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DEVELOPMENT AND EVALUATION OF A SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM OF A HERBAL EXTRACT

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ABSTRACT

The aim of this work was to develop a stable self micro emulsifying drug delivery system (SMEDDS) of herbal extract and evaluating its in vitro potential. The solubility of herbal extract was determined in various vehicles. Pseudoternary phase diagrams were used to evaluate the micro emulsification existence area. Release rate of herbal extract was investigated using a dissolution method. SMEDDS were characterized for clarity, precipitation and particle size distribution. Formulation development and screening was done based on results of solubility & from phase diagram. The optimized formulation used for in vitro dissolution was composed of herbal extract (30 %), Cremophor RH 40 (40 %), Plurol Oleique (30%). The SMEDDS formulation showed complete release in 10 min. as compared with the plain extract and conventional marketed formulation. SMEDDS subjected to various were conditions of storage as per ICH guidelines for 3 months. SMEDDS successfully withstood the stability testing. It has been found that dissolution profile of herbal extract from SMEDDS was much improved. SMEDDS appeared to be an interesting approach to improve solubility, and ultimately bioavailability

Key words: SMEDDS; herbal extract; Pseudo-ternary Phase diagram; Self-emulsification

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INTRODUCTION

Lipid-based formulation approaches, particularly the self-microemulsifying drug delivery system (SMEDDS), are well known for their potential as alternative strategies for delivery of hydrophobic drugs [1] which are associated with poor water solubility and low oral bioavailability [2-4.] SMEDDS formulations are isotropic mixtures of an oil, a surfactant, their co-surfactant (or solubilizers), and a drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions under gentle agitation following, dilution by aqueous phases; the digestive motility of the stomach and intestine provide the agitation required for self-emulsification in vivo in the lumen of the gut[5.] This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the fine size of the formed droplet provides a large interfacial surface area for drug absorption[6.] Apart from Solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption[1]. SMEDDS offers an opportunity to present lipophilic drugs to the GI tract in a dissolved state, avoiding the dissolution step and render more reproducible plasma concentration and enhanced bioavailability.

Selection of a suitable self emulsifying formulation depends upon the assessment of:

1. The solubility of the drug in various components,
2. The area of the self-emulsifying region as obtained in the phase diagram;
3. The droplet size distribution of the resultant emulsion following self- emulsification [7].

The ability to be able to fill liquids and semi-solids into hard gelatin capsules has been an option for several years. The technology potentially provides the industry with an in-house process to develop drugs which are poorly water soluble, have low melting points, are highly potent or low dosed or have a critical stability issue, into bioavailable, stable and safe dosage forms.

Liquid filling and sealing of hard gelatin capsules thus becomes a much more feasible option. It provides the formulation scientist with an in-house option to rapidly develop products for clinical trials. The processes have also been proven to be commercially viable for in-house manufacturing. Several pharmaceutical products currently under development are expected to reach the market within the coming years, increasing the number of commercial products using a liquid-filled and sealed capsule [11].

Drug Profile: Herbal Extract-Garlic Oil Macerate (GOM) was selected for its antiplatelet action [12-15].

Herbal extract obtained using Refined Soybean Oil as extraction solvent. Extraction by maceration done according to the Ph. Eur. Monograph "Extracta" Clear to slightly turbid oily liquid, light yellow colour, with a garlic odour which was used in formulation.

The main objectives of the study were to develop and evaluate an optimal SMEDDS formulation containing Herbal GOM (contains Ajoene). In present study trials were done to solubilize maximum amount of GOM so as to have optimal concentration of Ajoene in it.

MATERIALS AND METHODS

The following materials were donated by Gattefosse (Mumbai, India) and were used as received:Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) were obtained from BASF (Mumbai).Plurol Oleique were received from Colorcon Asia (Mumbai). Double distilled water was used throughout work. Empty hard gelatin capsule shells &sealing of hard gelatin capsules were generously done by ACG Capsules (Mumbai). All other chemicals and reagents used were of AR and HPLC grade.

Solubility Studies

The solubility of Herbal extract in various components (oils, surfactants, and co surfactants) was determined as follows: 500 mg of each of the selected vehicles was added to each cap vial containing an excess of herbal extract (1 g). After sealing, the mixture was heated at 40ºC in a water bath to facilitate the solubilization. Mixing of the systems was performed using a vortex mixer. Formed suspensions were then shaken with a shaker at 25ºC for 48 hours. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 minutes. observed for phase separation

Pseudoternary Phase Diagrams

Pseudo ternary phase diagrams of oil, surfactant/ co-surfactant (S/CoS), and water were developed using the water titration method. The mixtures of oil macerate and S/CoS at certain weight ratios were diluted with water in a drop wise manner. For each phase diagram at a specific ratio of S/CoS (for i.e., 1.33:1 wt/wt), a transparent and homogenous mixture of oil and S/CoS was formed by vortexing for 5 minutes. Then each mixture was titrated with water and visually observed for phase clarity and flow ability. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the micro emulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio.

Preparation of SMEDDS Formulations

A series of SMEDDS was prepared (Table-1) with varying ratio of oil to surfactant + co-surfactant mixtures (Cremophor RH 40 + Plurol oleique) was varied from 9:1 to 1:9. The ratio of surfactant to co surfactant kept constant at 3:1 and the concentration of HOM was also kept constant in all formulation and area for microemulsion was shown using pseudo ternary phase diagram (fig 1). Briefly, accurately weighed surfactant, and co surfactant was placed in a glass vial. Then, the components were mixed by gentle stirring and vortex mixer and heated at 37oC in an incubator to obtain a homogeneous isotropic mixture. The SMEDDS formulations were optimized by pseudo ternary diagram and stored at room temperature until used.

Table. 1. Developed Formulations with Their Compositions

Components %w/w	Batch A	Batch B	Batch C	Batch D	Batch E	Batch F	Batch G
GOM	10	15	25	27	30	32	35
Cremophor RH 40	60	50	48	46	40	25	41
Plurol Oleique	30	35	27	27	30	43	24

Reasons for selecting this ratio, ratio not as per procedure, ratios

Freeze Thawing

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at – 4°C for 24hours followed by thawing at 40°C for 24 hours. Centrifugation was performed at 3000 rpm for 5 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.

Microemulsion Droplet Size Analysis

One hundred micro liters of each SMEDDS formulation was diluted to 250 mL in a beaker and gently mixed using a glass rod. The resultant emulsion was then subjected to particle size analysis (using Beckman N 5 particle size analyzer) with a particle size measurement range of 0.02 to 2000 μm. Particle size was calculated from the volume size distribution. All studies were repeated in triplicate, with good agreement being found between measurements.

Self-Emulsification and Precipitation Assessment

Evaluation of the self-emulsifying properties of SMEDDS formulations was performed by visual assessment as previously reported [8]. In brief, different compositions were categorized on speed of emulsification, clarity, and apparent stability of the resultant emulsion. Visual assessment was performed by drop wise addition of the pre-concentrate (SMEDDS) into 250 mL of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred

magnetically at ~100 rpm. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 hours), or unstable. (showing precipitation within 24 hours)

Viscosity Determination

SMEDDS (1mL) was diluted 100 times with the distilled water in beaker with constant stirring on magnetic stirrer. Viscosity of resultant microemulsion and initial SMEDDS was measured using Brookfield viscometer.

In Vitro Dissolution Studies

The quantitative in vitro release test was performed in 900 mL of buffer pH 1.2 using US Pharmacopeia XXIV dissolution apparatus 2. The paddles were rotated at 100 rpm. The SMEDDS formulations were put into hard gelatin capsules (00 sizes) and used for drug release studies; results were compared with those of plain herbal extract. During the release studies, a 10-mL sample of medium was taken out and subjected to drug analysis using HPTLC. The removed volume was replaced each time with 10 mL of fresh medium. For determination of the *in vitro* dissolution of plain herbal extract, the medium was changed to buffer pH 1.2 containing Tween 80 (equivalent to the amounts used in the formulation). Dissolution studies were also performed in other media (buffer pH 7.2) to examine the effect of pH on drug release.

Stability Studies

The SMEDDS formulations will be put into empty hard gelatin capsules (size 00) and subjected to stability studies at 25°C/60% relative humidity (RH), 30°C/65% RH, and 40°C/75% RH.

They will be withdrawn at specified intervals for analysis over a period of 1 month for Drug content of the capsules analyzed using a previously developed and validated stability-indicating HPTLC method.

RESULTS AND DISCUSSION

Solubility Studies

One important consideration when formulating a self emulsifying formulation is avoiding precipitation of the drug on dilution in the gut lumen in vivo.[1] Therefore, the components used in the system should have high Solubilization capacity for the drug, ensuring the Solubilization of the drug in the resultant dispersion. Cremophor RH40 and Plurol oleique showed the highest Solubilization capacity for GOM. Thus, for our study we selected Cremophor RH40 and Plurol oleique as surfactant and co-surfactant, respectively.

Pseudoternary Phase Diagrams

Self-microemulsifying systems form fine oil-water emulsions with only gentle agitation, upon their introduction into aqueous media. Surfactant and co-surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of the micro emulsion formulation. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to S/CoS, play an important role in the formation of the micro emulsion. In the present Study soybean oil was tested for phase behavior studies with Cremophor RH 40 and Plurol Oleique as the S/CoS mixture. S/CoS ratio between 1:1 and 2:1 was selected for the formulation study. The micro emulsion existence area increased as the S/CoS ratio increased but it also found that micro emulsion existence area decreased as ratio of S/Cos increases beyond 1.5:1. The optimum micro emulsion existence area observed at s/cos 1.33:1. However, it was observed that increasing the surfactant ratio resulted in a loss of flowability. If this is optimum only one formulation is necessary

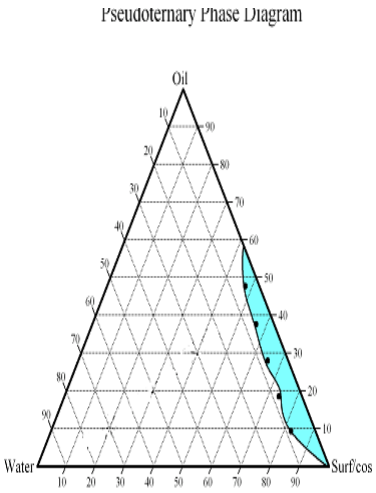

Figure 1 Pseudo ternary phase diagram of system with the following components: herbal extract, Surfactant = Cremophor RH 40, and Co-surfactant = Plurol Oleique. S/CoS ratio of 1: 1, the shaded area indicates existence of microemulsion area.

Droplet Size Analysis

The droplet size distribution of various formulations is given in table. An increase in the ratio of the oil phase resulted in a proportional increase in particle size, because of the simultaneous decrease in the S/CoS proportion. Increasing the S/CoS ratio led to a decrease in mean droplet size. Batch A, with the highest proportion of surfactant (60% wt/wt) at a fixed amount of oil (10% wt/wt), had the lowest mean particle diameter. This could be attributed to an increased surfactant proportion relative to co-surfactant. It is well known that the addition of surfactants to

the micro emulsion systems causes the interfacial film to stabilize and condense, while the addition of co-surfactant causes the film to expand; thus, the relative proportion of surfactant to co-surfactant has varied effects on the droplet size [9-10].

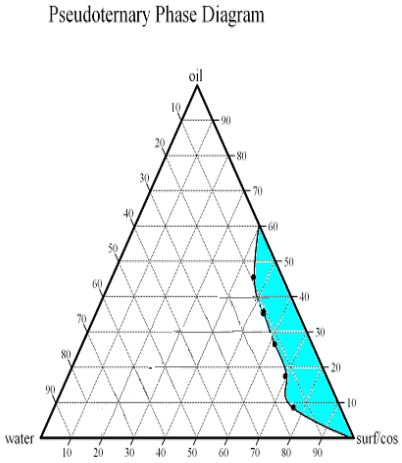

Figure 2. Pseudo ternary phase diagram of system with the components: herbal extract, surfactant = Cremophor RH 40, and co-surfactant = Plurol oleique. S/CoS ratio of 1.33:1, the shaded area indicates existence of microemulsion area.

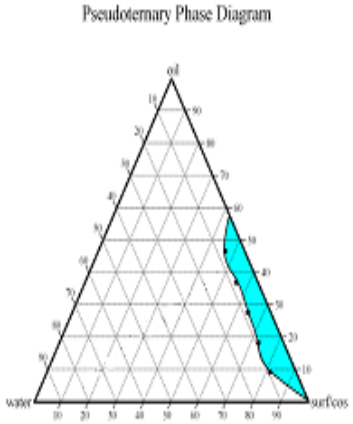

Figure 3 Pseudo ternary phase diagram of system with the following components: herbal extract, surfactant = Cremophor RH 40, and Co-surfactant = Plurol Oleique. S/CoS ratio of 2:1, the shaded area indicates existence of microemulsion area.

Self-Emulsification and Precipitation Studies

The results of self-emulsification and precipitation studies are given in Table 2. It was seen that an increase in the proportion of GOM in the composition resulted in increasing self-emulsification time. The increase in self-emulsification time can be assumed to be due the relative increase in surfactant concentration, leading to increased viscosity of the formulation. The S/CoS ratio of 1:1 was kept constant for the initial formulation study. However, it was found that the resultant dispersion showed precipitation and thus was not stable, because of the

presence of Plurol Oleique. Plurol Oleique can be assumed to act as a co solvent for GOM and thus it increases the Solubilization capacity of the vehicle (herbal extract). However, when the pre-concentrate (SMEDDS) is dispersed in water, Plurol Oleique, being water-soluble, is anticipated to enter the water phase and redistribute mainly between the water phase and the emulsion-water interface, resulting in a loss of solvent capacity of the vehicle. A similar observation was reported for a composition containing ethanol as the co solvent.

Thus, the problem of precipitation was solved by increasing the surfactant proportion (S/CoS [1.33:1]) in the system.

Table No. 2 Observation of Self-emulsification, Particle size, Precipitation Study

Formulations	Avg. Particle size(nm)	Polydispersibility Index method	Self-emulsification Time (sec)	Clarity	Precipitation
A (10 % oil)	33.4	0.674	40	Clear	Unstable
B (15% oil)	52.1	0.860	41	Clear	Unstable
C (25 % oil)	50.6	0.730	41	Clear	Unstable
D (27 % oil)	56	0.308	42	Clear	Stable
E (30 % oil)	40.6	0.287	42	Clear	Stable
F (32 % oil)	62.2	0.581	44	Clear	Unstable
G (35 % oil)	51.9	0.510	45	Clear	Unstable

Electroconductivity Study

The electroconductivity of the resultant system was measured by an electroconductometer. For the conductivity measurements, the tested microemulsions were prepared with a 0.01N aqueous solution of sodium chloride instead of distilled water. Electroconductance of optimized formulation (E) was done and observed to be 19.80 Ω^{-1}

Viscosity Determination

Initial viscosity of SMEDDS was found very high 201-228 cps which was quite suitable for filling of SMEDDS in hard gelatin capsule without risk of leaking problem. When SMEDDS was diluted 10 times and 100 that with water, viscosity of the system was decreased , which indicates that when SMEDDS formulation will be diluted with the stomach fluid it's viscosity will be decreased and therefore absorption from stomach will be fast.

At 10 rpm and at room temp. Spindle no.61 viscosity of pre-concentrate was found to be 206-228 cp. Also diluted microemulsion showed viscosity 1.0139 cp.

In Vitro Dissolution Studies

Drug release from the SMEDDS formulation was found to be significantly higher as compared with that of plain garlic oil macerate capsule. It could be suggested that the SMEDDS

formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of plain oil macerate. Thus, this greater availability of dissolved GOM from the SMEDDS formulation could lead to higher absorption and higher oral bioavailability.

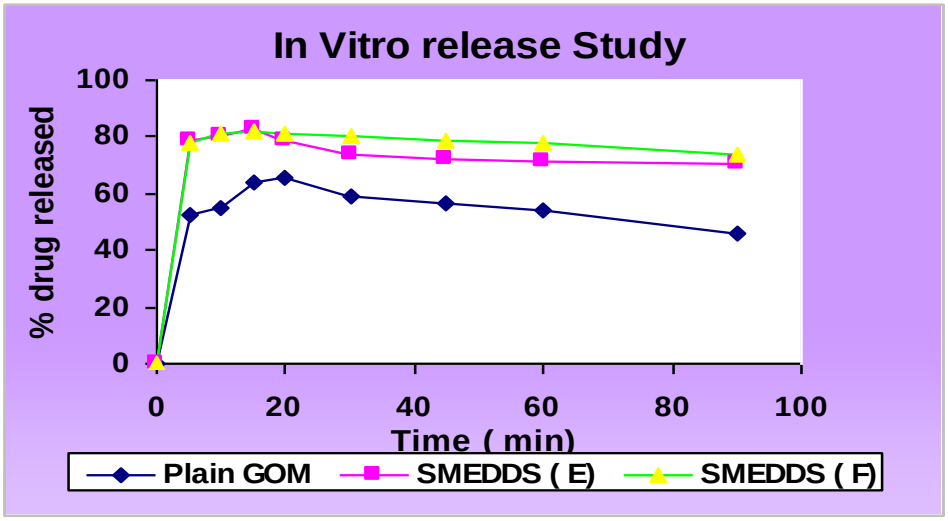

Figure 4. In Vitro Dissolution study of Plain HOM and SMEDDS of HOM.

Stability Studies

Generally, SMEDDS formulations are put into hard gelatin capsules as the final dosage form. However, liquid-filled hard gelatin capsules are susceptible to leakage, and the entire system has a very limited shelf life owing to its liquid characteristics and the possibility of precipitation of the drug from the system. Thus, the developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. Furthermore, the formulation was found to show no phase separation, drug precipitation, or capsule leaks. Thus, these studies confirmed the stability of the developed formulation and its compatibility with hard gelatin capsules.

CONCLUSION

SMEDDS appeared to be an interesting approach to improve problems associated with oral delivery of HOM using pseudo ternary diagram for optimization. An optimized SMEDDS formulation consisting of Garlic oil macerate (30% wt/wt), Cremophor RH 40 (40% wt/wt), Plurol Oleique (30% wt/wt), was successfully developed with an increased dissolution rate, increased solubility, and, ultimately, increased bioavailability. Thus SMEDDS can be considered as novel and commercially feasible alternative to current marketed soft gelatin capsules.

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