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ENHANCING SOLUBILITY AND BIOAVAILABILITY OF BACOSIDE A FROM BACOPA MONNIERI PLANT EXTRACT USING SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) FOR PARKINSON'S DISEASE TREATMENT

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ABSTRACT

Bacoside A, a bioactive compound from Bacopa monnieri, shows potential in treating Parkinson's disease. However, it's poor solubility and bioavailability limit it's therapeutic efficacy. To develop and optimize a self-nano Emulsifying Drug Delivery System (SNEDDS) for enhancing solubility and bioavailability of Bacoside A. The drug's solubility was evaluated using a saturation solubility study in a variety of oils, including synthetic and edible oils, surfactants, and co-surfactants. To determine the proper concentration ranges for the components—oil, surfactant, and co-surfactant—a pseudo-ternary phase diagram was employed. Oil, surfactant, and co-surfactant were determined to be oleic acid, tween 20, and ethanol based on the results of the saturation solubility study and phase diagram. Based on the drug's solubility and dilution potential, the formulation was optimized using the D-Optimal mixture design. The optimized SNEDDS formulation demonstrated 89% drug release in the in vitro dissolution testing, while the untreated drug extract only released 24% of the medication in 60 minutes. In comparison to pure extract, an ex vivo diffusion investigation revealed that over 90% of the drug diffused from the enhanced SNEDDS formulation. The design of experimentation technique was used to produce the SNEDDS formulation, which showed tremendous promise as a potential replacement for conventional oral formulations of poorly soluble Bacoside A in order to increase solubility and bioavailability.

Keywords: Bacoside A, Self-Nano Emulsifying Drug Delivery System (SNEDDS), Parkinson's Disease , Solubility Enhancement, Bioavailability Improvement.

I. INTRODUCTION

Monnieri Bacopa Linn. Called "Brahmi" in Hindi and "water hyssop" in English, this perennial herb belongs to the Schrophulariaceae family and is creeping. It has small leaves and white or purple blooms. It grows in East Asia, the United States, and warm wetlands. It is native to Australia and India (Barrett and Strother, 1978). In Ayurveda, it has been utilized as a medicinal herb for ages. According to Ramawat and Gopal (2004), it is used to treat tumors, ulcers, asthma, and epilepsy. It was first mentioned in writing in the sixth century A.D. in books such as the Susurtu Samhita, Atharva-ved, and Charaka Samhita. According to Singh and Dhawan (1997), bacopa monnieri is a member of the class of medications known as medhya rasayana, which is used in many constitutions to improve memory and promote mental wellness. When it comes to developing drugs, natural ingredients have proven invaluable as a biologically validated rostrum. For thousands of years, natural products have been utilized to treat a variety of illnesses. Certain chemicals found in plants have a unique physiological effect on humans, which gives them their medicinal significance. Alkaloids, flavonoids, tannins, and phenolic compounds are the most significant of these plant bioactive substances (Rajan et al., 2015). By investigating Bacopa monnieri's effects on several attributes and concentrating on the neuro-pharmacological mechanisms that disclose the herb's nootropic effect, this review seeks to provide light on the medicinal use of the herb.[1,2][3]

Taxonomic Classification

Drug delivery systems and pharmaceutical formulation technology are crucial to the search for novel pharmaceutical treatments. For lipophilic bioactive components to disperse in hydrophilic systems, drug delivery mechanisms are required. In the context of pharmaceutical applications, the oil-in-water (O/W) emulsion-based carrier system is a very suitable approach for the encapsulation, preservation, and delivery of water-insoluble bioactive components .Drug molecules with limited water solubility have been the subject of

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numerous strategies to improve their bioavailability, including liposomes, nanoemulsions, nanostructured lipid carriers (NLC), and self-nanoemulsifying drug delivery systems (SNEDDS). Because of their easy production and high intestine absorption efficacy, self-nanoemulsifying delivery systems have been extensively explored. This has increased the bioavailability of oral preparations of water-insoluble medicinal molecules. SNEDDS is a uniform complex. The homogeneous complex system known as SNEDDS is made up of co-surfactant, surfactant, and oil that is thermodynamically stable. Because of the tiny droplet size of the dispersed phase, the SNEDDS that forms is oil in water (O/W), appears clear and translucent, somewhat opaque, and opalescent .When SNEDDS is taken orally, it will quickly spread to create nano (<200 nm) droplets. In comparison to other lipid systems like solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), SNEDDS has been shown in numerous studies to have better thermodynamic stability as well as short- and long-term storage stability. This is because the formula only contains oil, surfactants, and cosurfactants at balanced concentrations, leaving the resultant droplet size more uniform and bioavailability higher. Research has extensively shown that SNEDDS can boost the bioavailability of medications that are poorly soluble in the systemic circulation. This feature is applicable to the following delivery modes: pulmonary, intravenous,and oral[4] .

Table 1:

Kingdom	Plantae
Division	Tracheophyta
Class	Magnoliopsida
Order	Lamiales
Family	Schrophulariaceae
Genus	Bacopa
Species	Monnieri

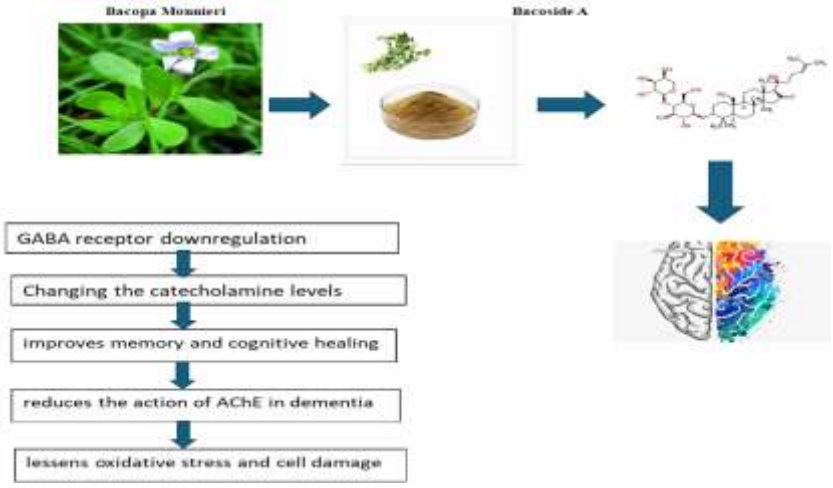

Figure 1:

The formula's concentration and composition dictate whether or not SNEDDS will successfully form. The stability and droplet size of the resulting nanoemulsion will be impacted by the oil in the SNEDDS recipe. In SNEDDS, the oil phase functions as a carrier that dissolves lipophilic active ingredients. In the presence of cosurfactants and surfactants, the oil phase in the gastrointestinal tract (GIT) forms droplets. The oil employed in this investigation, Miglyol 812, is a medium-chain triglyceride (MCT). Compared to short-chain triglycerides (SCT) and long-chain triglycerides (LCT) such oleic acid, olive oil, coconut oil, and virgin coconut oil, miglyol 812 has a greater dissolving capability and superior stability[5] .Interfacial tension can be decreased in part by surfactants. The value of the hydrophilic-lipophilic balance (HLB) and user safety are the two main factors considered while selecting a surfactant for SNEDDS. When the SNEDDS formula meets the stomach fluid, an oil's interfacial tension will be lessened more easily if the HLB number is high—greater than 10. Hydrophilic surfactants have high HLB values, while lipophilic surfactants have low HLB values. In order to create

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nanoemulsions when in contact with gastrointestinal medium (GIT) and stable the SNEDDS that are generated, it is crucial to choose surfactants with the appropriate HLB.Because Tween 80 may solubilize and reduce the surface tension and interfacial tension of immiscible phases, it was utilized as a surfactant with an HLB value of 15 .The co-surfactant, which will occupy the space between the surfactants, controls the droplet size and the length of time the medium takes to emulsify. In order to maintain the droplet size at the nanoscale, the interfacial tension between the two liquids will be lowered by the dense layer of surfactant and co-surfactant on the droplet surface. Co-surfactants, such glycerin and PEG 400 are frequently employed in the manufacture of SNEDDS. Due to its high HLB value (>10) of 11.6, PEG 400 was selected as a co-surfactant in the SNEDDS formulation of Dayak onion extract. It can assist surfactants in promoting the spontaneous production of nanoemulsions. The understanding, creation, and application of SNEDDS in innovative drug delivery systems are anticipated to benefit from the findings of this article review.[6]

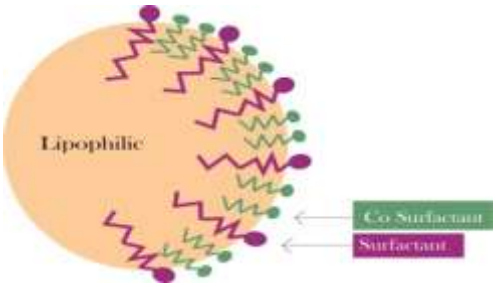

Figure 2:

Parkinson's disease (PD) is the second most common neurological ailment globally. It is predicted that over 6 million people already have PD, and in the next 25 years, the incidence of PD is expected to double. Regretfully, there is currently no treatment that can fully reverse this illness. Levodopa, the best treatment now available, only relieves symptoms by raising dopamine levels in the brain. However, there have been reports of severe adverse effects like depression, psychosis, and low blood pressure. We still need to find potential medications that can effectively cure or stop this condition. The body of research indicates that restoring mitochondrial activity and maintaining redox equilibrium would be crucial therapeutic approaches for Parkinson's disease. The broad range of neuropharmocological characteristics of phytochemicals obtained from Bacopa monnieri has been documented in numerous investigations. We will explicitly address B. monnieri extract's function in modifying Parkinson's disease in thi s chapter.[7][8]

Pathophysiology

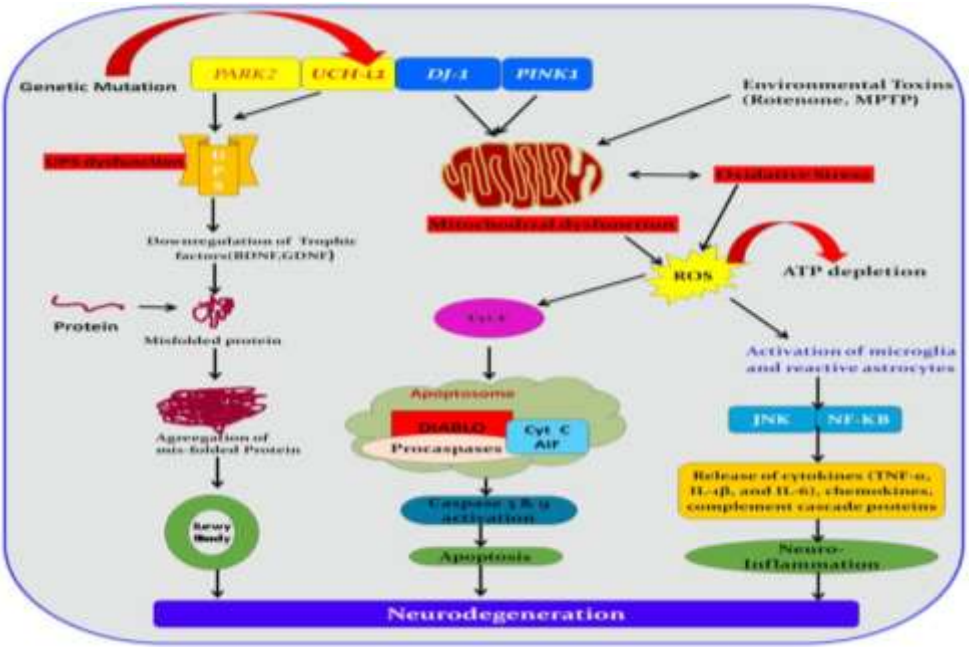

Figure 3:

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II. MATERIALS AND METHODS

Collection of Material

Pharmanza Herbal Pvt. Ltd., Dharmaj, India, offered an ex-gratis dried extract of Bacopa monnierii (45%). Gattefosse, Saint-Priest, France provided the lipid excipients, including Labrafac PG, Labrafac Lipophilic WL 1349, Labrafil M 2125CS, Labrasol, and Transcutol HP. We acquired Acconon, Captex 200, Capmul 300, and Capmul MCM from Abitec Corp. in Columbus, OH. We purchased Tween 80, Tween 20, Span 20, oleic acid, and isopropyl myristate from SD Fine Chemicals located in Ahmadabad, India. PEG 400 and propylene glycol were purchased from Astron Chemicals in Ahmadabad, India. During the investigations, the reagents and buffer components were of analytical grade. Throughout the investigation, deionized double-distilled water is utilized.[9)

Methods

Preliminary Component Screening

Screening of Oil

By pouring an excess of pure extract equivalent to Bacoside A in 2 ml of each oil separately in 5-mL-capacity stopper vials and mixing with a vortex mixer, the solubility of Bacoside A in different oils was ascertained. After that, the mixture vials were placed on an orbital shaker and held at 25±1.0 °C for 72 hours to reach equilibrium. After the samples had stabilized, they were taken out of the shaker and centrifuged for 15 minutes at 3,000 rpm. The supernatant was filtered through a 0.22 µm membrane filter. The oil's Bacoside A concentration was measured using a UV spectro-photometer.[10]

Screening of Surfactant

After preparing 2.5 ml of a 15% surfactant solution in water, 4 µl of oils were added and vigorously vortexed. If a clear, one-phase solution was produced, the oil was added again and again until the solution turned hazy. The drug's solubility in the surfactant and the surfactant's ability to bind oil were taken into consideration while choosing the surfactant.[10]

Screening of Co-Surfactant

After the selection of the surfactant as described above selected surfactant was combined with six types of solubilizers as co-surfactants namely, ethanol, PEG 200, PEG 400, and propylene glycol in different ratio 1:1, 1:2, 1:3, 2:1, 3:1 and selection of the co-surfactant was done on the basis of clarity with surfactant. Clarity of different blends of S mix was determined by measuring % Transmittance in Single beam U. V. Spectrometer. Selection of the co-surfactant also carried out on the basis of solubility of the drug in co-surfactant.

Following the above-described surfactant selection, the chosen surfactant was mixed in varying ratios (1:1, 1:2, 1:3, 2:1, and 3:1) with six different types of solubilizers (ethanol, PEG 200, PEG 400, and propylene glycol) as co-surfactants. The choice of co-surfactant was made based on the surfactant's clarity. A single beam UV spectrometer was used to measure the transmittance percentage in order to assess the clarity of various Smix blends. The drug's solubility in the co-surfactant was taken into consideration when choosing the co-surfactant.[10]

Pseudo-Ternary Phase Diagram Construction

To determine the component concentration range for the microemulsion's current region, pseudo-ternary phase diagrams were built. Prosim software was used to create pseudo-ternary phase diagrams. A mixture of chosen surfactant and co-surfactant was prepared with weight ratios of 4:1, 3:1, 2:1, 1:1, 1:2, and 1:3. Nine distinct combinations—1:9, 2:8, 3:7, 4:8, 5:5, 6:4, 7:3, 8:2, and 9:1—in varying weight ratios of oil and Smix were taken. The aqueous phase was represented by one axis of the pseudo three-component phase diagram, the oil phase by another, and a mixture of surfactant and co-surfactant at a set weight ratio (Smix) by the third axis.[11]

Compatibility of drug excipients

An FTIR spectrophotometer was used to perform the IR spectroscopy, and the wavelength range of 4000–400 cm−1 was recorded in the spectrum. The process involved dispersing the samples in KBr to prevent solid transition that could have been caused by prolonged grinding. The spectrum was scanned with a speed of 20

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scans per second and a resolution of 0.15 cm−1. Using a Fourier Transform Infrared Spectrophotometer, the Infra-Red spectra of pure Bacopa monnieri extract and a combination containing oleic acid, Tween 20, and ethanol were acquired in order to look for any drug-excipient interactions.[11]

D-optimal mixture design for Bacoside A SNEDDS optimization.

Due to its ability to reduce the generalized variance of the coefficient estimations, the D-optimal mixture design was chosen. A base design comprising factorial points (high and low level from the constraints on each factor, centers of edges, centroids of the constraint plane, axial checkpoint, and an overall center point) was chosen by the software. Additionally, fewer trials are needed overall. The SNEDDS formulation was optimized via eleven runs. The solubility of the medicine (mg/ml), the nepheloid turbidity index [NTU], and the viscosity were examined in relation to the effects of three formulation variables: the amount of oils, the surfactant, and the cosurfactant.

The study's ideal formulation is chosen to have the lowest NTU and the highest solubility possible. Second order polynomial equations were used to develop this design, which helped to explain why the response was non-linear. If the relevant p-values for the statistical analysis's results were less than 0.05, they were considered significant [12]

Table 2: Levels and factors with altered and coded values

Factors	Levels			
	Transformed value		Coded value	
	High level	Low level	High level	Low level
X1(Oleic acid)	18	2	1	0
X2(Tween 20)	36	15	1	0
X3(Ethanol)	12	5	1	0

Table 3: Design expert program produced the design matrix (8.0.7.1).

Formulation code	Oil	Surfactant	Co-surfactant
1	18	15	12
2	4.52	35.47	5
3	6.094	26.906	12
4	10.44	25.27	9.27
5	10.44	25.27	9.27
6	8.93	30.72	5.34
7	12.098	20.90	12
8	13.71	26.29	5
9	2	31	12
10	16.52	19.23	9.24
11	18	22	5
12	2	34.96	8.04

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Characterization and evaluation of SNEDDS

1) Self-Emulsification Time

A magnetic stirrer running at a steady speed is used to combine 0.5 ml of the SNEDDS formulation with 250 ml of 0.1N HCl in a beaker in order to calculate the emulsification time. Room temperature is used for emulsification, and turbidity is checked on the emulsion's surface.[13]

2) Percent transmittance and the refractive index.

The formulation's transparency was demonstrated by the refractive index and transmittance %. Using a Digital Abbe refractometer in Rochester, the system's refractive index was determined by measuring one drop of the formulation in triplicate on a slide at 25 °C and comparing it to water.[14,15]

3) Droplet size analysis and zeta potential measurement.

Using a zeta sizer capable of measuring sizes between 10 and 5000 nm, photon correlation spectroscopy—which examines variations in light scattering caused by the Brownian motion of the particles—was used to quantify the droplet size of the emulsions. The measurements were taken at a 90° angle and at 25 °C. In a glass beaker, the formulation was gently stirred into 100 ml of water. After that, 1 ml of the aliquot was taken out and put into a sample cell so that the droplet size could be determined. Every size value given was the mean of a minimum of three separate measurements.[16,17]

4) Determination of cloud points

Distilled water was used to dilute the optimum SNEDDS formulation in a 1:250 ratio. The temperature of the diluted sample was gradually raised while it was submerged in a water bath with temperature control. The temperature at which clouds suddenly appeared was identified as the cloud point.[18]

5) Transmission electron microscopy

Using the Technikai G2 Ultra twin FEI, Netherlands, the morphology of drug-loaded SNEDDS was examined. A drop of the sample was applied to a grid covered in carbon to create a thin liquid film. After removing the extra solution, the sample was imaged at 120 KV of acceleration.[19]

6) In vitro dissolution studies

The USP type II dissolving apparatus was used in the quantitative in vitro dissolution tests to evaluate drug release from the oil phase into the aqueous phase. 500 cc of 0.1 N HCL is employed as the dissolving media. The device has a temperature of 37±0.5 °C and revolves at 50 rpm. At0,10,20,30,40,50, and 60 minutes, 5 ml aliquots were taken out, filtered through 0.45 µm membrane filters, and the volume was taken out and refilled with new media. A UV spectrophotometer is then used to evaluate the samples that were obtained.[19]

7) Ex vivo intestinal permeability study

Male Wistar albino rats, weighing between 250 and 300 grams, and aged between 12 and 14 weeks, were kept in cages with unlimited access to a regular diet and water. Before the experiment, the rats were allowed to acclimate to their surroundings for one week. They were kept in cages and provided with unlimited access to standard feed and water. Under the direction of CPCSEA, the Ministry of Social Justice and Experiment, Government of India, the experimental protocol was approved by the Institutional Animal Experiment Ethics Committee of Anand Pharmacy College, Anand, Gujarat, India, with approved protocol No. 1409/APC/2014-15. The manner of sacrificing the animals was inhaling ether.

The intestine was thoroughly cleansed and separated, and then the untreated extract was added. The intestine was then knotted at both ends. The tissue was submerged in tyrode solution at 37 °C with constant aeration . Phosphate buffer solution pH 7.4 with 1% SLS was added to the beaker. Samples were taken out of the beaker at prearranged intervals, and each time new buffer was added. Spectrophotometric analysis was used to determine the drug content of the samples. The graph was plotted as absorption Vs. time after the percentage diffusion was computed.[19]

III. RESULTS AND DISCUSSION

Preliminary screening of component

Solubility study

With the exception of oleic acid (4.97±0.09 mg/2 ml) and turmeric oil, which contained 45% of Bacoside A in pure extract, Bacoside A demonstrated minimal solubility in all investigated oils. Oleic acid, also known as 18:1 cis-9 lipid number, is a monounsaturated omega-9 fatty acid. It is expressed as follows:

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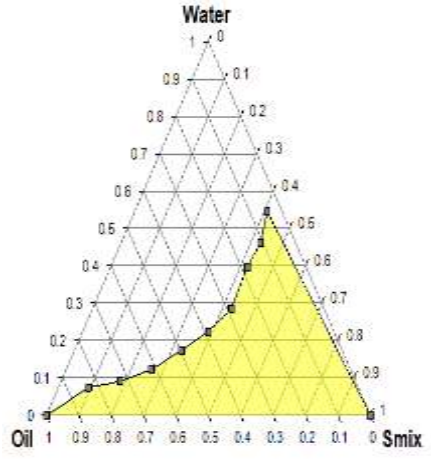
CH3(CH2)7CH=CH(CH2)7COOH.[14]. Finding the surfactant with the maximum oil solubilization capacity was the aim after oleic acid was chosen as the oil phase. The greatest solubility of Bacoside A (1.94±0.12 mg/2 ml) for 45% of the extract from Bacopa monnieri was observed in Tween 20. Tween 20 was therefore chosen as the surfactant for the SNEDDS formulation. Maximum solubility in ethanol (2.38±0.03 mg/2 ml) for 45% bacoside A in Bacopa monnieri extract was seen among the co-surfactants that were evaluated. As a result, ethanol was chosen to be the co-surfactant in the formulation of SNEDDS. On the other hand, different cosurfactants were examined for miscibility and solubility with a surfactant. Ethanol generates a transparent system (99.87 %T) more frequently than other evaluated cosurfactants with a chosen surfactant among different S mix blends.

Construction of pseudo-ternary phase diagram

First, using Tween 20, a surfactant, ethanol, a co-surfactant, and oleic acid, or oil, different pseudo-ternary phase diagrams were created based on the results of maximum solubility in order to determine the maximal region for the formation of the thermodynamically stable nanoemulsion, as shown in figure 1. After experimenting with several ratios of Tween 20 and ethanol (i.e., 1:1, 1:2, 1:3, 2:1, 3:1, and 4:1), the maximum region for nanoemulsion was found at 3:1. In the direction of the water-rich phase diagram's apex, an o/w microemulsion area was discovered. A larger microemulsion region was seen as the surfactant content in the S mix ratio rose. he most likely causes are a decrease in interfacial tension and an increase in interface fluidity. The hydrophobic area of the surfactant monomers is where more oil phase penetration is seen, according to research by Kawakami K and colleagues [16]. The formulations that could accommodate the ideal amount of Smix and distilled water and in which the amount of oil phase completely solubilized the medicine were chosen for the optimization study based on pseudo-ternary phase diagrams.



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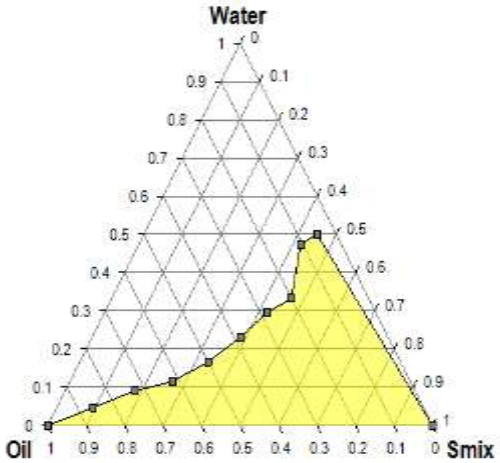

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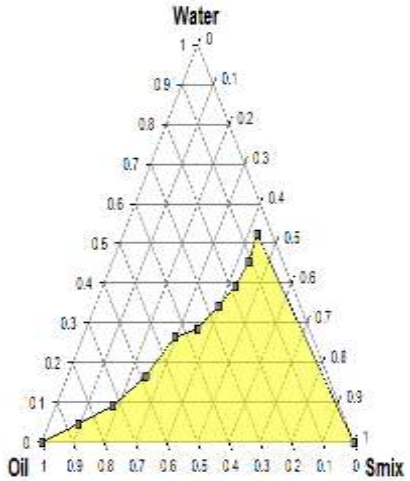

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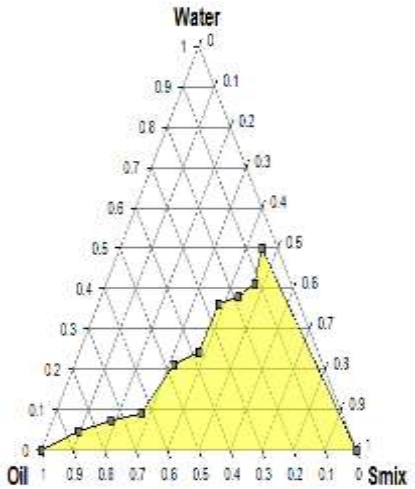

(3:1)

Fig 4: Pseudo ternary diagrams of Oil: Smix (1:1), (1:2), (2:1), (3:1)

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Drug–excipient compatibility study

FT-IR study

Studying the compatibility between excipients and Bacopa monnieri

Studies using FT-IR were conducted on both pure drugs and drugs in combination with excipients. The mixture contained all of the distinctive peaks of the pure extract, indicating that there is no interaction between the medication and the excipients.

Bacoside Optimization Using D-optimal mixture design, a loaded SNEDDS

D-optimal combination The current work used an experimental design to produce the best bacoside A loaded SNEDDS. The formulation factors were oleic acid (X1), Tween 20 (X2), and ethanol (X3); the response variables were viscosity (cp) (Y3), n. T. U (Nephlo turbidity unit) (Y2), and solubility of medication (mg/ml) (Y1). Table 3 provides an overview of these formulations' reactions.

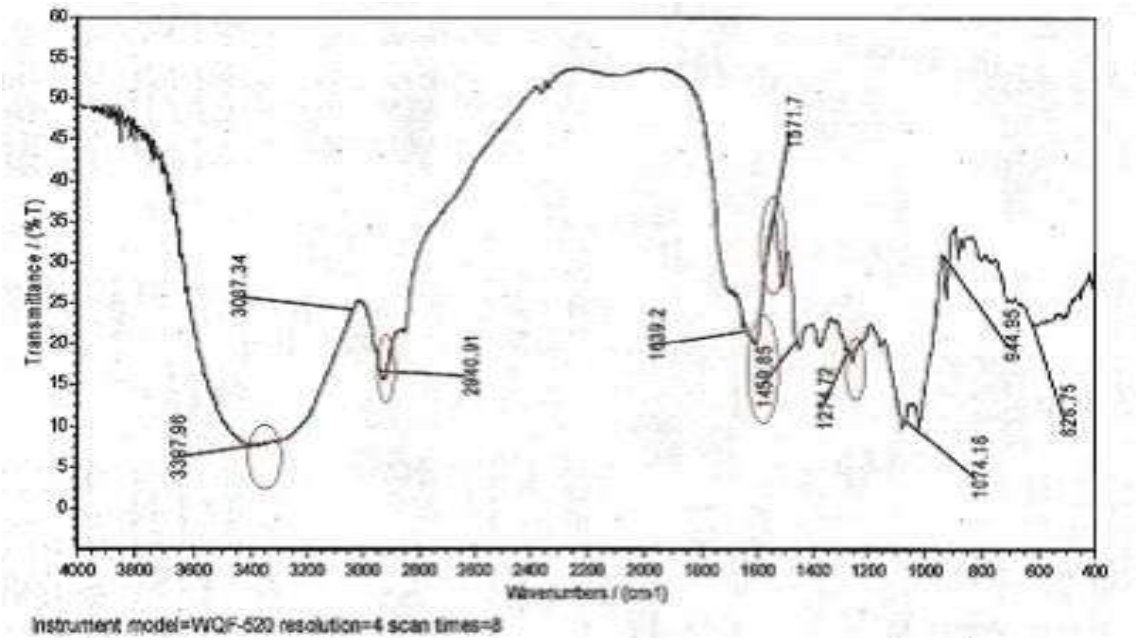

Fig 5: FT-IR spectra of ***Bacopa monnieri***

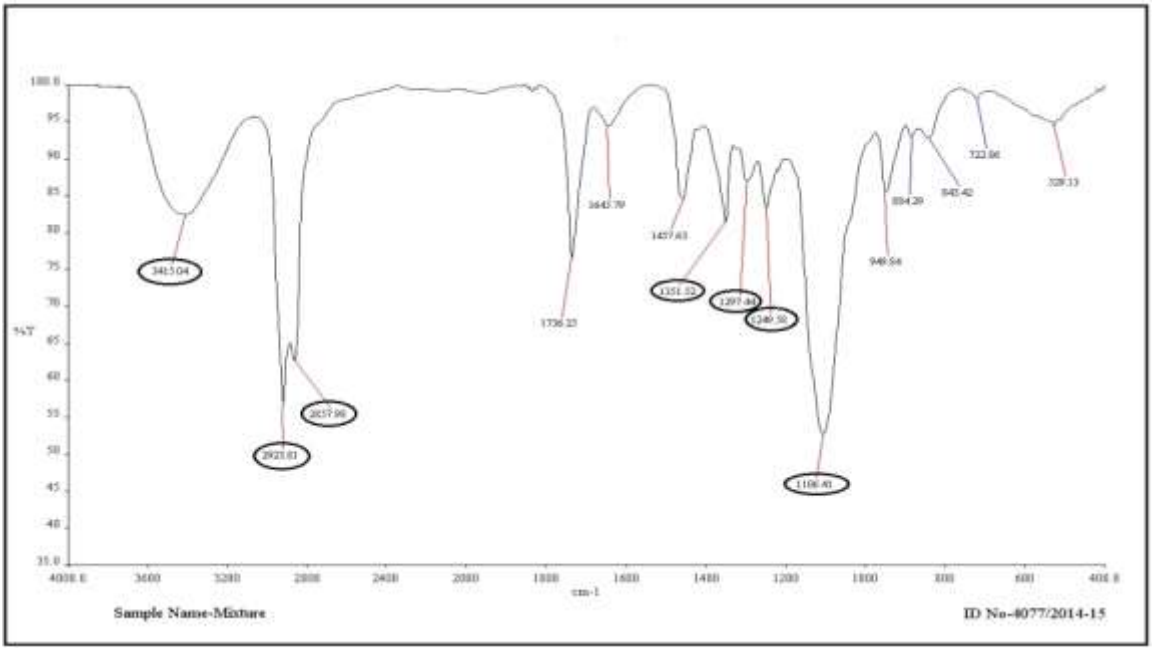

Fig 6: FT-IR spectra of ***Bacopa monnieri***+Excipient

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Table 4: Formulations' reactions according to the D-optimal mixture design

Formulation Code	Response		
	Solubility (mg/ml) for 45% bacoside A In pure extract	N. T. U (Dilution potential)	Viscosity (cp)
1	10.64±0.23	104.97±0.25	4.2±0.01
2	10.84±0.12	5.16±0.12	6.9±0.04
3	10.89±0.09	2.08±0.06	4.27±0.07
4	10.03±0.13	91.71±0.21	7.32±0.02
5	10.24±0.21	93.25±0.29	7.3±0.05
6	9.44±0.27	60.82±0.15	8±0.01
7	10.21±0.14	61.80±0.32	4.5±0.08
8	9.24±0.43	60.54±0.05	7.52±0.01
9	10.89±0.05	3.36±0.09	6.4±0.04
10	9.13±0.31	84.58±0.11	5.56±0.03
11	9.93±0.36	78.09±0.19	6.24±0.09
12	10.83±0.02	4.16±0.03	7.4±0.07

The data presented (n = 3) were mean±SEM.

Design Expert® Software was used to examine the results from the solubility (response Y1), N. T. U. (response Y2), and viscosity (response Y3) tests. Table 4 displays the coefficient of a cubic model of the independent variables.

Table 5: Quadratic equation coefficient for each independent variable

Co–efficient	Solubility(mg/ml)	N. T. U	Viscosity
B1(X_1)	+14.26	+105.44	+4.21
B2(X_2)	-1.22	+9071.03	+309
B3(X_3)	+1400.33	-65.48	+9.5
B12(X_1X_2)	+2.2	-16249.82	-507.33
B13(X_1X_3)	-1372	+33.59	-9.2
B23(X_2X_3)	+2.19	-16385.38	-554.94
B123($X_1X_2X_3$)	-2.27	+17748.12	+624.03

Using statistical analysis and the polynomial equation, the response variables and mixture components were related using Design-Expert® 7.0.1 software. The impact of these variables on the answer is demonstrated by the coefficient values. The coefficients for the intercept, primary first-order effects, and interaction term are included in the polynomial equations. An antagonistic effect on the response is indicated by a negative term in the coefficient, whereas a positive sign denotes a synergistic effect. Mixture components were optimized for answers Y1 and Y2, after the creation of polynomial equations linking the dependent and independent variables by MLRA (Multiple Linear Regression Analysis).

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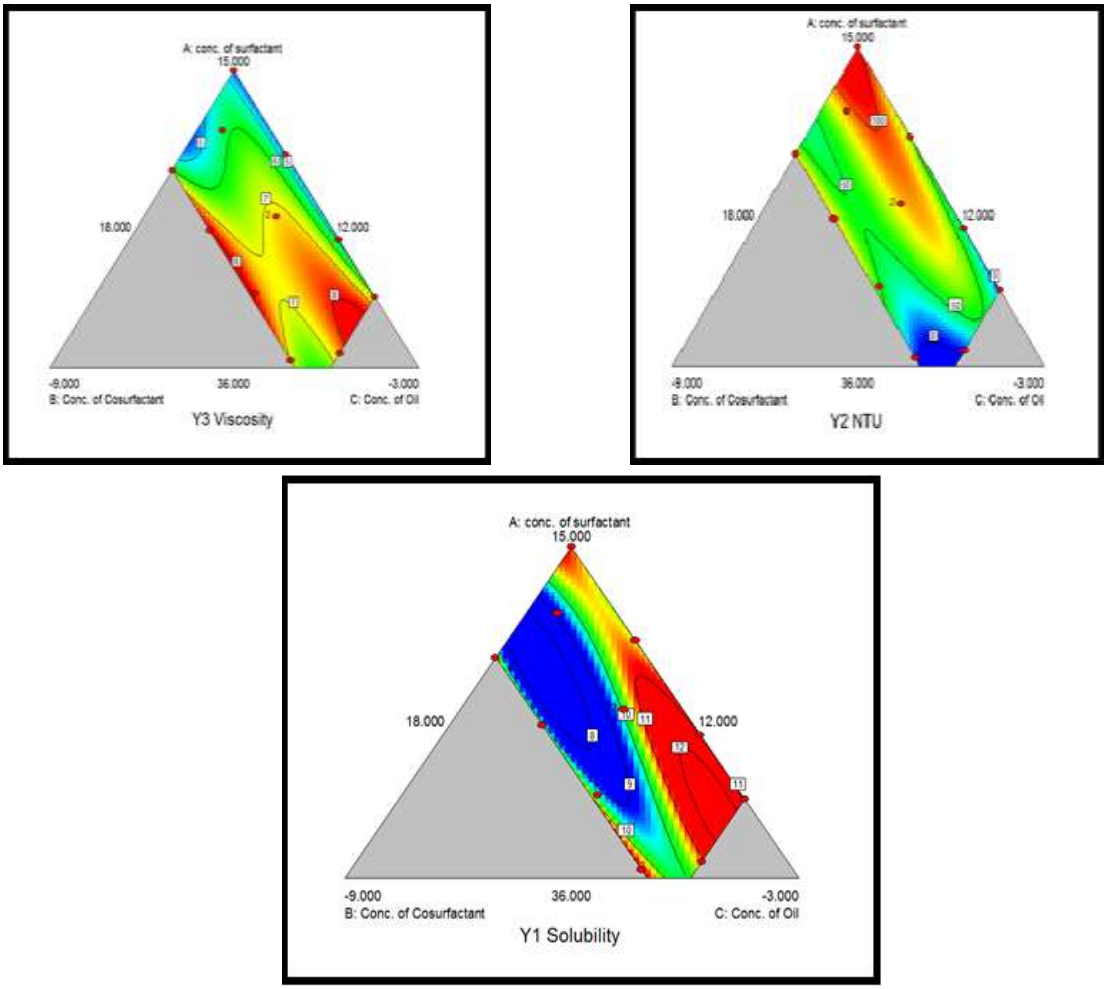

Fig 7: Response variable contour plots for solubility the viscosity and NTU

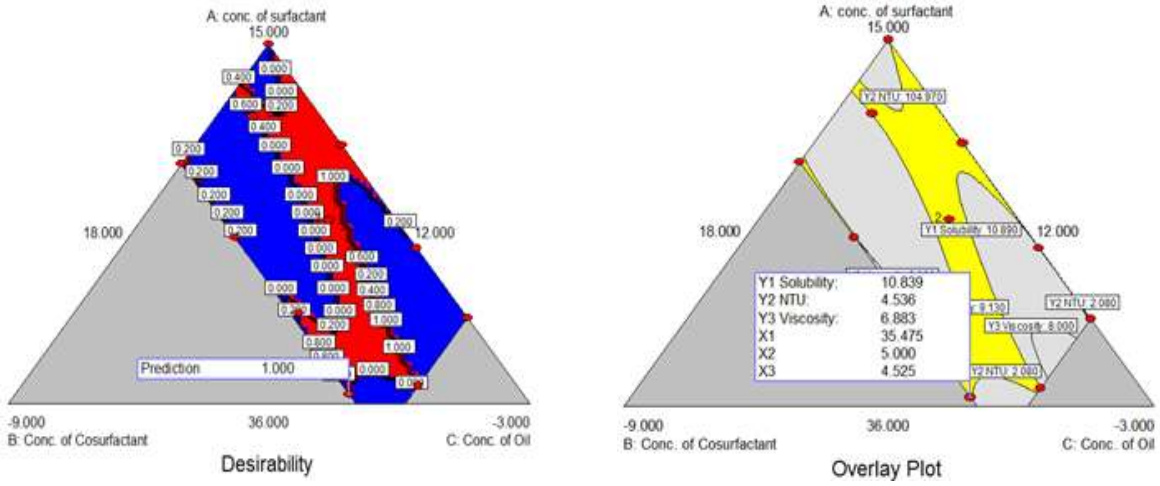

Fig 8: (a) Overlay plot and (b) Desirability plot

Figure 4 displays an overlaid plot, contour, and 3D response. To choose the design space, the contour plot should overlap. The design space is shown by the region that is overlaid. The surfactant content should be kept as low as possible in the optimal formulation to avoid any associated toxicity. Additionally, the model was fitted using a unique cubic polynomial model and optimized using the "total subset" variable selection approach after the maximum desirability function (0.97) value was calculated with a step width of 0.1. One batch of formulations with the ideal mixture was created in order to verify the model's suitability for prediction. Table 6's results showed that the model had good predictability.

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Table 6: Formulation composition optimized by a design specialist

Component	Amount in %w/w	Type
Oleic acid	4.52±0.12	Oil
Tween 20	35.47±0.36	Surfactant
Ethanol	5.01±0.58	Co-surfactant

Data expressed were of mean±SEM (n=3)

Table 7: Checkpoint analysis of optimized batch

Parameters	Predicted value	Observed value	% Bias
Solubility (mg/ml)	10.83±2.15	10.65±1.25	1.69
NTU	4.53±1.02	4.28±2.35	5.84
Viscosity (cp)	6.88±1.08	6.47±1.17	6.33

Data expressed were of mean±SEM (n=3), Bias (%) = (predicted value − experimental value)/experimental value × 100.

Characterization and evaluation of SNEDDS of *Bacoside A*

Refractive index and percent transmittance

Transmittance (%T) and Refractive index were used to measure the formulation's transparency. The refractive index, which represents the isotropic character of the formulation, is the net value of the microemulsion's constituent parts. The optimized SNEDDS formulation's refractive index, 1.33, was discovered to be clear and isotropic in nature, indicating transparency closer to water. The optimized SNEDDS's percentage transmittance was determined to be (98.7±0.08), indicating the microemulsion's exceptional clarity.

Self-emulsification time

When subjected to aqueous dilution under mild agitation, emulsification time was the metric used to assess the efficacy of emulsification, which should disperse entirely and promptly. The appropriate evaluation index for the emulsification process was two minutes. Self-emulsification needs to happen with the least amount of disturbance possible, not a negative free energy. It was reported that different mesomorphic phases are seen between the formulation and water when a self-emulsified system is diluted by the aqueous phase. The duration needed for the transition from one liquid crystalline structure to another during the emulsification process may be the source of the delay in the emulsification time with decreased Smix content. It was discovered that the ideal SNEDDS formulation has a self-emulsification time of 9 seconds.

Droplet size analysis and zeta potential measurement

The emulsion's droplet size plays a crucial role in the effectiveness of self-emulsification as it dictates both the rate and degree of drug absorption as well as release. It has been observed that increased absorption and enhanced bioavailability correspond with emulsion droplet size reduction. Because non-ionic surfactants are available to stabilize the oil-water interface, there may be a decrease in particle size. Moreover, the improved closed packed film of surfactant that is forming at the oil-water interface stabilizes the oil droplets, as seen by the decrease in droplet size behavior. he interfacial surface area available for medication absorption will increase with decreasing droplet size. Particle size seemed to be strongly correlated with S mix content and inversely correlated with oil concentration. The medication may release more quickly thanks to SNEDDS's smaller particle size. In water, the optimized batch's mean particle size is 33.84 nm.

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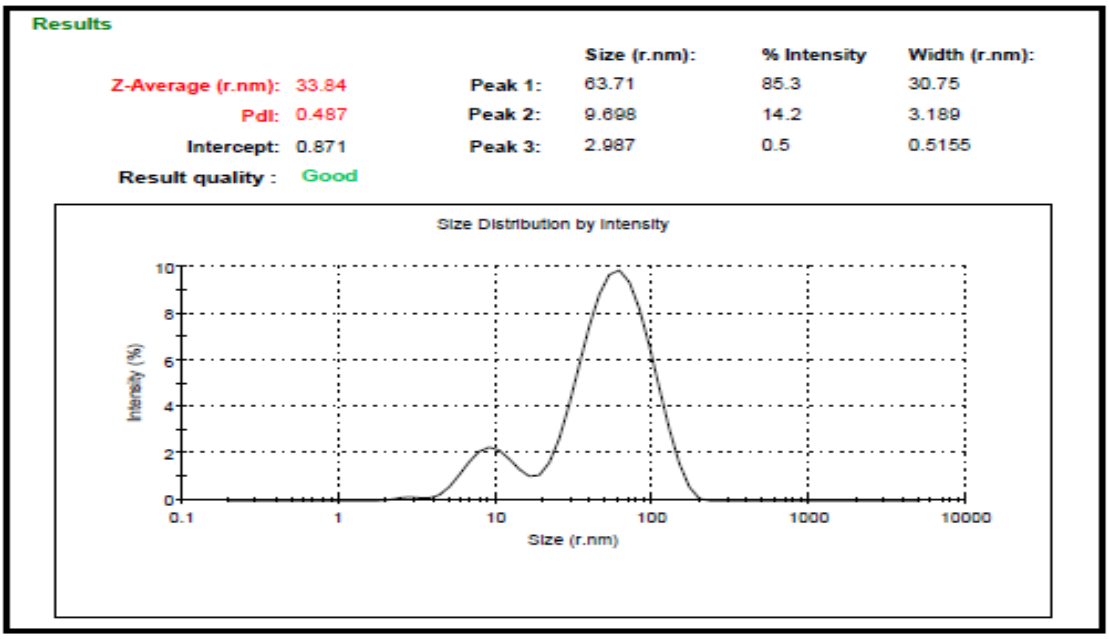

Fig 9: (a) Graph of particle size measurement

The stability of a microemulsion is determined by its zeta potential, which makes measuring it crucial for stability studies. Two droplets are repelled by electrostatic forces when the zeta potential is high. The DLVO theory states that in situations when the electrolyte concentration in the continuous phase is below a specific threshold, +electric double layer repulsion will stabilize the microemulsion. A negative potential between the droplets is indicated by a negative force. A unique SNEDDS causes adherence to the intestinal mucosa and subsequently medication uptake from the mucosa. It dilutions with an aqueous phase result in negatively charged dispersed oil droplets. As a result, these formulations improved oral bioavailability and oral absorption. The optimized batch's zeta potential was found to be −4.45 mV in this investigation. This outcome is ascribed to SNEDDS's non-ionic surfactant content.

Transmission electron microscopy (TEM)

Discrete particles with an exterior cubic structure could be seen when the samples were examined under an electron microscope, as seen in figure 10. It was discovered that the particle size ranged from 6.12 nm to 50nm

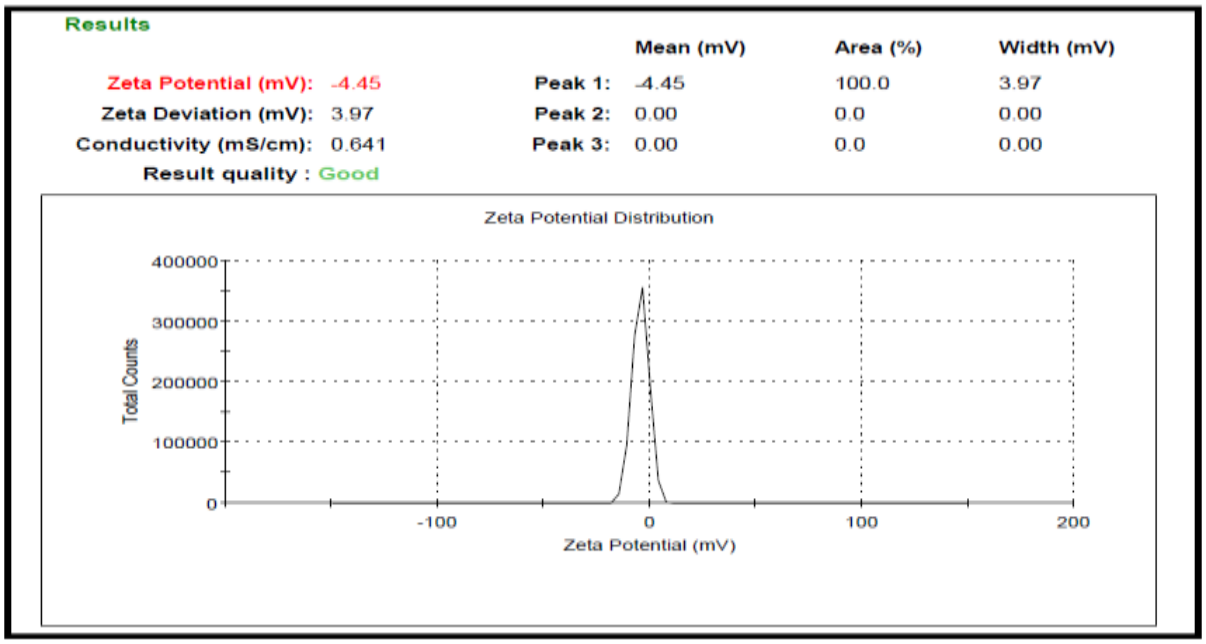

Fig 9: (b) Graph of zeta potential measurement

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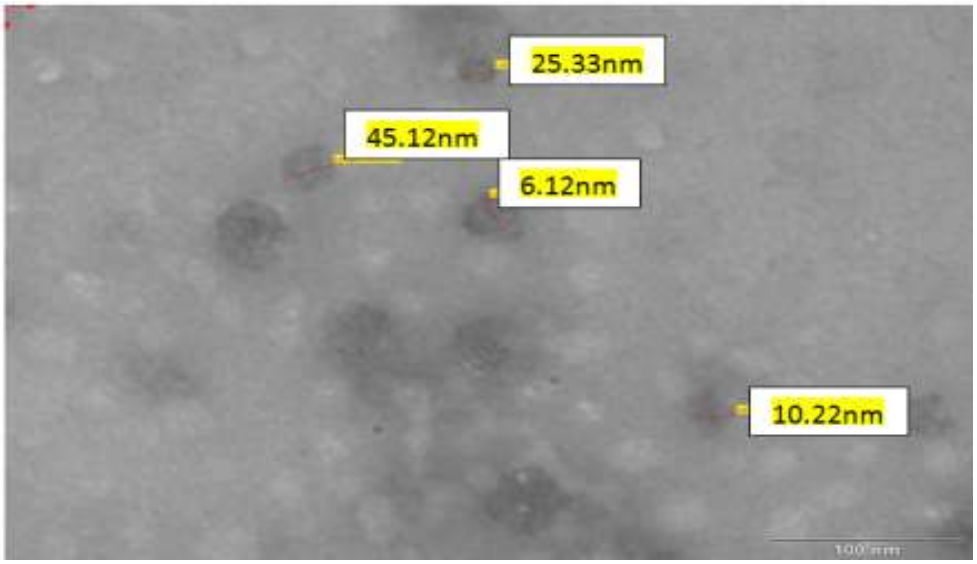

Fig 10: Transmission electron microscopic image of optimized formulation

***In vitro* dissolution study**

This study compares the solubility profiles of the medication Bacoside A in its pure form and the formulation with SNEDDS. Over 80% of the medicine is released from SNEDDS within 50 minutes when the unformulated bacoside A releases up to 24% of the drug within the same time frame. This is due to improved SNEDDS formulation. The medication is insolubilized in the optimized SNEDDS formulation, and when it is exposed to the dissolution media, it forms smaller droplets that dissolve more quickly in the dissolution medium. This explains why the formulation dissolves more quickly.

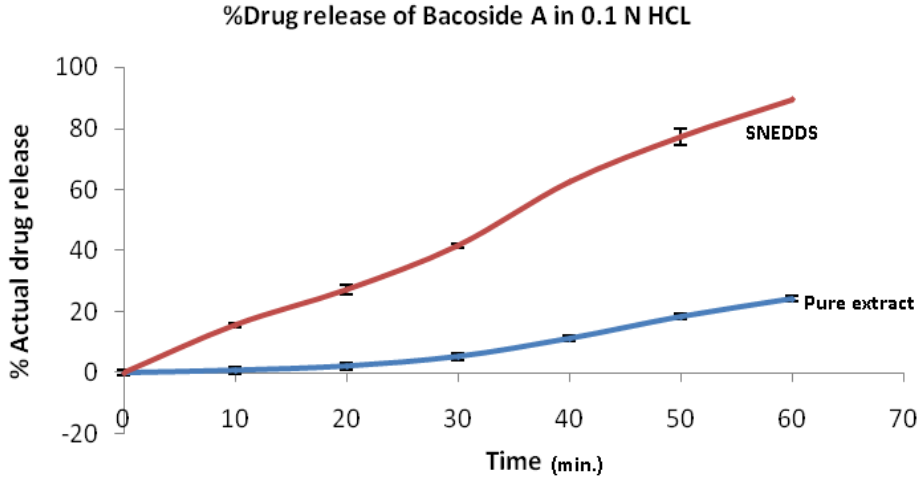

Fig 11: Optimized SNEDDS formulation and untreated extract in vitro dissolving profile; data expressed were mean±SEM (n=6)

This outcome might be explained by the emulsion's smaller droplet size and shorter emulsification time, which enable quicker drug release. Here, we've made the assumption that Vitro and Vivo are highly correlated. Therefore, it can be concluded that the NE formulation enhanced BA solubilization and produced consistent in vitro release.

Ex vivo intestinal permeability study

Because rat intestinal perfusion studies' absorption characteristics are most similar to those of humans, they are regarded as the most straightforward and applicable absorption screening approach available. Figure 9 displayed the findings of the ex vivo intestinal permeability investigation. Ninety-one percent of the medication had diffused from SNEDDS after four hours. Diffusion was determined to be 23.65% from the plain drug suspension (pure untreated extract).

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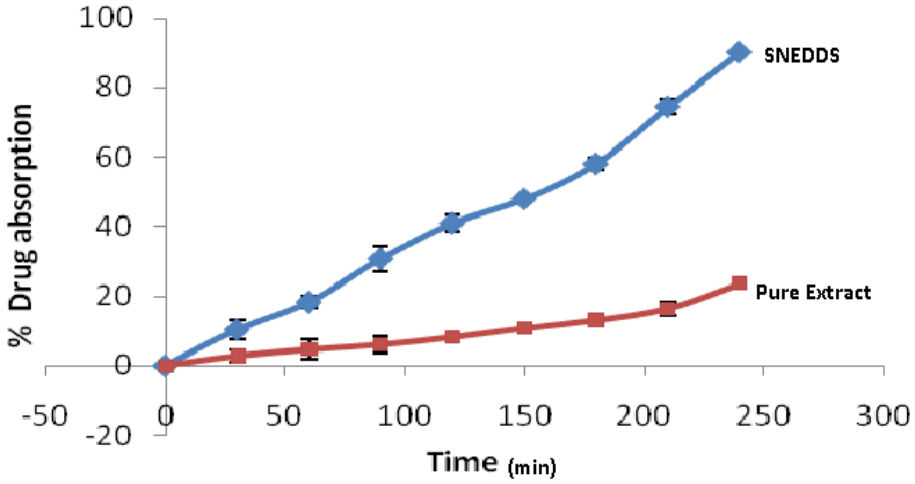

Fig 12: Ex vivo intestinal permeability behavior of pure extract and optimized SNEDD data were presented as mean±SEM (n=2).

The amount of drug diffused through the biological membrane has increased when it is administered in the form of SNEDDS because Bacoside A in the nano emulsifying form could be absorbed completely in the rat intestine at a faster rate than that in pure extract dispersion. Youenang Piemi et al .Revealed that the surface charge-modified droplets significantly impacted the droplets' affinity for adhering to the skin, potentially enhancing the absorption of medications. The improvement in diffusion is due to the formation of microemulsion droplets in the nanometer range and improved the permeation of the Bacoside A because of the presence of a surfactant, which lowers the interfacial tension of formulation."

IV. CONCLUSION

The current research work comprises the systematic development of optimized SNEDDS formulation of Bacoside A using formulation by design approach, followed by their evaluation using in vitro release studies, ex vivo permeation studies, and in vivo studies to determine their enhanced bioavailability potential. Studies on the equilibrium solubility of different oils, surfactants, and co-surfactants were conducted in order to rationally optimize the formulation utilizing D-optimal mixture design. Bacoside A-loaded SNEDDS were able to create small, self-emulsifying droplets on their own, with an average size of 6.12 nm to 50 nm. The dissolution percentage of in pH 1.2 buffer solutions was found to be much higher than that of Bacoside A, indicating a clear superiority in terms of prospective biopharmaceutical performance.

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