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Research Article

# FORMULATION, DEVELOPMENT AND EVALUATION OF SEDDS OF POORLY SOLUBLE DRUG (GUGGUL EXTRACT)

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## Abstract

The objective of the present study was to develop self-emulsifying drug delivery system (SEDDS) of guggul extraxt to improve its solubility, in vitro dissolution efficiencies, and further the bioavailability. The solubility of guggul extract in various oils, surfactants, and cosurfactants was determined. Prepared SEDDS was evaluated for emulsification time, drug content , in vitro dissolution and stability study . The optimized formulation had shown the maximum solubility, less emulsification time, good stability and improved in vitro release. In the present study, already existed historical data were used for importing data It was concluded that SEDDS would be a promising drug delivery system for poorly water-soluble plant extract through oral route.

**Keywords:** self-emulsifying drug delivery system, guggul extract, solubility, formulation.

## Introduction :

Medicinal plants contain inherent active ingredients to cure Approximately 40% of new drug candidates have poor water solubility, and the oral deliveries of such drugs are frequently associated with low bioavailability.To overcome these problems, various formulation strategies are exploited including the use of surfactants, lipids, permeation enhancers, and micronization. Majority of these approaches have their limitations because of the need for specialized equipment, complicated manufacturing process, longer processing time, and regulatory complexity. Lipid-based formulation approaches, particularly the self-emulsifying drug delivery system (SEDDS), are well known for their potential as an alternative approach for delivery of hydrophobic drugs, which are associated with poor water solubility and low oral bioavailability.SEDDS is among the methods used to improve the oral bioavailability of poorly soluble drugs by presenting and maintaining the drug in a dissolved state, in small droplets of oil, all over its transit through the gastrointestinal tract (GIT).

SEDDSs are the isotropic mixtures of oil, surfactant, cosurfactant, and drug which form oil in water microemulsion. These formulations spread readily in the GIT, and the digestive motility of the stomach and intestine the agitation necessary for self-emulsification. In a good self emulsifying system, small emulsion droplets containing dissolved drug are formed on contact with the gastrointestinal fluid. The drug in the fine emulsion droplets is exposed to a large interfacial area, thus allowing for greater diffusion through the membrane to take place..[1-5]

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## Materials and Methods[6-13]

**Formulation of self emulsifying drug delivery system (SEDDS)**

**Solubility Profile:** Solubility of Guggul extract was checked visually in distilled water, methanol, ethanol, DMSO, chloroform, acetone and phosphate buffer (pH 5.4). Accurately weighed 1 gm of drug was transferred in a clean and dry test tube followed by addition of the solvents individually and shaken vigorously and the solubility of drug was checked visually. Determination of solubility in DMSO and phosphate buffer pH 5.4 mixture for determination of ratio; accurately weighed 20 mg of Guggul extract was added individually to ten clean and dried volumetric flasks each of 10 ml capacity. DMSO and phosphate buffer pH 5.4 solvent system was added in the ratio 1:9, 2:8, 3:7, 4:6,5:5, 6:3, 7:3, 8:2, 9:1 and the samples were shaken for 1 hour on linear motion shaker (Model no. REMI RQ 123, Spectra Whirlmatic Lab,India). The solutions were checked visually for their clarity.

**Analytical Methodology:** The ultraviolet absorption spectrum of a solution of Guggul extract in DMSO and (8:2) mixture of DMSO and Phosphate buffer pH 5.4 was obtained using UV/VIS spectrophotometer over a wavelength range of 200 to 400 nm. Maximum absorption (λmax) values were determined and further used for plotting calibration curve.

**Characterization of Oil, Surfactant and Co-Surfactant for Microemulsion [8-9]**

**Determination of Solubility in various Oil, Surfactant and Co-surfactant:** Preformulation solubility analysis was done to select the vehicle in which drug is more soluble and suitable for formulation of SEDDS. The solubility of drug in various oils, surfactants and co surfactants was measured and the solvents for the study were selected based on the good solublising capacity for drug. In present study the solubility of drug was investigated in different oils like soyabean, olive oil, Capryol 90 etc, surfactants and co-surfactants like labrasol, Cremophor EL and PEG, Propylene glycol etc.

An excess amount of drug was added into each vehicle followed by vortex mixing for 30sec (Remi mixer, Mumbai). Mixtures were shaken for 48 h at 300 C, followed by equilibrium for 24 hr. The equilibrated samples were then centrifuged at 1000 rpm for 10 min to remove the insoluble drug and clear supernatant liquid was decanted. An aliquot of the supernatant was diluted with DMSO and solubility of drug was estimated by UV spectroscopy at 328 nm.

**Screening of oils and surfactant:** The oils and surfactants were selected on the basis of their tendency for instant emulsification and solubility in extract. The oils selected for this investigation were Capryol 90, Olive oil and Soyabean oil. The surfactants selected were Cremophor RH-40, Labrasol and Cremophor EL. The oils and surfactant were mixed in a ratio of 1:1. Briefly, 150 mg of the surfactants were added to 150 mg of the oily phase. Each mixture, 100 mg, was then diluted with distilled water to 100 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield homogenous emulsion. Emulsions were allowed to stand for 2hr and their % transmittance was evaluated at 638 nm by UV-Visible spectrophotometer using distilled water as a blank. Emulsions were furthermore observed visually for any turbidity or phase separation.

**Preliminary screening of co-surfactants:** The selected oily phase and surfactant were used for further screening of the different co- surfactants (Propylene glycol, PEG 400 and Tanscutol) for their emulsification ability. Mixtures of 200 mg of co-surfactant, 400 mg selected surfactant, and 600 mg screened oil were prepared and evaluated in a similar fashion as described in preliminary screening of surfactants.

**Formulation of Self Emulsifying Drug Delivery System[8-10]**

Self Emulsifying Drug Delivery system of Gum guggul extract was formulated by mixing oil, surfactant and co-surfactant with varying component ratio. In all the formulation amount of guggul extract was kept constant and varying ratio of oil and Surfactant and co surfactant mixture were added. The required amount of Gum Guggul extract was dissolved in selected oil at room temperature by permanent agitation and then mixture of surfactant and co-surfactant were added with gentle stirring and sonication. Then an appropriate amount of water was added to the mixture drop wise with constant stirring. Micro emulsion of guggul extracts was obtained spontaneously on stirring the mixture at ambient temperature. The various formulation ratios (F1 to F8) are given in Table 1. The process of self- emulsification was visually monitored for the rate of emulsification and for the appearance of the produced emulsions. The visual properties registered against the increment of the applied surfactant component in Ternary triangular diagrams. Plotting points of preferential combinations were selected according to calculation.

**Evaluation of Formulation Self Emulsifying Drug Delivery System [10-15]**

**Drug excipient compatibility studies:** A proper design and formulation of the dosage form requires considerations of the physical, chemical and biological characteristics of both drug and excipients used in the fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. If the excipients (s,) are new and if no previous literature regarding the use of those particular excipients with an active ingredient is available, then compatibility studies are of paramount importance. Infrared (IR) is related to covalent bonds, the spectra provided detailed information about molecular structure. Hence, before producing the actual formulation, compatibility of NVP with different polymers and other excipients were tested using the Fourier transform infrared (FT-IR) spectroscopy technique.

Fourier transforms infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between drug and other excipients used in the formulations. Drug and the intended excipients interaction were studied by FT-IR. The intended samples were powdered and intimately mixed with dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler, and the spectrum was recorded by scanning in the wavelength region of 4000-400 cm−1 in FT-IR spectrophotometer.

**Drug content:** Self-emulsifying drug delivery systems formulation equivalent to 100 mg of guggul extract was taken and dissolved in small quantity of methanol. Volume was made up to 100 ml with DMSO solution (1 mg/ml). From the above stock solution, 0.2 ml (200 µg/ml) was withdrawn and diluted up to 10 ml with methanol (20 µg/ml). Samples were prepared in triplicate and absorbance measured at 328 nm using UV-visible spectrophotometer. DMSO was used as a reference solution.

**Self emulsification assessment:** SMEDDS should form stable microemulsion instantaneously in GI fluids upon administration. Efficiency of selected combination of surfactant and co-surfactant in self microemulsification was assessed by dispersing the SMEDDS in 250 mL of water with magnetic stirring at 100 rpm to create gentle turbulence that mimic in vivo condition and assessed visually.

***In-vitro* dissolution studies:** The quantitative *in-vitro* dissolution studies are carried out to assess drug release from oil phase into aqueous phase by USP type II

dissolution apparatus use of 900 ml of pH 6.8 phosphate buffer solution at 75 rpm and maintain the temperature at 37°C ± 0.5°C. Aliquots of 5 ml samples were withdrawn at regular intervals of time (5, 10, 15, 30, 60 min) and volume withdrawn was replaced immediately with fresh medium. Samples taken were then analyzed by use of UV spectrophotometer at 328 nm.

**Accelerated Stability Studies**

The optimized formulations SEDDS were filled in the glass vial, sealed with rubber cap and crimped for storing in the stability chamber. Samples were subjected to a stability testing for six months as per ICH norms at a temperature and RH of 40°C ± 2°C/75% RH ± 5% RH respectively. The selected formulations were analyzed for the change in droplet size, zeta potential, self-emulsification capacity and drug content .

## Result and Discussion

**Solubility Profile**

Solubility of powdered extract of Gum guggul in various solvent are presented is in Table.2 .It can be revealed from table that Gum guggul is soluble in DMSO, thus DMSO was selected for further studies.

**Analytical Methodology UV-Visible Spectroscopy**

The Lamda max (λmax) of Gum guggul extract in DMSO was found to be 328 nm.

**Characterization of Oil, Surfactant and Co-Surfactant Selection of Excipients**

In this study, we selected Cremophor EL and Labrasol as a surfactant. Transient negative interfacial tension and fluid interfacial film are rarely achieved by the use of single surfactant; usually, addition of a co surfactant is necessary. The presence of co surfactant decreases the bending stress of interface and allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsions over a wide range of composition.

Thus, co surfactant selected for the study was Propylene glycol, which has an HLB value of 5-6. Surfactants and co-surfactants were selected on the basis of their emulsification efficiency and ability to solubilise guggul extract.

**Plot of pseudo ternary phase diagrams**

Phase diagrams of the systems containing Capryol as an oil phase, Labrasol & Cremophor EL as a surfactant and Propylene glycol a co-surfactant were constructed at the surfactant/co- surfactant (Smax) ratio of 1:3, 1:2, 1:1 and 2:1 (w/w) to determine the existence of microemulsion region. The phase study revealed that the obtained microemulsion region of composition 8 Smax ratios was low while composition 3 Smax ratio was maximum microemulsion region when compared with all other ternary plots. The composition 3 ratio of Smax showed maximum microemulsion region when compared to all other ternary plots, which points that an increase in the concentration of surfactant gives the highest microemulsion regions among all other ternary plots. It indicates that the concentration of surfactant has a major effect on the microemulsion region forming capability of SEDDS.

**Drug content**

The % drug content of all SEDDS formulations was found to be within the acceptable limits of drug content test. The Assay results are shown in table no7.4.

**Standard calibration curve**

Assay of prepared guggul extract SEDDS was carried out by UV-visible spectrophotometer. A linear calibration curve was obtained at 328 nm in the range of (2-10 µg/ml) with a correlation coefficient (R2) of 0.998. Standard calibraction curve of Commiphora mukul extract was determined by plotting absorbace vs concentraction at 328 nm and it follow the beer's law. The results are shown in Table.5.

**Determination of self-emulsification time**

Emulsification time is an important index for the assessment of the efficiency of emulsion formation. SEDDS should disperse completely and rapidly when subjected to aqueous dilutionunder mild agitation. Formulation should disperse quickly when subjected to aqueous dilution under gentle agitation of GIT due to peristaltic activity. The emulsification time of all formulations was reported in Table The lowest emulsification time 59 seconds was found in F3 formulation and highest emulsification time 160 seconds was found in F8 formulation .After observation it was found that the F3 formulation forms microemulsion in a short time relatively among all other formulations which indicate that the F3 was best of all prepared formulations.

***In-vitro* dissolution study**

*In-vitro* dissolution study was performed to compare the pure extract release from the developed guggul extract SEDDS formulations. The quantitative in vitro dissolution studies are carried out to assess drug-release from the oil phase into the aqueous phase by USP type II dissolution apparatus.

The results of In vitro dissolution studies were listed in table and Figures below. After observing the results, it was found that, nearly 92.14 %of drug was released from guggul SEDDS F3 formulation within 60 min compared to the other formulations, that is, F1, F2, F4, F5, F6 ,F7 and F8 which released 67.45% , 84.21%, 57.81%, 62.45%, 78.81,88.56 % and 51.45% of the drug respectively. Thus, the drug release from the guggul SEDDS F3 formulation was found to be significantly higher as compared to that of the remaining SEDDS formulations and pure extract. It could be suggested that the SEDDS F3 formulation resulted in a spontaneous formation of a microemulsion with a small droplet size,

which permitted a faster rate of drug release into the aqueous phase. Thus, this greater availability of dissolved guggul extract from the SEDDS F3 formulation could lead to higher absorption and higher oral bioavailability.

The release data obtained in this study were extrapolated by the zero order, first order, Higuchi, Korsmeyer–Peppas, Hixson-Crowell equations to know the mechanism of drug release from the formulations. The in vitro drug release profiles of optimized formulation F3 was best expressed by Higuchi equation as the plots showed highest linearity (Coefficient of determination, R2 = 0.993). The formulations showed good linearity when plotted according to Higuchi equation. It can be inferred that the release was dependent on both motility and polymer relaxation.

**Stability Studies**

Samples from stability chamber were withdrawn at regular intervals and evaluated for self emulsification efficiency, droplet size and zeta potential measurements. Results were represented in Table. There was no significant change in the droplet size, zeta potential and self-emulsification capacity. Clear dispersion with closer droplet size with initial samples indicates the stability of SMEDDS.

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**Table 1: Compositions of Guggul extract (SNEDDS) (1–8)**

| Compositions | Formulation code | Capryol | Propylene Glycol | Cremophore EL | Labrasol |
|---|---|---|---|---|---|
| Composition 1 | F1 | 33 % | 33 % | 33 % | - |
| Composition 2 | F2 | 25 % | 50 % | 25 % | - |
| Composition 3 | F3 | 20 % | 60 % | 20 % | - |
| Composition 4 | F4 | 25 % | 25 % | 50 % | - |
| Composition 5 | F5 | 33 % | 33 % | - | 33 % |
| Composition 6 | F6 | 25 % | 50 % | - | 25 % |
| Composition 7 | F7 | 15 % | 60 % | - | 15 % |
| Composition 8 | F8 | 25 % | 25 % | - | 5 |

**Table 2: Solubility Profile of Gum guggul extract**

| S. No | Solvent | Solubility |
|---|---|---|
| 1. | Distilled Water | Insoluble |
| 2. | Methanol | Sparingly Soluble |
| 3. | Ethanol | Sparingly Soluble |
| 4. | Acetone | Sparingly Soluble |
| 5. | Chloroform | Sparingly Soluble |
| 6. | Phosphate Buffer (5.4 pH) | Sparingly Soluble |
| 7. | DMSO | Soluble |

**Table 3: Solubility of Gum guggul in Various Oil, Surfactant and Co-surfactants**

| S. No. | Solvent | | Solubility (µg/ml) of gum guggul |
|---|---|---|---|
| 1. | Oil | Olive Oil | 24.1 |
| | | Capryol 90 | 65.4 |
| | | Soyabean Oil | 32.5 |
| 2. | Surfactant | Cremophor EL | 71.23 |
| | | Labrasol | 74.4 |
| | | CremophorRH-40 | 70.4 |
| 3. | Co-surfactant | Propylene Glycol | 56.2 |
| | | PEG 400 | 38.9 |
| | | Transcutol P | 40.3 |

**Table 4: Drug Content of SEDD formulation with guggul extract**

| S. No. | Formulation | Percentage of Drug contents (X ± SD) |
|---|---|---|
| 1 | F1 | 98.2±1.7 |
| 2 | F2 | 98.5±0.5 |
| 3 | F3 | 98.9±0.7 |
| 4 | F4 | 97.3±96 |
| 5 | F5 | 98.5±0.9 |
| 6 | F6 | 98.5±0.8 |
| 7 | F7 | 98.5±1.3 |
| 8 | F8 | 95.8±1.8 |

SD = Standard deviation

**Table 5: Standard calibration curve of Commiphora at 328 nm**

| S. No. | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | Blank | 0.000 |
| 2 | 2 | 0.096 |
| 3 | 4 | 0.167 |
| 4 | 6 | 0.238 |
| 5 | 8 | 0.318 |
| 6 | 10 | 0.385 |

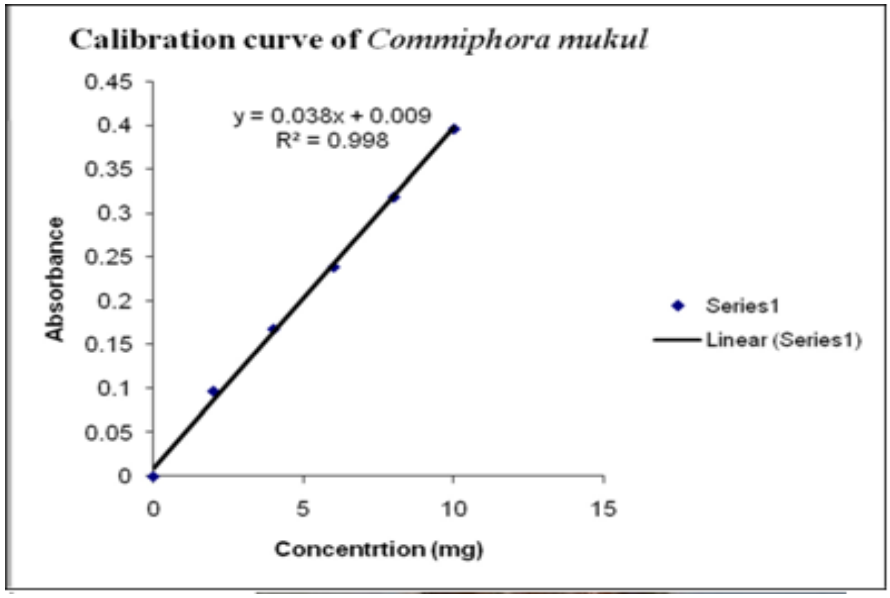


**Figure 1: Standard calibration curve of Commiphora at 328 nm**

**Table No.6: Self Emulsification time of SEDDS formulation**

| S. No. | Formulation | Self Emulsification Time |
|---|---|---|
| 1 | F1 | 97 ± 1.8 |
| 2 | F2 | 66 ± 0.4 |
| 3 | F3 | 59 ± 0.6 |
| 4 | F4 | 110 ± 2.8 |
| 5 | F5 | 98 ± 0.7 |
| 6 | F6 | 96 ± 5.6 |
| 7 | F7 | 65 ± 1.3 |
| 8 | F8 | 160 ± 2.4 |

**Table 7: In-vitro drug release profile of SEDDS formulation**

| Time | SEDDS Formulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| 5 | 21.63 | 26.85 | 31.85 | 17.45 | 18.69 | 21.82 | 26.4 | 14.95 |
| 10 | 38.32 | 39.88 | 45.88 | 30.98 | 33.32 | 35.64 | 37.97 | 24.61 |
| 15 | 43.23 | 51.89 | 53.55 | 39.43 | 40.22 | 48.76 | 48.89 | 32.86 |
| 30 | 52.83 | 62.68 | 71.68 | 47.44 | 48.87 | 58.98 | 65.67 | 42.74 |
| 45 | 61.25 | 73.45 | 86.45 | 51.47 | 56.81 | 68.75 | 76.98 | 46.67 |
| 60 | 67.45 | 84.21 | 92.14 | 57.81 | 62.45 | 78.81 | 88.56 | 51.45 |

**Table 8: Stability studies of Formulation**

| Formulation Code | Self emulsification time (min) | Drug contents |
|---|---|---|
| F3 | 67 ±0.4 | 98.23 |
| F7 | 69 ±1.3 | 97.83 |