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Development and Pharmacokinetic Assessment of Tetrahydrocurcumin Solid Lipid Nanoparticles

SHIEK ABDUL KADHAR MOHAMED EBRAHIM HABIBUR RAHMAN[1]; TELNY THOMAS CHUNGATH[2]; HARIPRASAD RANGANATHAN[3]; SIVASELVAKUMAR MUTHUSAMY[4]; MANOGARAN ELUMALAI[1]; KARTHIK SRIDHAR[3]; KARTHIK SIRAM[5]

[1] Faculty of Pharmaceutical Sceinces, UCSI University, Taman Connaught, Kuala Lumpur, Malaysia 56000
[2] Dept. of Pharmaceutical Analysis, Chemists College of Pharmaceutical Sciecnes and Research, Ernakulam, India - 682308
[3] PSG College of Pharmacy, Coimbatore, India 641004.
[4] Centre for Molecular Medicine, PSG Institute of Medical Sciences and Research, Coimbatore, India 641004
[5] Post-Doctoral Research Associate, University of Montana, Missoula, Montana 59812, USA

Correspondence: hablet1@gmail.com; habibur@ucsiuniversity.edu.my

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1. Introduction

Recently nutraceuticals have gained much importance as drug supplements. These nutraceuticals exhibit pharmacological actions of many synthetic drug substances in combined. Though they are pharmacologically potent compared to synthetic drugs, their bioavailability is low due to their poor aqueous solubility. Attempts were made in improving the solubility and systemic availability of these nutraceuticals. SLNs serve as the suitable carriers in enhancing the solubility of these hydrophobic entities and SLNs of few nutraceuticals were developed and their potency as carriers was evaluated. Curcumin when taken orally gets metabolized to form different metabolites dihydrocurcumin, tetrahydrocurcumin and hexahydrocurcumin. Tetrahydrocurcumin is a major metabolite of curcumin that was found to exhibit similar pharmacological actions as that of curcumin. THC and curcumin have similar β-diketone structure and phenolic groups, but THC differs from curcumin in lack of the double bonds. THC has several advantages over curcumin, unlike curcumin it is non staining, photo stable, has better stability in the physiological pH and in some cases exhibit better pharmacological actions than curcumin. But, the pharmacological actions of THC are limited due to its poor aqueous solubility and hence suffer low bioavailability. In the present study, SLNs of THC was developed with an aim to enhance its oral bioavailability.

2. Materials And Methods

THC was a gift sample from Sami labs, Bangalore. Stearic acid, tween 80, PVP, PG, poloxamer 188, pluronic F68, PEG 400, PEG 6000, methanol, tri fluoro acetic acid and acetonitrile were purchased from Sigma Aldrich, India. Sterotex HM was a kind gift sample from Abitech Corp, USA.

High shear homoginization followed by probe sonication was employed to prepare THC loaded solid lipid nanoparticles. Formulations were prepared using Sterotex HM and Stearic acid as lipids and hydrophilic surfactant Tween 80 as the surfactant and PVP, PEG 6000, PEG 400, Propylene glycol (PG) and Poloxamer 188 as co- surfactants. The prepared formulations were evaluated for particle size, surface morphology, drug content, entrapment efficiency and thermal analysis. As there is no specified dissolution method for THC in pharmacopoeia, discriminative dissolution method is developed and validated for release studies of THC solid lipid nanoparticle. Further, the optimized THC loaded SLN is subjected to pharmacokinetic studies in wistar rats.

3. Results

SLNs were prepared by hot melt technique using Tween 80 as the main surfactant. The effect of different co-surfactants on the characteristics of the SLNs like entrapment and also on *in vitro* drug release was evaluated. The optimized formulations were selected based on the entrapment and in vitro release data and further animal studies were carried out using these formulations. The particle size was found to be in the range of 25 to 877 nm. A high drug loading of 94% in the lipid nanoparticles was observed. The *in vitro* study showed a

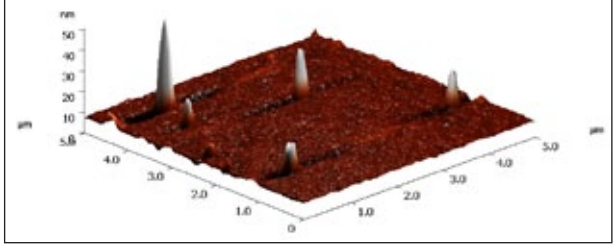

Figure 1 *AFM images of THC loaded solid lipid nanoparticles prepared using Sterotex HM*

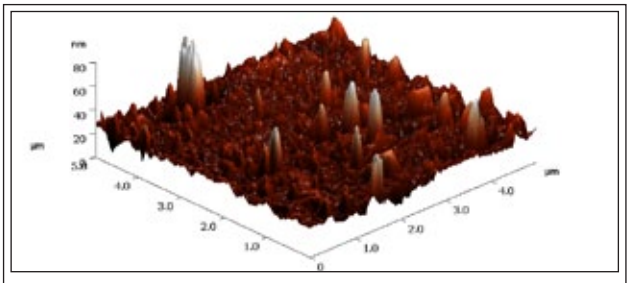

Figure 2 *AFM images of THC loaded solid lipid nanoparticles prepared using Stearic acid*

slow and sustained release of the drug for over 24 hrs. The thermogram of the pure drug showed melting point for the drug at 95° C. The thermograms of the formulations TF1 and TF9 showed the absence of the drug peak. An evident decrease of enthalpy with respect to raw lipid (from 124 to 53 J/g) was noted in the Sterotex HM – THC SLN thermogram. And decrease in enthalpy of stearic acid (from 184 to 68j/g) was noted in SA-THC SLN thermogram. The small difference in melting point and large difference in the enthalpy is evident that the tetrahydrocurcumin is dispersed uniformly in the lipid matrix and the THC-SA, THC-SHM complex formation is confirmed. The average particle size from atomic force microscopy (AFM) was found out to be in bounds with that of the values obtained with photon correlation spectroscopy. The AFM images of a group of particles represented in the figures clearly shows that the particles are well separated, ruling out the possibility of the aggregation of the particles. The pharmacokinetic parameters like C_{max}, T_{max}, $T_{1/2}$, AUC_{0-t}, MRT were measured using winNonlin software. There was a good improvement in the plasma drug concentration when formulated as SLNs compared to the pure form of the drug.

Conclusion: Based on the results it is evident that tetrahydrocurcumin bioavailability was promisingly improved when administered orally in the form of SLN. Further pharmacokinetic modelling and IVIVC should be carried out to establish the terahydrocurcumin role as drug.

4. Conclusions

An attempt was made through this research work for the first time to check if incorporation of THC in SLNs could enhance the oral bioavailability. The results clearly indicated enhancement of bioavailability and this approach can be used to enhance the bioavailability of drugs with poor bioavailability. SLNs remain a promising carrier to enhance the bioavailability of drugs.

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