, Bax and caspase-3 were examined to delve into the mechanistic insights of the anticancer activity of curcumin.

Results
The pharmacokinetic parameters of curcumin (Cmax, 487.7±53.4 ng/ml; elimination half-life, 21.0±0.6 h) from CPC-SNEDDS treated group of rats was significantly higher (p <0.01) than that from the curcumin suspension (Cmax, 21.6±3.6 ng/ml; elimination half-life, 4.1±0.3 h) treated group of rats; eventually the clearance (46.0±3.4 L/h) was lower. Thus, the curcumin in the form of CPC-SNEDDS persisted for a longer period of time in the body. As compared with the curcumin suspension, the relative bioavailability (%) of curcumin from CPC-SNEDDS was 5255.7%. The effective permeability (Peff, 10-4) of curcumin in the jejunum from CPC-SNEDDS (1.97±0.31 cm/s) was significantly higher (p <0.05) than the values (0.68±0.24 cm/s) obtained from curcumin solution indicating an increase in the intestinal permeability. As evident from the pharmacokinetic studies and in situ single pass intestinal perfusion studies in Sprague Dawley rats, the optimized SNEDDS of curcumin-phospholipid complex has shown enhanced oral absorption and bioavailability of curcumin. The cytotoxicity study in metastatic breast carcinoma cell line showed the enhancement of cytotoxic action by 38.7%. The primary tumor growth reduction by 58.9% as compared to the control group in 4T1 tumor-bearing BALB/c mice further supported the theory of enhancement of anticancer activity of curcumin in SNEDDS. The maximum up regulation of pro-apoptotic proteins like Bax and caspase-3 was observed on CPC-SNEDDS treatment. The down regulation of anti-apoptotic protein like Bcl-2 was also maximal on CPC-SNEDDS treatment.

Conclusion
The corroborative results of all experiments have evidenced the potential of CPC-SNEDDS for enhancing the oral bioavailability and anti-cancer activity of curcumin. The developed formulation can be a potential and safe carrier for the oral delivery of curcumin.