Invitro and invivo evaluation of anticonvulsant herbal drug loaded self nano emulsifying drug delivery system

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ABSTRACT

The aim of present study was to formulate and invitro-in vivo evaluate self-nano emulsifying drug delivery system (SNEDDS) of poorly water soluble and bioavailable herbal drug like Linalool (coriandrol) extract, which was extracted from Coriandrum sativum seeds by using dichloromethane (Soxhlet method extraction process). Linalool fractionates are isolated by using column chromatography and concentrated under reduced pressure by using rotary flash evaporator. Linalool, an essential of Coriandrum sativum with anti-epileptic activity, the oil phase like Captex, Tween 80 and PEG-200 were selected as surfactant and co-surfactant respectively for the formulation of linalool SNEDDS (9 formulation). Among all the formulation S9 shows maximum invitro cumulative amount of drug release of about 97.72%. The linalool self-nanoemulsion stored in temperature range of 40°C/75% RH shown better stability up to 3 months. In invivo anticonvulsant activity shows that the recovery time period from convulsion of linalool SNEDDS (200mg/kg) treated animal is as quick and almost same as reference compound (eptoin 6mg/kg). Finally concluded that SNEDDS is promising drug delivery system to improve the solubility, dissolution rate and therapeutic efficacy of insoluble herbal drugs like linalool.

INTRODUCTION

In pharmaceutical formulations there are about 40% of (API) active pharmaceutical ingredients are hydrophobic in nature which indicates they poorly soluble and bioavailable. Oral absorption of drug is mainly depends on solubility of drug as well as permeability of drug compound. To overcome the problem of solubility and bioavailability, there are number of techniques developed, such as nanoemulsion, nanosuspension, micro emulsions, SLN nano particles, etc. to improve the solubility and permeability of drug, but this type of formulations having their own limitations. In its place of all these formulations, SNEDDS can be best option for the improvement of oral bioavailability and dissolution of lipophilic drugs due to less particle size of <100nm. SNEDDS are isotropic mixtures of natural or synthetic oils, surfactants and co-surfactants. These SNEDDS forms fine (o/w) oil-in-water nanoemulsion upon mild agitation followed by dilution in aqueous media, such as GI fluids and

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GI contents. Intestine provides agitation to form self-emulsion in GI tract. Upon dilution SNEDDS forms transparent nanoemulsion with droplet size less than 100nm [1–3].

To target the site, the use of self-nanoemulsion in oral dosage form achieves promising results in increasing effectiveness of drug at target site and increases the bioavailability. Low positive or negative free energy required for emulsification process to form emulsions the size of particle plays an important role in self-emulsifying drug delivery systems because it regulate the rate and extent of drug release and absorption [4, 5]. Additionally, in most cases the surfactant used for such formulations increases the bioavailability of the drug by activation of different mechanisms, keeping the drug in solution and, therefore, avoiding the dissolution step from the crystalline state and enhancing intestinal epithelial permeability at the same time. Furthermore, the oil droplets leads to a faster and more uniform distribution of drug in GI tract, and minimize the irritation due to contact between the drug and the gut wall. Lipids protects drug from degradation (enzymatic, chemical) and lipoproteins promotes the lymphatic transport of drugs. These systems may be filled to capsules or transformed into tablet, powders, granules, pellets, or many other dosage forms to incorporate the formulation orally or by any other route. The various methods to formulate SNEDDS, the method like aqueous titration, melt granulation, spray drying, spray cooling, and melt extrusion/spheronization, supercritical fluid based methods, and adsorption on a solid support [6, 7].

Coriander (Coriandrum Sativum L.) is a well-known aromatic/herbal plant, which grows in Mediterranean countries, and possesses a lot of pharmacological activities. In traditional medicine, seeds are used in the treatment of gastrointestinal problems, rheumatism and joint pains, hypoglycemic action and anticonvulsant action. Coriandrum sativum is a medicinal plant, comes under family-Umbelliferae, plant is cultivated for leaves and seeds. The seeds contain essential oil about 60–80% and monoterpenoid-linalool as a major component. A wide range of studies confirmed the usage of this herbal extracts in management of many disorders [8–11]. The aim of present study was to formulate and invitro-in vivo evaluation of self-nano emulsifying drug delivery system (SNEDDS) of poorly water soluble and bioavailable herbal drug like Linalool (coriandrol) extract and to prove the enhancement of anticonvulsant effect by linalool SNEEDS when compare to marketed formulation.

**Materials**

The following materials are used in the experiment are of laboratory and industrial grade. All chemicals were of analytical reagent grade. Tween 80, Polyethylene glycol-200 (PEG-200), Captex are purchased from S.d fine chemicals limited Mumbai.

**METHODOLOGY**

**Preparation of self Nanoemulsifying d rug deliv-ery systems**

A series of SNEDDS were prepared using captex-200 as the oil, tween80 as the surfactant and PEG-200 as the co-surfactant. In all formulations, the amount of linalool was kept constant. Accurately weighed Linalool was placed in a beaker and oil, surfactant, and co-surfactant were added. The components were mixed by gentle stirring with magnetic stirrer and the resulting mixture was placed in ultra-sonication about 10-15 min for size reduction. Then the mixture was heated at 40°C, until the drug was completely dissolved. The homogenous mixture was stored at room temperature until further use [12, 13].

**In-vitro drug release study**

The percentage (%) in-vitro drug release from formulations was used to measure the consistency of self-emulsifying property. The usp06 station, dissolution apparatus used to study the drug release from the oil in aqueous medium. Hard gelatin capsule containing SNEDDS was stick to the paddle by using double side sticking tape to prevent floating of capsule in dissolution media. 900 ml of phosphate buffer pH (6.8) was used as dissolution media. The bath temperature as well as bowl temperature was maintained about 37±0.5°C and paddle allowed rotating 75 rpm. 1ml of sample was withdrawn at time intervals 5, 10, 15, 20, 25, 30 min and dilution was made to 5ml. 1ml of fresh medium was replaced. The diluted samples are analyzed spectrophotometrically at 665nm and % drug release was calculated [14–19].

**In-vivo anti convulsant activity evaluation**

**Species** : Male albino mice
**No of animals** : 30
**Body weight** : 27-40g
**Cages** : 6 cages
**Age** : 8-10 weeks
**Instrument used** : Digital electro Convulsiometer
**Experimental animals**

**Animal Selection**
Male albino mice weighing 27-40 g were obtained from a random-bred colony of mice which were maintained on a special diet in the animal house of Sri Venkateswara University (Tirupathi) of Medical Sciences.

**Acclimatization**

Mice were allowed to adapt to experimental room conditions for a period of five days prior to randomization and treatment. During the acclimatization period the mice are observed for the clinical signs.

**Housing Conditions**

The mice will be housed three animals in polycarbonate cages provided with paddy husk as bedding material. The cages will be labeled with details of the study number, test item code, group number, sex, dose, and type of study and animal numbers. Every day, the floor of the experimental room will be swept and washed with a disinfectant solution.

**Feeding Conditions**

Fresh feed will be provided at least once a week. Every feed consignment received will be accompanied by a certificate of analysis of nutrient content from the supplier.

**Environmental conditions**

The animals were housed in colony rooms with 12/12 h light/dark cycle at 21°C ± 2°C and had free access to food and water.

**Acute toxicity study**

According to the OECD (Organization for Economic Co-operation and Development) guideline 423 acute toxicity studies were performed for the isolated linalool from crude extract of Coriandrum Sativum. Different doses of 100 mg/kg, 500 mg/kg, 1000 mg/kg, 2000 mg/kg, and 3000 mg/kg of body weight of isolated linalool were given orally into groups (A, B, C, D, and E) of six mice. The number of deaths was calculated after 24 hrs from the time of treatment. By using Litchfield and Wilcoxon method the LD50 and corresponding confidence limit values was determined.

**Number of mice, Dose Levels and Administration**

Six animals of one sex will be used at each dose level. Two dose levels and one control and reference control will be used. The doses were given orally.

**Group- 1 Control**: Induce Seizure without treatment

**Group- 11 Test Dose 1**: S9 test dose 1

**Group- 111 Test Dose 11**: S9 test dose 2

**Group- 1V Reference Control**: Phenytoin Sodium Tablet (EPTOIN).

**Preparation of oral administration of SNEDDS**

By conducting various evaluation tests for formulations (S1 to S9) S9 formulation selected as a best formulation based on stability, size, and drug release etc. Oral treatment of S9 formulation were prepared in different doses 60 mg/kg body weight it can be taken as test dose 1 and 120 mg/kg body weight it can be taken as test dose 2.

Eptoin was used as a reference drug in this experiment at a concentration dose of 6 mg/kg body weight.

**Experimental design for Anticonvulsant Activity**

**Maximum electric shock – induced seizure (MES)**

A total of 30 mice were weighed individually and divided into 4 groups (n=6 in each group) according to their body weights.

**Group-1**: mice were referred as sham control here these mice were received vehicle only (without drug)

**Group-2**: mice were received test dose-1 (60 mg/kg body weight)

**Group-3**: mice were received test dose-2 (120 mg/kg body weight)

**Group-4**: mice were referred as reference controls here mice were received phenytoin sodium (EPTOIN) tablet (6 mg/kg body weight).

**Procedure to induce convulsions**

The animals receive a current of 50 Hz and 150 mA for 0.2 sec duration through digital electroconvulsimeter using bicorneal electrodes, after 45 min of oral administration of Linalool SNEDDS or phenytoin. A drop of 0.9% saline solution was poured into each eye prior to placing the electrodes. Duration of tonic convulsion (a tonic extension of the hind-limb) and percentage of mortality were recorded.

**Statistical analysis**

Data were expressed as mean values SEM and tested with variance analysis followed by the multiple comparison test of student t-test (one-tailed t-test).

**Stability studies**

The optimized formulation was subjected to short term stability study as per the ICH guideline at 40°C ± 2°C of stress temperature condition and 75±5% of relative humidity for 3 months.

The optimized formulations are measurable for visual assessment, self-emulsification time and drug content in each month and tabulated the results in tabular column.
Table 1: Effect of linalool snedds on the onset and inhibition of seizure induced by maximal electric shock in mice (MES)

| Treatment                  | Dose     | Recovery Time period | Recovery/Death |
|----------------------------|----------|----------------------|----------------|
| Control (Vehicle Only)     | 05ml/kg  | 50 sec               | Recovery       |
|                            | 05ml/kg  | 52 sec               | Death          |
|                            | 05ml/kg  | 49 sec               | Recovery       |
|                            | 05ml/kg  | 53 sec               | Death          |
|                            | 05ml/kg  | 48 sec               | Recovery       |
|                            | 05ml/kg  | 51 sec               | Recovery       |
| F-S9 Test Dose 1 Low Dose  | 100 mg/kg| 22 sec               | Recovery       |
|                            | 100 mg/kg| 21 sec               | Recovery       |
|                            | 100 mg/kg| 24 sec               | Death          |
|                            | 100 mg/kg| 21 sec               | Recovery       |
|                            | 100 mg/kg| 23 sec               | Recovery       |
|                            | 100 mg/kg| 25 sec               | Death          |
| F-S9 Test Dose 2 High Dose | 200 mg/kg| 15 sec               | Recovery       |
|                            | 200 mg/kg| 17 sec               | Recovery       |
|                            | 200 mg/kg| 14 sec               | Recovery       |
|                            | 200 mg/kg| 15 sec               | Recovery       |
|                            | 200 mg/kg| 16 sec               | Recovery       |
|                            | 200 mg/kg| 18 sec               | Recovery       |
| Reference Control (Eptoin) | 06 mg/kg | 16 sec               | Recovery       |
|                            | 06 mg/kg | 15 sec               | Recovery       |
|                            | 06 mg/kg | 15 sec               | Death          |
|                            | 06 mg/kg | 14 sec               | Recovery       |
|                            | 06 mg/kg | 16 sec               | Recovery       |
|                            | 06 mg/kg | 15 sec               | Recovery       |

Table 2: Recovery and mortality protection % of S9 Linalool SNEDDS in two different doses

| Treatment                          | Dose (Orally) | Recovery Time Mean ±Sem | Mortality Protection (%) |
|------------------------------------|---------------|-------------------------|--------------------------|
| Control (Vehicle Only)             | 05 ml/kg      | 50.50 ±0.69             | 100                      |
| F-S9 Test Dose 1                   | 100 mg/kg     | 22.6 ±0.60              | 67                       |
| F-S9 Test Dose 2                   | 200 mg/kg     | 15.8 ±0.33              | 100                      |
| Reference (Eptoin)                 | 06 mg/kg      | 15.1 ±0.44              | 83                       |

RESULTS AND DISCUSSION

In vitro drug release study

The drug release profile of linalool SNEDDS was investigated in phosphate buffer (pH 6.8) the dissolution study reveals that as the droplet size decreased, surface area increased allowing more dissolution and drug release. The release of drug from formulation mainly depends on Smix: Oil ratio. When concentration Smix increased in formulation result in smaller nano droplet was formed this result in increase in the dissolution profile of drug. When Smix: oil ratio was 1:9, the droplet formed was larger in comparison with ratios 8:2 and 9:1 of Smix: Oil. Thus, the drug release from formulation S9 was found to be highest (97.72%) at and after 30 min as shown in Figure no 1. The drug release increases with increase in Smix ratio from S4 to S9 and the effective drug delivery from SNEDDS is proposed to be governed primarily by nano particle size and the polarity of the resulting oil droplets, which permits a faster rate of drug release into the aqueous phase.

The appropriate combination of oil and surfactant results the optimal polarity of formulation. The solubilized drug may not precipitate in the lumen, and undergo rapid absorption which is independent of
Table 3: Stability study results of optimized linalool snedds formulations

| Formulation | Month       | Temperature/ R.H     | Drug content (%) | Self-emulsification time | Phase separation |
|-------------|-------------|----------------------|------------------|--------------------------|-----------------|
|             | 1 month     | 400 ± 20C/ 20C/ 75± 5%| 97.98            | 52 Sec                   | No separation   |
|             | 2 month     | 400 ± 20C/ 20C/ 75± 5%| 97.64            | 56 Sec                   | No separation   |
|             | 3 month     | 400 ± 20C/ 20C/ 75± 5%| 96.98            | 53 Sec                   | No separation   |
| S5          | 1 month     | 400 ± 20C/ 20C/ 75± 5%| 97.31            | 52 Sec                   | No separation   |
|             | 2 month     | 400 ± 20C/ 20C/ 75± 5%| 97.43            | 52 Sec                   | No separation   |
|             | 3 month     | 400 ± 20C/ 20C/ 75± 5%| 97.05            | 53 Sec                   | No separation   |
| S6          | 1 month     | 400 ± 20C/ 20C/ 75± 5%| 98.31            | 52 Sec                   | No separation   |
|             | 2 month     | 400 ± 20C/ 20C/ 75± 5%| 98.23            | 55 Sec                   | No separation   |
|             | 3 month     | 400 ± 20C/ 20C/ 75± 5%| 98.25            | 55 Sec                   | No separation   |
| S7          | 1 month     | 400 ± 20C/ 20C/ 75± 5%| 98.02            | 55 Sec                   | No separation   |
|             | 2 month     | 400 ± 20C/ 20C/ 75± 5%| 98.07            | 56 Sec                   | No separation   |
|             | 3 month     | 400 ± 20C/ 20C/ 75± 5%| 98.04            | 55 Sec                   | No separation   |
| S8          | 1 month     | 400 ± 20C/ 20C/ 75± 5%| 98.65            | 58 Sec                   | No separation   |
|             | 2 month     | 400 ± 20C/ 20C/ 75± 5%| 98.64            | 56 Sec                   | No separation   |
|             | 3 month     | 400 ± 20C/ 20C/ 75± 5%| 99.27            | 57 Sec                   | No separation   |
| S9          | 1 month     | 400 ± 20C/ 20C/ 75± 5%| 99.65            | 50 Sec                   | No separation   |
|             | 2 month     | 400 ± 20C/ 20C/ 75± 5%| 98.27            | 60 Sec                   | No separation   |
|             | 3 month     | 400 ± 20C/ 20C/ 75± 5%| 99.04            | 64 Sec                   | No separation   |

Figure 1: *In vitro* drug release profile of linalool snedds formulation (s4-s9)

Figure 2: Recovery time period for s9 linalool snedds treated animals

of Linalool SNEDDS treated group shows a very short time recovery of convulsion than less dose 100mg/kg treated group with a significant difference in p value of <0.05. And also the recovery time of high dose treated group shows a same recovery effect as like marketed eptoin (6mg/kg) treated group. The results are shown in table no.1, 2 and figure no 2. From the results it infer the Linalool SNEDDS with 200mg/kg dose is suitable dose to treat convulsion in mice.

Stability studies
The optimized formulation was subjected to stability study as per the ICH guideline as shown in Table 3. The optimized formulations did not show any measurable in Visual assessment, self-emulsiﬁcation time, and drug content. All formulations subjected to determine drug content, self-emulsiﬁcation time, and phase separation studies formulations from S4 to S9 shows good stability upto 3 months and there is no evidence of phase separation or any flocculation or precipitation was observed in SNEDDS formulation.

CONCLUSION

In this study SNEDDS of linalool could be effectively developed and measured for its invitro and in vivo performance. From the studies, it shows that the formulation S9 shown 97.72% cumulative release higher than other selected formulations(S4-S8). The linalool self-nanoemulsion stored in temperature range of 40°C- 75% R.H shown better stability up to 3 months. The linalool self-nanoemulsion stored in temperature range of 40°C/75% RH shown better stability up to 3 months. In in vivo anticonvulsant activity shows that the recovery time period from convulsion of linalool SNEDDS (200mg/kg) treated animal is as quick and almost same as reference compound (eptoin 6mg/kg). Finally concluded that SNEDDS is promising drug delivery system to improve the solubility, dissolution rate and therapeutic efficacy of insoluble herbal drugs like linalool.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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