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Development of curcumin (nutraceutical) loaded Solid lipid nanoparticle and its Pharmacokinetic assessment

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1. Introduction

Curcumin (diferuloylmethane), a traditional herb and active ingredient of curcuma longa (Turmeric) are known for its wide pharmacological actions. Poor bioavailability of curcumin curtails the therapeutic utility of this potent molecule as drug. Lipid technology is one of the recent approaches developed to enhance bioavailability. In this line, the present investigation focused on the development of solid lipid nanoparticle (SLN) loaded with curcumin for enhanced bioavailability. The clinical development of curcumin as a drug has been hampered due to poor bioavailability and extensive first pass metabolism. Many approaches have been made to enhance the bioavailability of curcumin which include use of adjuvants such as piperine to prevent glucuronidation, conversion to liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complex and structural analogs of curcumin. Typically, clinical trials showed negligible unconjugated curcumin plasma levels with oral dosing, development of more bioavailable curcumin and/or potent metabolite may achieve better *in vivo* efficacy of curcumin.

2. Materials and methods

Curcumin (HiMedia Labs, Mumbai, India), Sterotex HM and Sterotex NF (ABITECK Corp, Mumbai, India), Gelucire 33/01 and gelucire 44/14 (Gattefossa, France), Tween 80 and poly vinyl pyrollidine (Loba Chemie Pvt Ltd, Mumbai) and propylene glycol (Qualigens Fine Chemical, Mumbai) were obtained for the research. All other chemicals and reagents were of analytical grade. Animal experiment protocol complies with the recommendation and protocol approval was obtained from Institution Ethical Committee.

Curcumin SLN was prepared using stearic acid, sterotex NF, Gelucire 33/01 and sterotex HM as lipids, Tween 80, Gelucire 44/14, Polyethyleneglycol (PEG), Polyvinylpyrrolidone (PVP) and Propylene Glycol (PG) as surfactants and co-surfactants. High shear Homoginization technique was applied for the preparation of SLN. The developed formulation is subjected to various characterization studies viz., particle size, entrapment efficiency, drug content, release profile and stability studies for optimization of SLN. Further, MTT assay in neuroblastoma cells were assessed for optimized formulation and subjected to pharmacokinetic studies in rabbit and rat animal model to establish bioavailability parameters.

3. Results

Stearic acid loaded curcumin SLN was characterized using zeta sizer, TEM analysis and the average particle size was in the range of 80 nm – 200nm. Drug content and entrapment efficiency was found to be from 78.12±1.21% to 93.33±2.12 and 58.98±2.12% to 85.32±3.2% respectively. The drug content results suggest that the drug loading capacity of the lipid is significantly influenced by addition of different co-surfactants. Based on the co-surfactant optimization PVP and PG was chosen to develop curcumin SLN with other lipids

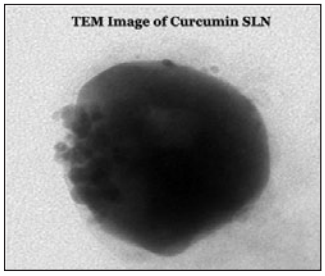

Figure 1 *TEM Images of Curcumin Loaded Solid Lipid Nanoparticle prepared using Sterotex HM, Tween 80 and Propylene Glycol (Cu5b) and lyophilized in freeze dryer adding cryoprotectant aerosi*

Sterotex HM, Sterotex NF and Gelucire 33/01. The results suggest that the formulation prepared using Sterotex HM, Tween 80 and PG (CU5b) to be optimized formulation based on the particle size (127nm), drug entrapment (90.40%) and *in vitro* drug release (82% at the end of 24hr) analysis. MTT assay was performed using IMR 32 (Neuroblastoma) cell line on the optimized formulation and the results are indicative that curcumin SLN showed better cytotoxicity in low dose while compared to plain curcumin. The optimized formulation has been subjected to pharmacokinetic studies in rabbit animal model. The optimizised formulation was administered to rabbits at different dose levels to know the dose dependent effect on pharmacokientics and bioavailability. The AUC0-t for the curcumin (100mg/kg) and curcumin SLN (25mg & 50mg/kg) was found to be 913.36, 7238.15, 10045.13 respectively. The results indicate that the curcumin delivered through SLN found to have enhanced bioavailability while compared to curcumin. Dose dependent increase in bioavailability was observed. Further, the optimized curcumin SLN is subjected to pharmacokinetic and brain distribution studies in rats. The drug concentration in plasma and brain was quantified by developed HPLC method. The curcumin SLN showed more than 10 fold increase in bioavailability and dose dependent increase in bioavailability was observed for the developed optimized formulation.

4. Conclusions

Based on the results it is evident that curcumin bioavailability and brain availability was promisingly improved in the form of SLN. To conclude, the developed curcumin SLN showed promising results of enhanced bioavailability. Further pharmacokinetic modelling and IVIVC should be carried out to establish the curcumin role as drug.

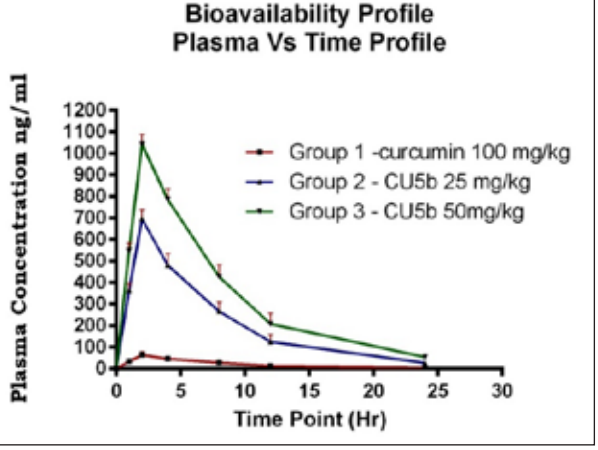

Figure 2 *Bioavailability profile of Cu-SLN (Cu5b) compared with pure curcumin*

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