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Formulation and Characterization of Self Emulsifying Drug Delivery System of Simvastatin Using Maringa Oleifera and Banished Oil Extract For Potential Pharmaceutical Application

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Abstract: *Poor aqueous solubility of some chemical entities presents a major challenge to modern drug delivery. Self emulsifying drug delivery systems (SEDDS) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDS are mixtures of oil, surfactant and co-surfactant which are emulsified in aqueous media under conditions of mild agitation and digestive motility that are encountered in the gastrointestinal (GI) tract. The aim of this study was to develop a novel formulation of SEDDs using simvastatin which is a poorly water soluble drug. The study was conducted by preparing SEDDS with moringa oleifera and beniseed oils, tween 80 (surfactant) and polyethylene glycol (co-surfactant). After screening of various vehicles (oil, surfactant and co-surfactant) based on better drug solubilising power, liquid SEDDS were formulated. Prepared formulation were characterized on the basis of self emulsification ability, emulsification time, phase separation, spontaneity of formation, viscosity. A total of 8 samples were prepared comprising samples F1-F8 (tween 80, BSO, MSO and PEG-200). F1-F3 formed clear transparent and stable mixtures and were selected for further studies. The formulations that showed otherwise were rejected. Prepared SEDDS with simvastatin were made to undergo thermal stability tests which comprise heating cooling cycle, centrifugation test and freeze thawing test and were all found to be stable at different temperature conditions. Percentage drug content showed good result as most of the formulations showed good drug content of 70% and above. IR spectra of the formulations also showed good drug absorption and no drug interaction with the formulation. Cloud point determination of the formulation showed that the formulations were stable at physiological temperature. This study shows that the formulation will help to overcome the problem of poor solubility, bioavailability and fast drug release and therefore can be suitable for oral delivery systems.*

Keyword: *Characterisation,Formulation,oil,SEDDS,Simvastatin,*

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I. Introduction

Self emulsifying drug delivery systems (SEDDS) have gained high publicity in the pharmaceutical industry. SEDDS emulsify spontaneously to produce fine oil in water emulsions when introduced into an aqueous phase under gentle agitation. SEDDS can be orally administered in soft or hard gelatine capsules and form fine relatively stable oil in water emulsion upon aqueous dilution [1]

In recent years, the formulation of poorly soluble compounds presents interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industries are poorly soluble or lipophillic compounds, which leads to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality [2].

In the oral formulation of such compounds, a number of attempts such as decreasing particle size, use of wetting agents, co-precipitation and preparation of solid dispersions have been made to modify the dissolution profile and thereby improve the absorption rate [2]. Recently, much attention has been focused on lipid-based formulations to improve the bioavailability of poorly water soluble drugs. Among many such delivery options like incorporation of drugs in oils [1], surfactant dispersion [3], emulsion [4] and liposomes [5], one of the most popular approaches are the self – emulsifying drug delivery systems (SEDDS).

SEDDS are mixtures of oils and surfactants, ideally isotropic and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation [6]. Self emulsifying formulations spread readily in the gastrointestinal (GI) tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self emulsification. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial

area for the drug absorption [7]. SEDDS typically produce emulsions with a droplet size between 100 – 300nm while self microemulsifying drug delivery systems (SMEDDDs) form transparent microemulsions with a droplet size of less than 50nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophillic drug compounds that exhibit dissolution rate – limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood – time profiles [6].

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophillic surfactants, to water soluble co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions.

This study aims at exploring the potential of using moringa oleifera and beniseed oil extract in formulating a self emulsifying drug delivery system using simvastatin as the therapeutic drug.

II. Materials and methods

Moringa oleifera and beniseed were both purchased at jimeta main market in Yola Adamawa state. The surfactant (tween 80) was purchased from Manlec scientific merchant in jimeta yola. The drug simvastatin was obtained as a gift from Pharmacist Vitalis Onyirioha of Ovis pharmaceutical ltd jimeta yola. All other chemicals used were of analytical grade. Pods and shells of moringa and beniseed were removed manually and the seed were grounded in a domestic blender.

2.1 Formulation design

A total of eight (8) formulations were prepared comprising samples F1-F8 which is composed of tween 80, moringa seed oil (MSO), beniseed oil (BSO) and poly ethylene glycol 200 (PEG-200). The produced blends were then stirred continuously and left to equilibrate for 24 hrs at ambient temperature to obtain a homogeneous isotropic mixture. The SEDDS formulations were stored at ambient temperature until further use.

2.2 Characterisation of SEDDS

2.2.1 Determination of Emulsification time

The emulsification time i.e the time required for the pre-concentrates to form micro emulsion upon dilution were monitored by visual observation. The emulsification time of SEEDS were determined by dispersing formulation in 500ml of purified water at 37^{o}c in USP dissolution apparatus type II (paddle type) at 50rpm.

2.3 Solubility of drug

The solubility of the drug in the different oils (MOO and BSO), was determined by dissolving an excess amount of the drug in 500 mg of each of the oils, surfactants, co-surfactant in stoppered vials. The mixtures were continuously stirred using vortex mixer for 10 min and kept at $37^{o}C \pm 0.5^{o}C$ in a water bath shaker for 72 h to attain equilibrium. The equilibrated samples were centrifuged (3000rpm for 15 min)

and supernatant were filtered through 0.45µm membrane filter and diluted with mobile phase. Drug content was quantified using ultraviolet-visible (UV-VIS) spectrophotometer at 296nm [8].

2.4 Screening of components

Screening of the tween 80 was done on the basis of percent transmittance. Emulsification ability of the surfactants was assessed by adding each; 300 mg to MOO and BSO (300 mg). The mixture was gently heated to $40\text{-}45^{o}C$ for 30 s to achieve homogenization. Out of this mixture, 50 mg was weighed and diluted up to 50 cm^3 with double distilled water to yield fine emulsion. The resulting mixture was observed visually for the relative turbidity. The emulsion was allowed to stand for 2 h and transmittance was assessed by UV-VIS spectrophotometer at 638nm, using double distilled water as blank.

III. Preparation of Self-Emulsifying Drug Delivery Systems (Seeds)

The amount of oil, surfactant and co-surfactant to be taken were decided on the basis of micro emulsification region obtained by visual observations made on the SEDD formulations. The formulations that showed clear transparent appearance, were completely miscible, did not show any phase separation, were homogeneous, were selected for preparation with simvastatin,.

Simvastatin was accurately weighed into screw-capped glass vials and dissolved in oil. The mixture was warmed in a water bath at 37°C. Surfactant and co-surfactant were added to the mixture and stirred for 10 min using a magnetic bar. The formulations were further sonicated at 45°C for 15 min. Three formulations (F1-F3) with different concentrations of oil, surfactant and co-surfactant, each containing simvastatin at a final loading of 40 mg and 20 mg drug was prepared [9].

3.1 Physicochemical characteristics of self-emulsifying drug delivery system

3.1.1 Drug content

3.1.2 Self-emulsifying drug delivery system containing simvastatin was added in 50 mL volumetric flask containing methanol and mixed well with shaking and was sonicated for 10-15 min. 0.1 mL of this solution was diluted with 25 cm^3 fresh methanol and the percentage drug content was determined using UV- spectrophotometer at λ_{max} 296 nm [10].

3.1.3 Thermal stability studies of SEDD

Each formulation of SEDD containing different ratios of oil, surfactant and co-surfactant were taken in a test tube and diluted with 10ml of distilled water at 37^{o}C. The thermal stability study was determined by carrying out heating cooling cycle, centrifugation test and freeze thaw cycle.

3.1.4 Heating cooling cycle

Six cycles between refrigeration temperature of 4^{o}C and 45^{o}C, with storage at each temperature for not less than 48 hrs was studied. The stable formulations were subjected to centrifugation test.

3.1.5 Centrifugation test

Passed SMEDDS were centrifuged at 3500 rpm for 30 min using digital centrifuge. If SMEDDS did not show any phase separation, it will be taken for freeze-thaw stress test.

3.1.6 Freeze thawing

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3-4hrs of freeze thaw cycles, which include freezing at – 4^{o}c for 24hrs followed by thawing at 40^{o}c for 24hrs.

3.1.7 Viscosity determination

20 g of each of formulation of SMEDDS were weighed and transferred to beaker and the viscosity of the formulation was determined with the help of Brookfield Viscometer DV- E model spindle no 6, at 10 rpm for 5 min and the corresponding dial reading on the viscometer were noted.

3.1.8 Cloud point measurement

The SEDDS formulations were diluted with distilled water in the ratio of 1:250, placed in a water bath and their temperature was increased gradually. Cloud point was measured as the temperature at which there was a sudden appearance of cloudiness visually studied

IV. Results and Discussion

Formulation of self emulsifying drug delivery system (sedds)

Different formulations of SEDDS were produced. 8 different samples of SEDDS formulations were produced comprising:

SAMPLE F: 8 formulations of F1-F8 comprising tween 80, MSO, BSO and PEG 200

Table 1; formulation of self emulsifying drug delivery system

Formulations	MSO in ml	BSO in ml	Tween 80 in ml	PEG 200 in ml
F1	**0.5**	**0.5**	**8**	**1**
F2	**0.5**	**0.5**	**7**	**2**
F3	**0.5**	**0.5**	**6**	**3**
F4	**0.5**	**0.5**	**5**	**4**
F5	**0.5**	**0.5**	**4**	**5**
F6	**0.5**	**0.5**	**3**	**6**
F7	**0.5**	**0.5**	**2**	**7**
F8	**0.5**	**0.5**	**1**	**8**

4.1 Screening study

Table 2: Data showing solubility of simvastatin in each of the components

Vehicle	Solubility of symvastatin
PEG 200	97.8
Tween 80	72.1
BSO	65.3
MSO	62.9

Drug loading per formulation is a critical design factor which can be dependent on its solubility in various formulation components. Drug may be solubilized in the oily core and/or on the interface of these structures, so the selected vehicles should have a good solubilizing power to the drug. As a pre-formulation step, drug solubility in different components was determined visually till no drug crystals were detected indicating that it was dissolved. The selected oils have fair fluidity, proper self-emulsification properties and are efficiently digested. The surfactants have similar high solubilizing properties with those of Labrasol and curcumin [11].

Regarding the co-surfactant (PEG-200) according to earlier report [12], the co-surfactant can lower the interfacial tension of the surfactant in micro emulsions resulting in a more flexible and dynamic layer. The drug in this energy rich system can diffuse across the flexible interfacial surfactant film between the phases: a thermodynamic process that increases partitioning and diffusion. It can decrease the fluidity of SEDDS, enhance drug incorporation into the SEDDS, improves self-emulsification properties and possesses penetration enhancement effect [13]. It can also reduce the required amount of surfactant [14].

The self-emulsifying formulation consisted of BSO, MSO (oil), tween 80 (surfactant), PEG 200 (co-surfactant). Each showed a clear and monophasic liquid at ambient temperature when introduced to an aqueous phase. This is important because good solvent property is desired in order to allow presentation of the drug in solution. Tween 80 is highly hydrophilic due to the presence of polyoxyethylene chain in the molecule of tween [9].

4.2 Preparation and assessment of self- emulsification of sedds

SEDDS were prepared and their self-emulsifying properties were visually observed. These systems should be a clear, monophasic liquid when introduced into aqueous medium and should have good solubilizing properties to present the drug in a solution. Also individual components should have good miscibility with each other to produce a stable formulation. The visual grading of the process of self-emulsification upon dilution is shown below.

Table 3: Visual grading of the process of self emulsification
Sample F

Formulation	Mutual Miscibility	Spontaneiity of formulation	Homogenity	Dispersibility	Appearance	Overall performance
F1	Miscible	Good	Good	Good	Transparent	Good
F2	Miscible	Good	Good	Good	Transparent	Good
F3	Miscible	Good	Good	Good	Transparent	Good
F4	Miscible	Good	Good	Good	Milky	Good
F5	Miscible	Good	Poor	Poor	Milky	Poor
F6	Miscible	Good	Poor	Poor	Milky	Good
F7	Miscible	Good	Good	Good	Milky	Good
F8	Miscible	Good	Good	Good	Milky	Poor

Sample F1-F3 gave good stable transparent mixture. Sample F4 gave a stable turbid mixture. Samples F1-F3 were accepted as SEDDS/SMEDD. Samples F5-F7 formed poor formulations because they phase separated and formed suspended particles. Sample F8 gave moderate stable milky formulations

Selected sedds formulations for further studies
Sample A: F1-F3, Comprising tween 80, MSO, BSO and PEG-200

4.3 Emulsification time and viscosity:

The rate of emulsification is an important index for the assessment of the efficiency of emulsification [15], that is the SEDD should disperse completely and quickly when subjected to aqueous dilution under mild agitation. The result of the emulsification times and viscosities obtained for the selected formulations for the different Beniseed/*Moringa*/tween 80/PEG-200 compositions is presented in table 4

Table 4: Evaluation parameters for the developed sedds

Formulations	**Oil/surfactant/Co-Surfactant proportion**	**Mean EM (sec)**	**Dynamic viscosity**
F1	**10/80/10**	**6**	**0.0317**
F2	**10/70/20**	**5**	**0.0254**
F3	**10/60/30**	**4**	**0.0254**

Also all the formulations recorded emulsification time below 1 min. This result shows a very good performance of all the selected SEDDS formulations as it agrees with the study where 2 mins was used as an evaluation index by some researchers in the emulsification process [10]. A trend observed from the result above showed a noticeable increase in emulsification time as the surfactant concentration increases. In the work of

[16], they used only oil and surfactant without a co-surfactant and obtained highest emulsification time of 1 min and 54 sec which was attributed to effect of the surfactant on the formulation due to its high viscosity. Looking at viscosities in table 4, some solvents like tween 80 have a high viscosity [17] and in this study, its use as a surfactant with a gradual increase in its concentration in the various SEDDS formulations resulted in incremental viscosities and corresponding increase in emulsification time recorded.

4.4 Solubility of drug in oil, surfactant and co-surfactant:

The oil, surfactant and co-surfactants were screened on the basis of maximum drug solubility. This is important in the case of oral formulation development because of other components in solubilisation of target dose could lead to risk of drug precipitation in the GI lumen due to lowering of solvent capacity. The MSO and BSO showed good solubility of the drug as there was no precipitation of the drug. PEG also showed good solubility as there was no precipitate. Drug loading is a key factor for the selection of the suitable formulation. A good balance between drug loading and efficient emulsification is required. In this case, the simvastatin can be to have a good wetting property.

4.5 Table 5: Formulation of sedd with simvastatin

Formulation	Drug (simvastatin)	MSO in ml	BSO in ml	Tween 80 in ml	PEG 200 in ml
F1	**40**	**5**	**5**	**80**	**10**
F2	**20**	**5**	**5**	**70**	**20**
F3	**40**	**5**	**5**	**60**	**30**

IR spectra of the formulation

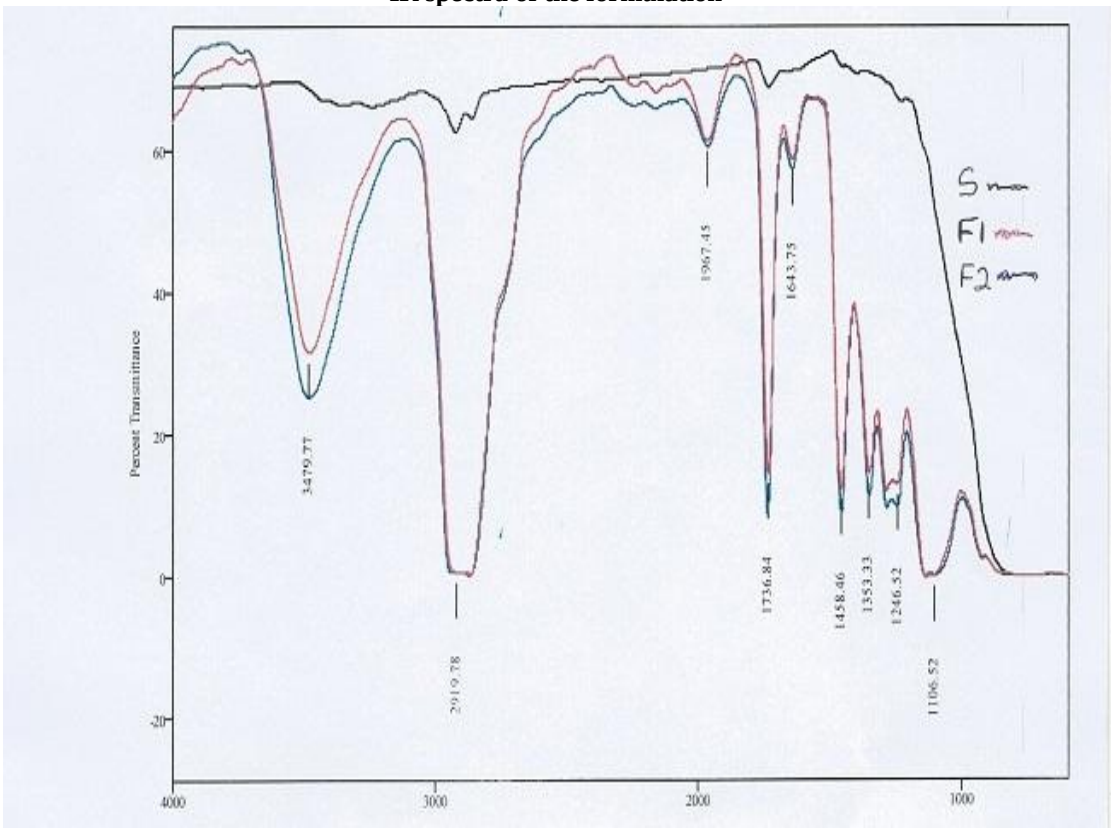

Fig 1. IR spectra of formulation F comprising: S (Simvastatin), F1 (MSO + BSO + tween 80 + PEG 200, F2 (MSO + BSO + tween 80 + PEG 200 + Simvastatin.

IR spectra of the formulation shows the complete incorporation of the drug within the formulation and also indicating that there is no chemical interaction within the formulation.'

4.6 Drug content

Table 8: Data showing percent drug content of the formulations

Formulations	Abs of drug	Abs of formulations	Percentage (%) drug Content
F1	**0.432**	**0.329**	**76**
F2	**0.432**	**0.300**	**75**
F3	**0.432**	**0.320**	**74**

In all the formulations the drug was well absorbed showing the highest drug content of 76%. The good solubility of the drug in the surfactant, co-surfactant and oil together with proper S/CoS/oil combination may be the causes of the high drug loading in the above formulations.

4.7 Thermal stability test

All the 3 samples passed the thermal stability test. These formulations were used for further studies. The thermal stability study was designed to identify and avoid the unstable systems. SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and co-surfactant, with no phase separation, no creaming or cracking. It is the thermal stability which differentiates nano or microemulsion from emulsions that have kinetic stability and will eventually phase separate [18].

4.8 Cloud point determination of self emulsifying drug delivery system

Cloud point is that temperature that there is sudden appearance of cloudiness visually. All the 3 formulations had their cloud points higher than 85^0C which shows that these formulations are stable at physiological temperature. Other formulations had their cloud points below 50^0C which showed that there was phase separation below that temperature. This may be due to drug precipitation [18].

V. Conclusion

In this novel o/w type of SEDDS prepared using moringa oleifera and beniseed in combination with the non ionic surfactant tween 80 in the various proportions, micro emulsions with very low emulsification times below 2 mins (120 sec) were achieved. Three formulations from the sample were very stable. The viscosities of the formulations were shown to be related to the emulsification time. The developed formulation containg moringa and beniseed oil at different concentration of the surfactant/co-surfactant ratios is expected to be welcome and novel addition to the clinical trials for the delivery of poorly water soluble drugs. Further study is required in the area of the release profile of this formulation to ascertain the rate at which the embedded drug is released from the system for easy regulation.

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