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DEVELOPMENT AND OPTIMIZATION OF A LIPID-BASED SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) FOR ENHANCING THE LYMPHATIC ABSORPTION AND BIOAVAILABILITY OF SILYMARIN.

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ABSTRACT

Background: Silymarin, a potent hepatoprotective agent, suffers from poor aqueous solubility (BCS Class II/IV) and extensive first-pass metabolism, leading to low oral bioavailability (<5%). **Objective:** To formulate a lipid-based SNEDDS to facilitate lymphatic transport and bypass hepatic metabolism. **Methods:** Solubility studies in various oils, surfactants, and co-surfactants. Pseudo-ternary phase diagrams were constructed. Optimization was done using a Box-Behnken design. **Results:** The optimized formula showed a globule size of <100 nm and significantly higher drug release compared to pure Silymarin. **Conclusion:** The SNEDDS formulation is a promising strategy for improving the therapeutic efficacy of Silymarin.

KEYWORDS: Silymarin, SNEDDS, surfactants, bioavailability.

INTRODUCTION

Self-nanoemulsifying drug delivery systems (SNEDDS) have gained popularity due to the issue of poor oral medication absorption, especially for permeants with low water solubility.[1] The GI tract's digestive motility makes it possible for the churning necessary to create nanoemulsions. The benefits of SNEDDS include enhanced oral drug bioavailability, thermodynamic stability, ease of large-scale synthesis, and no requirement for organic solvents.[2] In the present work, Silymarin (from *Silybum marianum*) is the "gold standard" for liver cirrhosis and fatty liver, but its clinical use is limited by its "greasy" nature and the fact that the liver destroys it before it can work. Self-nanoemulsifying drug delivery systems (SNEDDSs) are said to be better because of their scalability, thermodynamic stability, and straight forward preparation process., surfactants, and cosurfactants makeup their composition. and, when exposed to the gastrointestinal (GI) tract's digestive motility environment, create mixed micelles nano-droplets of an emulsified lipid. Compared to traditional medication solutions, these nano-micelles enable a comparatively greater drug uptake when they penetrate the GI tract's mucosal surface.[3]

The plant Silybum marianum, also known as milk thistle, contains silymarin as its active pharmaceutical ingredient (API). Scientists are interested in this flavonolignan complex.

Since the start of the studies on flavonolignan.[4] Silymarin's antioxidant qualities prevent skin cancer by reducing oxidative stress.[5,6] Topical silymarin can affect the skin's enzymatic (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase) and non-enzymatic physiological defence systems, thereby reducing the production of ROS (reactive oxygen species), the primary cause of oxidative stress, inflammation, and skin cancer.[7] However, silymarin is mostly used orally as a hepatoprotective drug that can be used to prevent and cure cancer, gastrointestinal issues, cardiac issues, nephropathy, neuropathy, and being a remedy for several poisons.[8,9,10,11] According to research, the effects of oral silymarin include the stimulation of ribonucleic acid

(RNA) polymerase I, ribosomal RNA synthesis, and proteo-synthesis.[12] the ability to scavenge free radicals and raise cellular glutathione levels, which results in activity against lipid peroxidation, the ability to control nuclear expression, the inhibition of hepatocyte myofibroblast formation, and the capacity to control membrane permeability and increase membrane stability in the presence of xenobiotic damage.[13]

Several articles regarding the history, uses, and effects of Silybum marianum have been written. Due to the limited availability of hepatoprotective medications, Silybum marianum has been the subject of intricate research. In recent years, silymarin is typically taken orally as regular tablets or mostly capsules that contain powdered milk thistle extracts. There are much less oil, syrup or suspension products on the market.[14] Nevertheless, silymarin has limited bioavailability and few viable dose formulations due to its weak water solubility. To completely reap the benefits, better preparations are required.[15] The problem of silymarin can be avoided by using new silybin derivatives, liposomes and targeted liposomes, phytosomes, microemulsion and Self-Micro-Emulsifying Drug Delivery Systems (SMEDDS), solid dispersion systems, various carriers like lipid nanoparticles, polymeric micelles, or fulvic acid, floating tablets, and micronization.[16,17]

Although a number of drug delivery methods have been developed to improve solubility and dissolution, including crystallisation, particle size reduction, inclusion complexes, solid lipid nanoparticles, solid dispersions, and nanocrystals, due to numerousrestrictions (such as morphological alterations, the use of organic solvents, tediousness, cost, etc.), they are useless both pharmaceutically and therapeutically.[18] As a result, an appropriate medication delivery method that offers high therapeutic efficacy and minimal adverse effects is required. Self-nanoemulsifying drug delivery systems, or SNEDDS, are currently among the expanding techniques used in both academia and the pharmaceutical industry to increase the therapeutic efficacy of medications by keeping them soluble throughout the gastrointestinal system.[19] The Food and Drug Administration has deemed the fundamental elements of the self-nanoemulsifying drug delivery system to be "generally regarded as safe" (GRAS), safe, and biocompatible.[20] When gastrointestinal fluids come into touch with SNEDDSs—an isotropic mixture of oil, surfactant, and cosolvent—they spontaneously form nano-sized droplets (SNEDDS) after slight agitation.[21] The current research developed SNEDDS represents a superior alternative to traditional oral dosage forms of Silymarin. This platform technology could be further extended to other lipophilic phytopharmaceuticals to enhance their clinical efficacy and reduce dose-related side effects.

MATERIALS AND METHODS

UV studies and construction of calibration curve

In the original stock solution formulation, methanol was utilised as a solvent, yielding a concentration of 100 µg/ml. The stock solution was diluted in a number of steps to produce standard solutions with concentrations ranging from 1 to 25 µg/ml. Their UV absorbance was measured between 200 and 400 nm using a UV-visible spectrophotometer. The λmax of Silymarin was determined using spectral scanning. After determining its λmax, Silymarin absorbance was measured at this specific wavelength. The process was repeated three times to ensure accuracy and precision.

Pre-formulation Studies

Solubility Studies: Add an excess of the medication to vials holding two millilitres of different oils, surfactants, and co-surfactants to test the solubility of silymarin. To achieve thermodynamic equilibrium, these mixtures are shaken in a water bath at 25°C for 72 hours. Then, undissolved particles are removed by centrifugation at 5000 rpm for 15 minutes. To measure the concentration and determine the best solvent, the resultant supernatant is diluted and subjected to UV-Spectrophotometry analysis at 287 nm.

Construction of Pseudo-Ternary Phase Diagram

first prepare Smix by blending surfactant and co-surfactant in fixed weight ratios. Combine this Smix with the selected oil in ratios ranging from 9:1 to 1:9, and then gradually titrate with distilled water while stirring constantly. To identify the nano-emulsion area, note the locations on a triangle graph where the mixture changes from clear to turbid.

Preparation of Silymarin SNEDDS

To make the drug-loaded SNEDDS, accurately weigh a sufficient amount of Silymarin and use a magnetic stirrer or sonicator to completely dissolve it in the chosen oil phase. The drug-loaded oil should be gradually mixed with the Smix (surfactant/co-surfactant combination) using a vortex mixer for five to ten minutes. A clear, isotropic pre-concentrate that is thermodynamically stable and prepared for encapsulation or additional characterisation is the end product of this method.

Table No. 1: Formulation of Silymarin SNEDDS.

Formulation Code	Oleic Acid (Oil) (%)	Tween 80 (Surfactant) (%)	PEG 400 (Co-surfactant) (%)
F1	20	40	40
F2	30	50	20
F3	40	30	30

Characterization

Self-Emulsification Time: Add 1 mL of the SNEDDS pre-concentrate to 200 mL of 0.1N HCl that has been kept at 37°C while being gently stirred by a magnetic stirrer. Check the mixture for bluish-white nano-emulsion production, clarity, and spontaneous emulsification. This test simulates gastric conditions to ensure the formulation will disperse rapidly and maintain the drug in a solubilized state upon ingestion.

Droplet Size Analysis: In order to use a Zetasizer (Dynamic Light Scattering) for analysis, transfer the emulsion created in the preceding step to a disposable cuvette. To verify that a uniform nano-emulsion has formed, measure the Polydispersity Index (PDI) and Mean Particle Size (Z-average) at 25°C.

Thermodynamic Stability

Heating-Cooling Cycles: The SNEDDS pre-concentrate is heated and cooled six times between 4 and 45 degrees Celsius, with 48 hours of storage at each temperature, in order to assess thermodynamic stability. To check for phase separation, creaming, or drug precipitation, the formulation is then centrifuged for 30 minutes at 3500 rpm. By passing these stress tests, the formulation is guaranteed to be stable under a variety of environmental circumstances and for the duration of its shelf life.

In-Vitro Dissolution Study: Place the Silymarin-loaded SNEDDS in a dialysis bag or capsule and immerse it in a USP Dissolution Apparatus filled with simulated stomach fluid to assess the drug release profile. To maintain sink conditions, remove samples at predetermined intervals (5, 10, 15, 30, and 60 minutes) and replace each one with fresh medium. Plot the cumulative percentage of drug release against time after analysing the samples using UV spectrophotometry at 287 nm. When compared to pure silymarin powder, a successful formulation should show noticeably faster and higher solubility.

Robustness to Dilution:

1. Take 1 ml of the pre-concentrate of Silymarin SNEDDS.
2. Add distilled water, 0.1N HCl (pH 1.2), and phosphate buffer (pH 6.8) to dilute it 10, 100, and 1000 times.
3. Store the diluted samples for an entire day.

Droplet Size and Polydispersity Index (PDI)

1. To make an emulsion, dilute the SNEDDS with distilled water in a 1:100 ratio and gently swirl the mixture.
2. Fill a cuvette with the sample and put it within a Dynamic Light Scattering (DLS) device, such as a Malvern Zetasizer.
3. Calculate the PDI, which gauges the droplets' homogeneity, and the Mean Particle Size.

Zeta Potential

1. Take use of the Droplet Size test's diluted sample.
2. Measure the droplets' electrophoretic mobility using a specialised Zeta-cell in the Zetasizer.

RESULT AND DISCUSSION

UV studies and construction of calibration curve

The correctness of the approach is confirmed by the calibration curve for Silymarin at 287 nm, which shows excellent linearity (R^2 > 0.999) within the 2–25 µg/mL range. This wide range makes it possible to precisely quantify the medication during dissolution, demonstrating that even slight concentration increases cause a predictable and proportionate rise in absorbance.

Table No. 2: UV studies and construction of calibration curve.

Concentration (µg/mL)	Absorbance (at 287 nm)
2	0.065
5	0.168
10	0.332
15	0.495
20	0.654
25	0.821

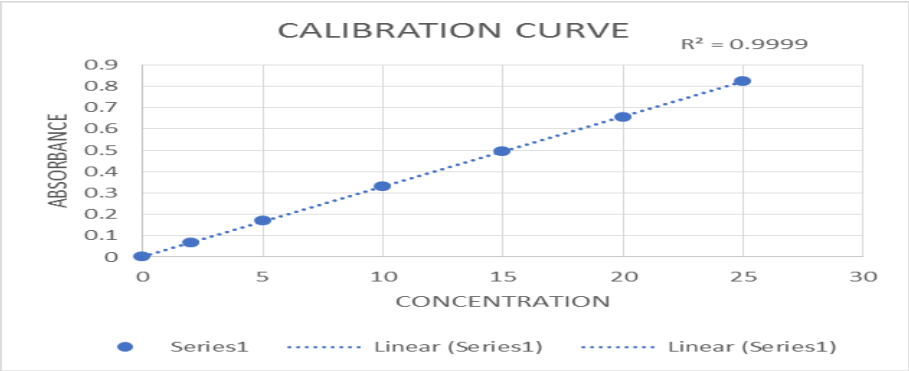


Fig No. 1: UV studies and construction of calibration curve.

Construction of Pseudo-Ternary Phase Diagram

The self-nanoemulsifying region (the grey area) is clearly mapped out once the pseudo-ternary phase diagram is constructed. Higher surfactant concentrations offer the optimal stability and droplet size reduction, as seen by the wider region seen with the Smix 3:1 ratio. An ideal formula (such as 20% oil, 50% smix, and 30% water) is chosen from this diagram to guarantee that the silymarin stays completely dissolved and stable.

Table No. 3: Construction of Pseudo-Ternary Phase Diagram.

Parameter	Observation
Ratio	3:1
Appearance	Transparent / Clear isotropic liquid
Efficiency	High (Spontaneous emulsification in < 1 minute)

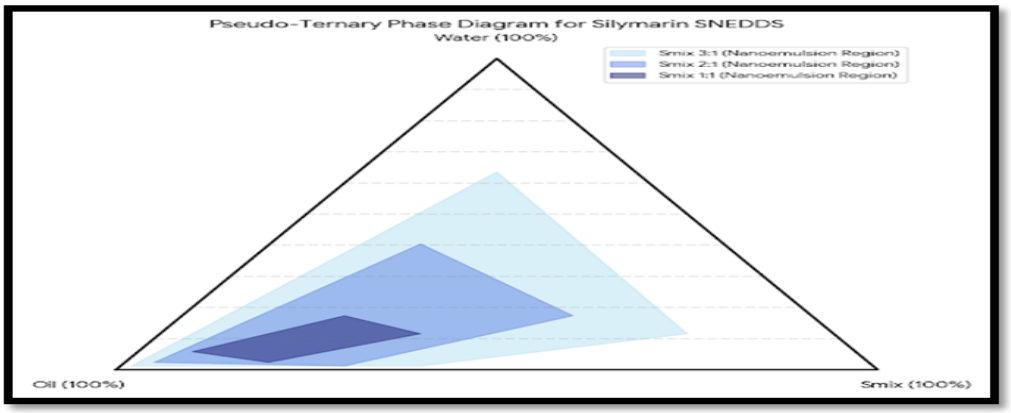


Fig. No. 2: Construction of Pseudo-Ternary Phase Diagram.

Characterization and Performance Evaluation of Optimized Silymarin SNEDDS

Given a droplet size of 20–100 nm and an emulsification duration of less than 60 seconds, the characterisation results verify that the Silymarin SNEDDS satisfies all pharmaceutical standards. In the gastrointestinal tract, these features guarantee a large surface area for quick medication absorption and spontaneous dispersion. Additionally, the formulation maintains its physical stability throughout storage thanks to the electrostatic repulsion required to stop droplet aggregation, which is provided by a Zeta Potential > ±20 mV.

Table No.3: Characterization Parameters and Success Criteria for Optimized Silymarin SNEDDS.

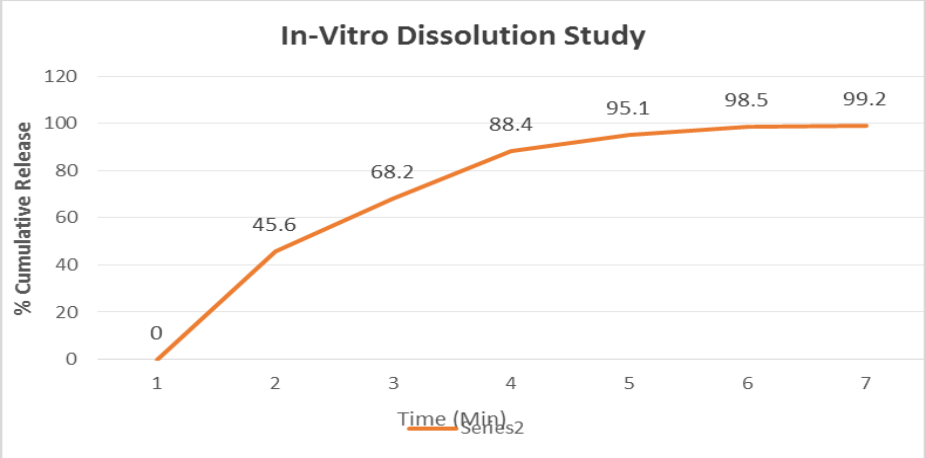
Parameter	Goal	Success Criteria
Visual Appearance	Transparency	Clear/Translucent
Emulsification Time	Speed	<60 seconds
Droplet Size	Small Surface Asrea	20 - 100 nm
Zeta Potential	Stability	> 20 mV

In-Vitro Dissolution Study

The Silymarin SNEDDS obtained over 99% release within 60 minutes, whereas pure Silymarin only achieved 18.2%, indicating a considerable improvement in drug release, according to the in-vitro dissolution research. This quick release is explained by the spontaneous creation of nanodroplets, which have a large surface area and successfully get beyond the drug's natural solubility restrictions. The SNEDDS's superiority in increasing the oral bioavailability of weakly water-soluble drugs is demonstrated by the burst release seen in the first 15 minutes (88.4%), which guarantees a quicker beginning of action.

Table No.3: In-Vitro Dissolution Study

Time (min)	% Cumulative Release (Pure Silymarin)	% Cumulative Release (Silymarin SNEDDS)
0	0.0	0.0
5	2.1	45.6
10	4.5	68.2
15	7.2	88.4
30	12.8	95.1
45	15.3	98.5
60	18.2	99.2



CONCLUSION

A Silymarin-loaded SNEDDS was successfully developed by the study. Through systematic optimisation, a formulation with a droplet size of less than 100 nm was obtained, which is perfect for lymphatic targeting. By using lipid-based excipients, the formulation facilitates the absorption of Silymarin through the intestinal lymphatic system, thereby avoiding the hepatic first-pass metabolism and possibly lowering the necessary clinical dose.

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