ISSN: 2347-6567

International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR |Vol.12 | Issue 2 | Apr - Jun -2024

www.ijamscr.com

DOI : https://doi.org/10.61096/ijamscr.v12.iss2.2024.208-220

Research

Optimization And Evaluation Of Soymida Febrifuga Nano Emulsion For Treating Epilepsy

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Published on: 08 Jun 2024

Published by:
DrSriram Publications

Abstract

Natural plants have always been a very potent source of pharmaceuticals; Indians in particular have been employing a variety of plants, as well as their parts and extracts, for medicinal purposes since the Vedic era. The current study aims to assess the antiepileptic activity of a nanoemulsion made from Soymida febrifuga leaf extract. The Soxhlet device is used to perform the extraction. The ethanol extract was used at dosages of 2000 mg/kg, 1000 mg/kg, 900 mg/kg, 850 mg/kg, 800 mg/kg, and 750 mg/kg for the acute toxicity test. The Soymida febrifuga sample's IR spectra showed that the absorption peaks of different functional groups are consistent with reference spectra. The particle stability index is represented by the zeta potential. The prevention of particle aggregation depends on this stability. The improved formulation's zeta potential was the millivolt (mV) was discovered. The stability of nanoparticles is higher at higher zeta potential maximum. The release study was conducted in accordance with the steps outlined in the section on materials and procedures. The medication was required for the slow, continuous release of the medicine. In the 12-hour release testing, F6, out of the nine formulations, had the highest drug release value. In convulsion models generated by MES and PTZ, the chloroform extract of Soymida febrifuga delayed the onset and decreased the duration of convulsions. It can be utilized as an adjuvant therapy against cognitive deficiency in convulsions.

Keywords: Soymida Febrifuga, Nano Emulsion, Formulation, Epilepsy.

INTRODUCTION

Natural plants have always been a very potent source of pharmaceuticals; Indians in particular have been employing a variety of plants, as well as their parts and extracts, for medicinal purposes since the Vedic era. Eighty percent of the world's population, mostly in developing nations, gets their medical care from plants, according to the World Health Organization. People still rely on traditional herbal treatments as their primary source of

healthcare, particularly in rural India. Plants continue to be a rich source of newly discovered chemicals, and this has led to decades of research into developing novel medications to treat a variety of illnesses [1].

The symptoms of epilepsy, a persistent brain illness, include increased EEG output and brief episodes of seizures. It is typically accompanied by autonomic hyperactivity, convulsions, or severe spasmodic spasms of the skeletal muscles, and loss of consciousness.[2] Nowadays, antiepileptic drug therapy for epilepsy is associated with teratogenic consequences, dose-related and chronic toxicity, and side effects. About thirty percent of patients still experience seizures when on antiepileptic drug therapy. The discovery of low-cost, safe, and effective anticonvulsant medicines derived from plants and other sources is therefore desperately needed.[3] The specific symptoms generated are contingent upon the functioning of the impacted brain area. Therefore, When the hypothalamus is involved, peripheral autonomic discharge is induced, convulsions are caused by, and loss of consciousness is the outcome of, contact with the reticular formation in the upper brain stem [4].

The brain is where all forms of epilepsy begin. The various forms of epilepsies have multiple origins rather than a single underlying mechanism. When numerous neurons fire together at a high level of excitement, a well-organized pattern of the brain's integrative activity is eliminated, leading to epilepsy. According to John Jackson's theory, these seizures are brought on by sporadic, abrupt, excessive, fast, and localized discharges of grey matter. After being started by the abnormal focus, the seizures target the nearby normal brain, resulting in widespread convulsions. Ischemia, the loss of sensitive cell inhibitory systems, or local metabolic alterations could all be the cause of this aberrant focus. But some physiological alterations might cause the focus to shift, which would make it easier for aberrant electrical activity to propagate to healthy tissue [5].

It is challenging to link syndromes with current epilepsy classification groups when the underlying cause is unclear. For some circumstances, the classification process was fairly arbitrary. The 2011 classification, which falls under the idiopathic group, covers syndromes where the age specificity and/or general clinical aspects strongly suggest a genetic basis. Benign rolandic epilepsy is one of the pediatric epilepsy syndromes that fall under the category of uncertain causes, where the underlying cause is thought to be genetic. Some, like Lennox-Gastaut syndrome, are symptomatic in certain situations even though a hereditary etiology is thought to be responsible. Clinical syndromes (like Angelman syndrome) that do not primarily involve seizures were classified as symptomatic; nevertheless, it has been suggested that they belong in the idiopathic category. As research progresses, the classification of epilepsies, and in particular, epileptic syndromes, will shift.[6]

Pathophysiology

The fundamental mechanism underlying neuronal excitability is the action potential. A voltage-gated ion channel change, an increase in excitatory synaptic neurotransmission, a decrease in inhibitory neurotransmission, or a change in intra- or extracellular ion concentrations in favor of membrane depolarization can all lead to an action potential, which is a hyperexcitable condition. Membrane potential can fluctuate in response to changes in intracellular ion compartmentalization, voltage-gated channel activation (whose conductance is influenced by transmembrane potential variations), and ligand-gated channel activation (whose conductance is affected by binding to neurotransmitters). GABA, glutamate, acetylcholine (ACh), norepinephrine, dopamine, serotonin, and histamine are the main neurotransmitters in the brain. Glutamate is the primary excitatory neurotransmitter. Every ionotropic glutamate receptor has a Na^+ and K^+ permeability, and the action potential is produced by the entrance of Na^+ and outflow of K^+ via these channels, which causes membrane depolarization. The calcium channel of the NMDA receptor is also present, and when the channel is at rest, magnesium ions block it. However, when the membrane depolarizes locally, Mg^{++} is displaced, allowing Ca^{++} to pass through. The process known as excitotoxicity, which occurs when there is an excessive amount of neuronal activation, such as in status epilepticus and ischemia, is believed to be facilitated by Ca^{++} influx, which also tends to further depolarize the cell [7].

By using electrodes spread across the scalp to record electroencephalography (EEG), abnormal electrical activity during and after a seizure can be identified. Based on the characteristics of the aberrant discharge and its distribution, several types of seizures can be identified. These days, structural abnormalities (such as lesions or tumors) that cause certain epilepsies are commonly identified in epilepsy diagnoses using modern brain imaging techniques like positron emission tomography and magnetic resonance imaging.[8]

Treatment for epilepsy should start as soon as a diagnosis is made. Research indicates that existing medications and other therapies for epilepsy may be less effective after seizures and their effects are established.

Prescription medication for antiepileptic seizures is by far the most used method of treating epilepsy. When a patient is diagnosed with newly formed epilepsy, doctors typically start treating them with antiepileptic medications such as carbamazepine, valproate, lamotrigine, oxcarbazepine, or phenytoin, unless the type of epilepsy is recognized to require a particular kind of treatment. Most typically, ethosuximide is used as the main treatment for absence seizures. Primidone, phenobarbital, and clonazepam are among the other medications that are often administered. Topiramate, felbamate, levetiracetam, gabapentin, and tiagabine are a few relatively new medications for epilepsy.[9,10]

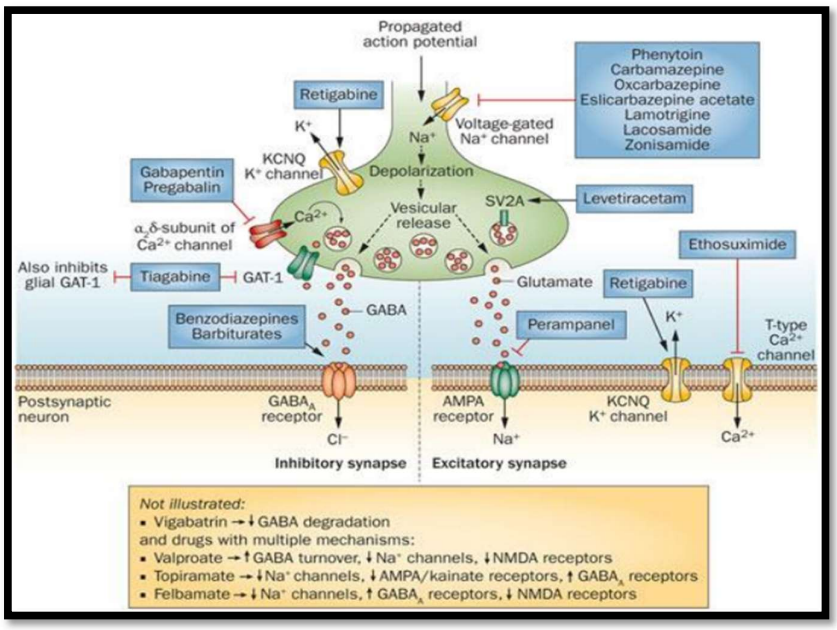


Fig 1: Mechanism of action of Antiepileptic drugs

Aim, objective

The current study aims to assess the antiepileptic activity of a nanoemulsion made from Soymida febrifuga leaf extract. The following are the goals of the research proposal: To make an ethanolic extract from the leaves of Soymida febrifuga, To create and describe a nanoemulsion of extract from Soymida febrifuga. To use in vitro experiments to assess the proposed formulation's antiepileptic efficacy.

MATERIALS & METHODS

Materials

Table 1: List of chemicals with name of supplier

S.No	Name of the raw material	Name of the supplier
1	Tween 80	S D fine chemicals ltd, Mumbai
2	Cinnamon oil	Yucca enterprises, Mumbai
3	Sodium dihydrogen orthophosphate	Fine chemical industries, Chennai
4	Di sodium hydrogen orthophosphate	S D fine chemicals ltd, Mumbai
5	Di methyl sulphoxide	Thermo electron LLS pvt ltd
6	Soybean oil	Lipoid purified soybean oil 700
7	Egg lecithin	S D fine chemicals ltd, Mumbai
8	Chloroform	Loba Chemie Pvt. Ltd., India
9	Ethanol	Himedia Lab Pvt. Ltd., Indi

Equiments

Table 2: List of equipments with company name

S.No	Name of the equipments	Name of the supplier
1	Hot air oven	Texcare instruments
2	Sonicator	Vibronics ltd
3	Centrifuge	Remi instruments
4	Zeta potential	Malvern instruments
5	Weighing balance	Essae - Teraoka ltd
6	Uv- spectrometer	Lab India instruments
7	Particle size analysis	Malvern instruments
8	Magnetic stirrer	Remi equipments

9	SEM	Joel JSM,Japan

This thesis includes an in-depth analysis, as well as in-vitro and invivo investigations of crude extracts and fractions derived from the ethanolic extract of Soymida febrifuga leaves.

Plant Collection and Authentication

The Soymida febrifuga leaf powder was gathered from Andhra Pradesh and verified by Sri Venkateswara University in Tirupati. No is the number of the authentication certificate.

Extraction of the Plant Material[50]

The Soxhlet device is used to perform the extraction. First, petroleum ether was used to extract the coarsely powdered leaves. Ethanol is used once more to extract the obtained defatted substance. Following extraction, the ethanol extract was dried at room temperature to produce a viscous mass before being evaporated or concentrated using a rotary evaporator. For subsequent examination, the resulting crude extracts were weighed and kept at 40C.

RESULTS & DISCUSSION

Acute Toxicity Study

The ethanol extract was used at dosages of 2000 mg/kg, 1000 mg/kg, 900 mg/kg, 850 mg/kg, 800 mg/kg, and 750 mg/kg for the acute toxicity test. Given that it is a naturally occurring substance, it shouldn't be overly toxic. Thus, oral dosages of 2000 mg/kg and 1500 mg/kg were given to the test animal. Additionally, two animals perished. Following the observation of mortality following the delivery of 2 grams per kilogram of body weight, two animals that had received lesser doses of 1000 mg and 900 mg per kilogram died. As a result, after receiving a lesser dose of 850 mg/kg, three animals survived. Because of this, all animals survived when given a lesser dose of 800 mg/kg. Subsequently, 750 mg/kg was administered. After being given 850 to 750 mg/kg, all animals survived for 750 mg/kg, and no toxicity symptoms were seen. Thus, it was determined that Soymida febrifuga at 750 mg/kg was safe.

Preformulation studies

In order to evaluate the physiochemical characteristics of the chosen medication (Soymida febrifuga), which impact the formulation's stability and performance, preformulation studies were conducted. These studies included drug identification, solubility, analytical method development, drug-excipient interaction analysis, and oil phase optimization.

Melting point

The capillary tube method was employed to ascertain Soymida febrifuga's melting point. The melting point, as indicated in the table, complied with the requirements listed in the medication's monograph.

Table 3: Melting point of Soymida febrifuga

S. No	Parameters	Reference	Observed
1	Meting Point	200^0C	198-205^0C

Identification of standard drug by UV spectroscopy

The Soymida febrifuga sample's UV spectrum and absorbance maxima (λ max) were measured using UV spectroscopy and compared to pharmacological reference spectra. Figure displays the UV spectra of the reference and sample samples of Soymida febrifuga. The Soymida febrifuga sample's UV spectrum revealed a distinctive UV absorption pattern with λ max at 353 nm that was consistent with the reference spectra.

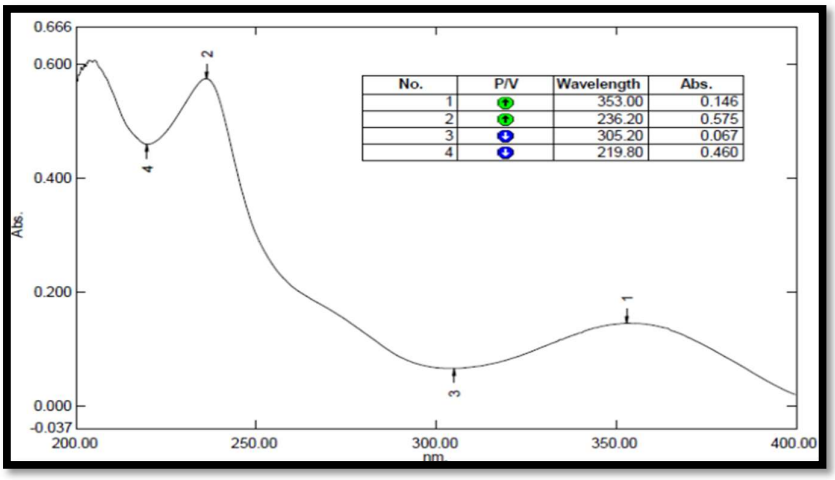


Fig 2: UV spectrum of Soymida febrifuga sample

Identification of standard drug by IR spectroscopy

The sample medicine, Soymida febrifuga, was further identified by taking FT-IR spectra in the 400–4000 cm-1 IR band and comparing them to the drug's reference spectra. IR spectra of Soymida febrifuga sample are shown in figure.

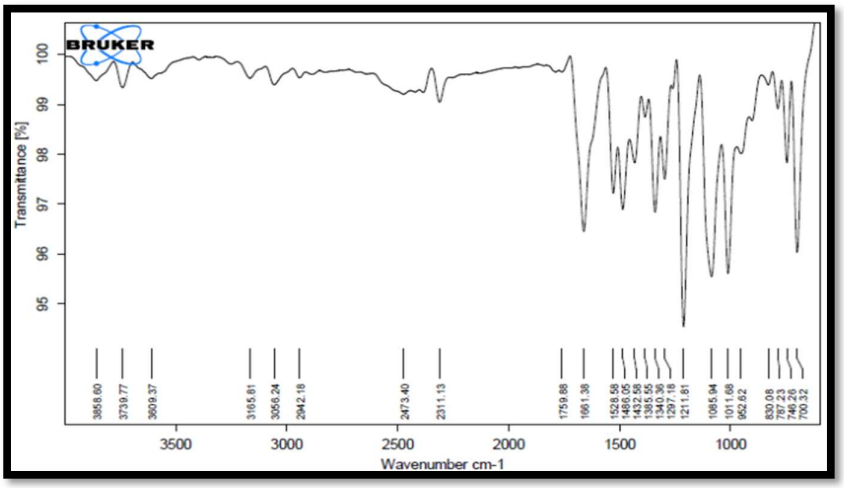


Fig 3: IR spectra of Soymida febrifuga sample

The Soymida febrifuga sample's IR spectra show that the absorption peaks of different functional groups are consistent with reference spectra148. 3165 cm-1 Aromatic C–H group, 3065 cm-1 Aromatic C–H group, 2942 cm-1 -CH3, -CH2 groups, 1759 cm-1 Ester C=O group, 1661 cm-1 C=O group, 1528 cm-1 NO2 group, 1486 cm-1 C=C, 1432 cm-1 CH bending in CH3–N group, 1340 cm-1 NO2 group, 1297 cm-1 C–N group, 1211 cm-1 C–O–C group, 1085 cm-1 C–O–C group, 1011 cm-1 C–N–H group, 952, 830 cm-1 C-N bending in aromatic ring, 746 cm-1 C–H bending, 70 cm-1 Aromatic C–H bending. We came to the conclusion that our acquired Soymida febrifuga medicine sample complies with the standard specifications listed in the drug's monograph based on the findings of many identification tests.

Development of UV- spectrophotometric method for estimation of the drug

Calibration curve in ethanol

Using a standard stock solution of Soymida febrifuga sample medication, six solutions with varying doses (2, 4, 6, 8, and 10 µg/ml) were produced in ethanol, and the absorbance of each solution was recorded in triplicate at 353 nm. The table displays the results, while the picture displays the absorbance versus concentration curve.

Table 4: Calibration curve data of Soymida febrifuga in ethanol

S.No	Concentration (µg/ml)	Absorbance (Mean±SD); n=3
1	0	0.153
2	2.0	0.294
3	4.0	0.384
4	6.0	0.476
5	8.0	0.612
6	10.0	0.849

The value of the correlation coefficient (R2), which is 0.9682, is quite near to 1. This demonstrated a direct relationship between UV absorbance and Soymida febrifuga concentration.

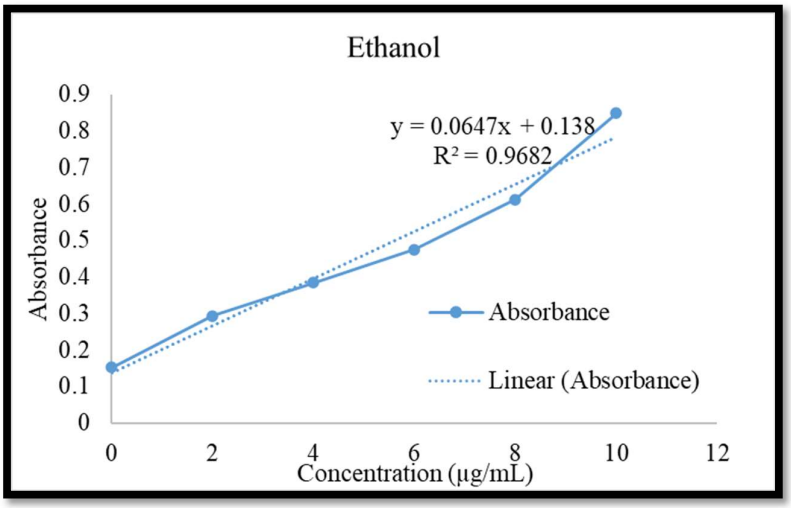


Fig 4: Calibration curve of Soymida febrifuga in ethanol

Calibration curve in 0.1 N HCl

A standard stock solution of Soymida febrifuga sample medication was used to generate five solutions with varying doses (2, 4, 6, 8, and 10 µg/ml). Each solution's absorbance was measured in triplicate at 236 nm. The table displays the results, while the image displays the calibration curve between absorbance and concentration.

Table 5: Calibration curve data of Soymida febrifuga in 0.1 N HCl

S.No	Concentration (µg/ml)	Absorbance (Mean±SD); n=3
1	0	0.176
2	2.0	0.304
3	4.0	0.468
4	6.0	0.579
5	8.0	0.705
6	10.0	0.859

Table 4.8 shows that the correlation coefficient (R2) value, which is 0.9978, is extremely near to 1. This demonstrated a direct relationship between UV absorbance and Soymida febrifuga concentration.

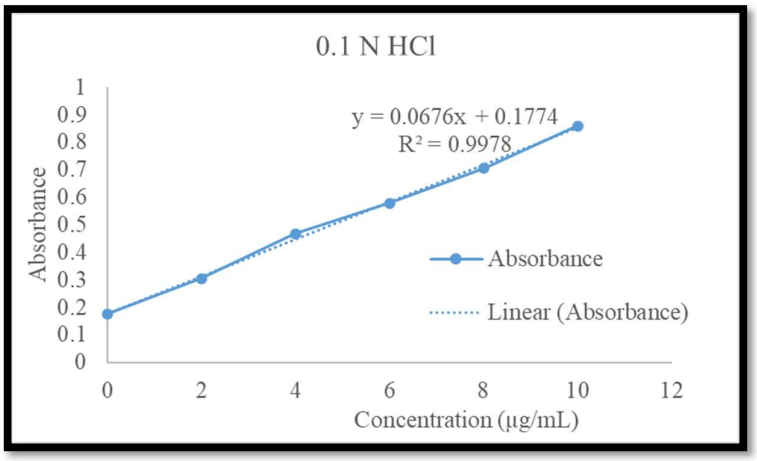


Fig 5: Calibration curve of Soymida febrifuga in 0.1 N HCl

Calibration curve in phosphate buffer pH 6.8

A stock solution of Soymida febrifuga sample medication was used to generate five solutions with varying doses (2, 4, 6, 8, and 10 µg/ml). Each solution's absorbance was measured in triplicate at 236 nm. The table displays the results, and figure 4.7 displays the calibration curve between absorbance and concentration.

Table 6: Calibration curve data of Soymida febrifuga in phosphate buffer pH 6.8

S.No	Concentration (µg/ml)	Absorbance (Mean±SD); n=3
1	0	0.264
2	2.0	0.413
3	4.0	0.598
4	6.0	0.713
5	8.0	0.894
6	10.0	0.997

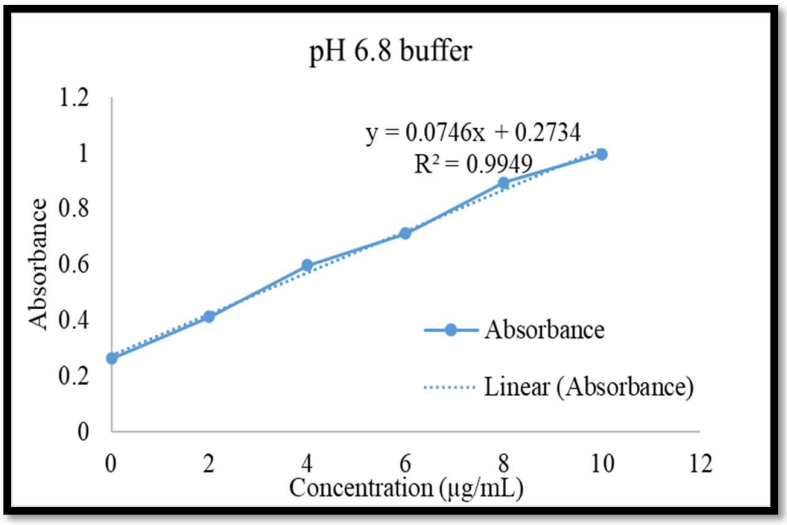


Fig 6: Calibration curve of Soymida febrifuga in phosphate buffer pH 6.8

The value of 0.9949., the correlation coefficient (R2), is extremely near to 1. This demonstrated a direct relationship between UV absorbance and Soymida febrifuga concentration.

Solubility of drug in oil, surfactant and co-surfactant

The oil, surfactant, and co-surfactant should have a high drug solubilization capacity in order to create a stable nanoemulsion system. It was established how soluble Soymida febrifuga was in various oils, co-surfactants, and surfactants. The table presents the solubility data for the medication Soymida febrifuga.

Table 7: Solubility of Soymida febrifuga in various oils

S. No	Long chain triglyceride (LCT) oils	Solubility in mg/ml (Mean±SD); n=3
1	Castor oil	3.68±0.35
2	Arachis oil	2.41±0.52
3	Soybean oil	1.69±0.41
4	Olive oil	3.46±0.13
5	Oleic acid	6.95±0.58
Medium chain triglycerides (MCT) oils		
1	MCT oil (50-52% caprylic acid and 40-48% of caproic acid)	2.01±0.12
2	Caprylic acid	1.64±0.34
3	Triacetin	1.23±0.21
Essential oils		
1	Lemon oil	1.64±0.31
2	Eucalyptus oil	2.54±0.11
3	Cinnamon oil	16.52±0.52

Table 8: Solubility of Soymida febrifuga in various surfactants and co-surfactants

S. No	Surfactant	Solubility in mg/ml (Mean±SD); n=3
1	Tween 80	35.64±0.46
2	Tween 20	15.94±0.86
3	Triton-X- 100	23.51±0.95
	Co-surfactant	
1	Transcutol-P	5.63±0.13
2	Polyethylene glycol (PEG) 400	12.43±0.46
3	Propylene Glycol	28.64±0.53
4	Glycerol	5.84±0.11

As previously mentioned, oleic acid (LCT oil) and cinnamon oil (essential oil) exhibited the highest solubility of Soymida febrifuga in oils. The greatest solubility of Soymida febrifuga was seen in tween 80 (a surfactant) and propylene glycol (a co-surfactant), among other surfactants and co-surfactants.

Optimization of oil phase

The drug's greatest solubility was discovered in cinnamon oil (16.52±0.52 mg/ml) and oleic acid (6.95±0.58 mg/ml). In order to prepare for the oil phase, oleic acid (LCT oil) and essential oil (cinnamon oil) were combined with MCT oil (52% caprylic acid and 48% caproic acid) in the proportions shown in the table. Following that, an emulsification efficiency test was run, and the results are shown in a table.

Table 9: Results of emulsification efficiency test for oil phase optimization

S.No	Oil blend code	Essential oil Cinnamon (% v/v)	LCT oil Oleic acid (% v/v)	MCT oil (% v/v)	Appearance	Phase separation
1	OBC 1	30	60	10	Turbid	NO
2	OBC 2	30	50	20	Translucent	NO
3	OBC 3	30	40	30	Translucent	NO
4	OBC 4	30	30	40	Translucent	NO

OBC-3 and OBC-4 oil blends (30% v/v of cinnamon oil, 40% v/v of oleic acid, and 30% v/v of MCT oil, respectively) were quickly and easily emulsified to create a transparent system without phase separation. OBC-3

contain larger proportion of LCT oil (oleic acid) as compared to OBC-4. Therefore, oil blend OBC-3 was utilized as the oil phase in the creation of drug delivery systems for nanoemulsions.

Preparation of nanoemulsion of the extract

The process outlined in the materials and methods section was followed to prepare the nanoemulsion. The schematic picture below shows the step-by-step process for creating nanoemulsion.

Characterization of prepared nanoemulsion

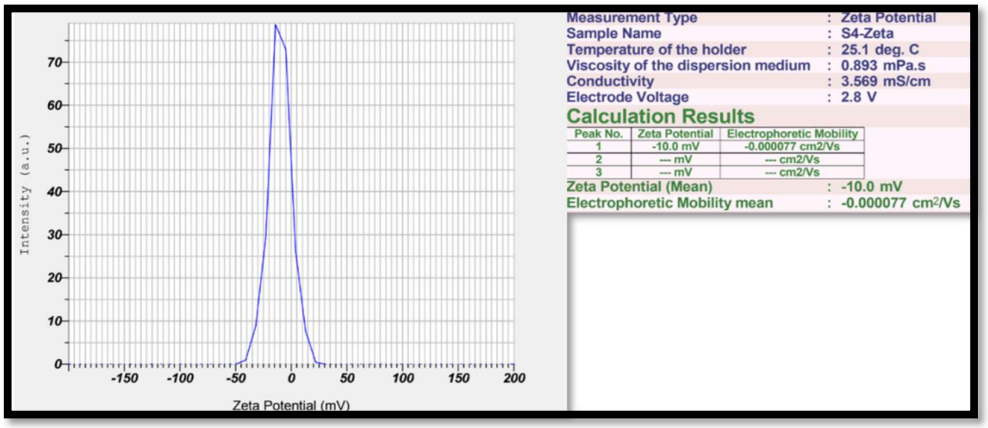
Particle size analysis

Particle size analysis was performed in accordance with the guidelines provided in the section on materials and procedures. For the drug administration of nanoparticles, the size and dispersion of the particles are crucial. The polydispersibility index provided the size distribution. The more homogeneous the nanoparticles or the narrower the size dispersion, the lower the value.

Zeta potential determination

Zeta potential determination was done in accordance with the steps outlined in the section on materials and methodology. The particle stability index is represented by the zeta potential. The prevention of particle aggregation depends on this stability. The improved formulation's zeta potential was the millivolt (mV) was discovered. The stability of nanoparticles is higher at higher zeta potential maximum.

Fig 7: Zetapotential of the prepared nanoemulsion.



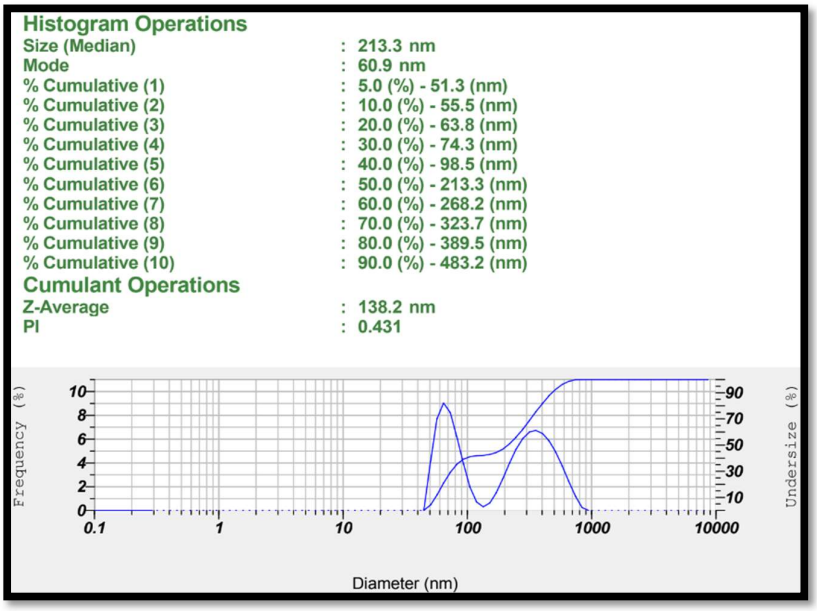


Fig 8: Particle size distribution of the prepared nanoemulsion.

Particle morphology study

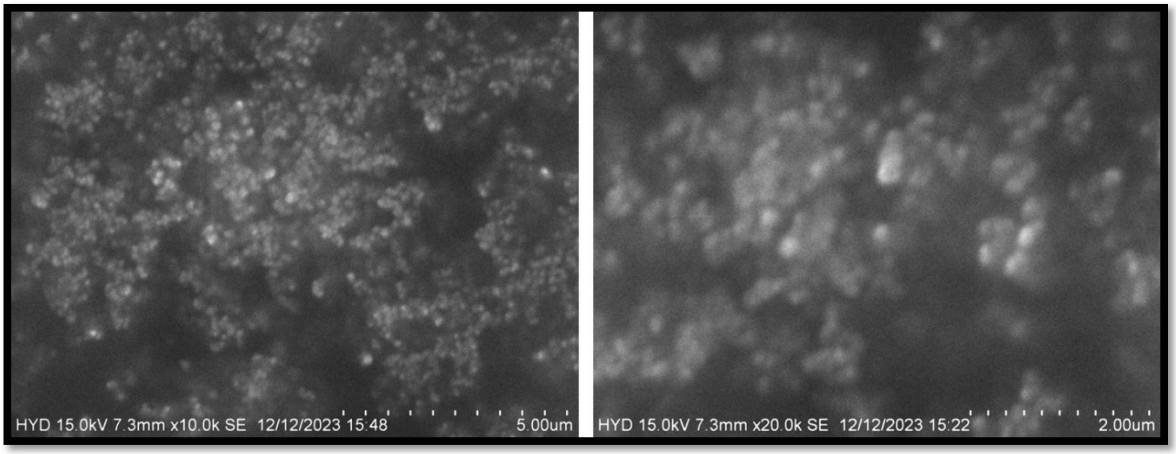


Fig 9: SEM imagesof the prepared nanoemulsion.

The methodology outlined in the materials and methods section was followed in conducting the particle morphology investigation. The generated nanoemulsion is examined using scanning electron microscopy (SEM) for morphological analysis.

In-vitro releae study

The release study was conducted in accordance with the steps outlined in the section on materials and procedures. The medication was required for the slow, continuous release of the medicine. In the 12-hour release testing, F6, out of the nine formulations, had the highest drug release value.

Table 10: Cumulative in-vitro release profile of the prepared nanoemulsion

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	15.46	10.83	49.72	24.37	13.45	12.56	28.45	39.5	12.51
2	26.63	26.72	60.16	31.68	25.67	28.34	35.28	46.35	26.38
4	35.64	36.16	68.15	49.37	31.73	34.58	48.9	56.28	35.17
6	40.38	47.46	72.56	58.35	34.56	41.29	66.83	69.71	47.37
8	46.44	58.57	78.41	74.37	41.91	52.34	72.54	76.26	54.96
12	53.64	68.25	83.27	81.34	62.48	61.32	78.17	80.14	62.56
16	69.82	73.19	87.45	88.18	76.89	67.83	82.45	85.26	78.35
20	75.67	86.87	91.35	94.65	81.19	72.54	87.16	89.54	82.34
24	80.56	90.16	94.26	98.16	89.5	79.62	92.18	95.28	89.26

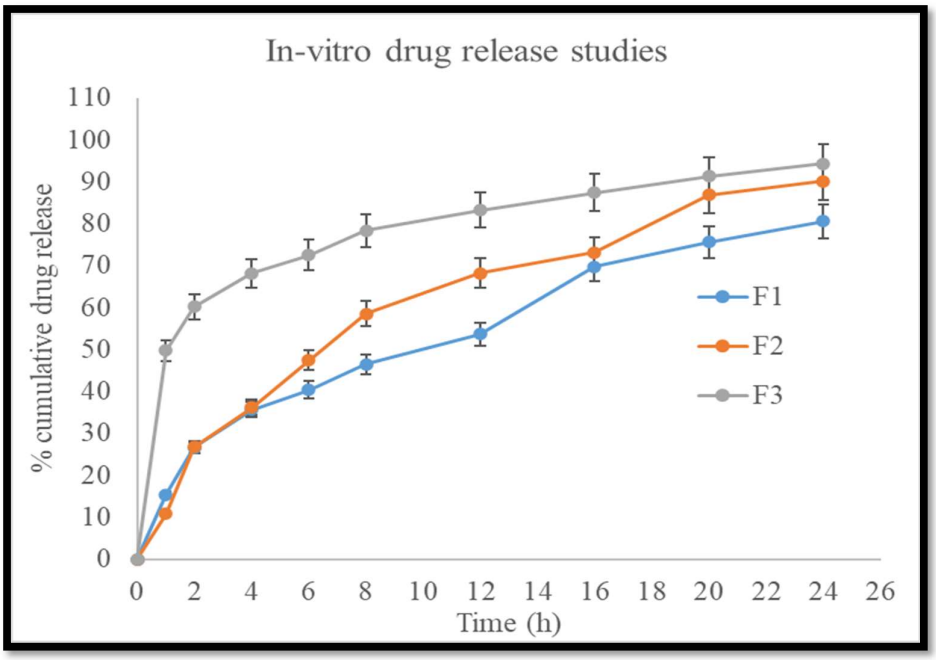


Fig 10: Invitro drug release studies of formulation F1-F3

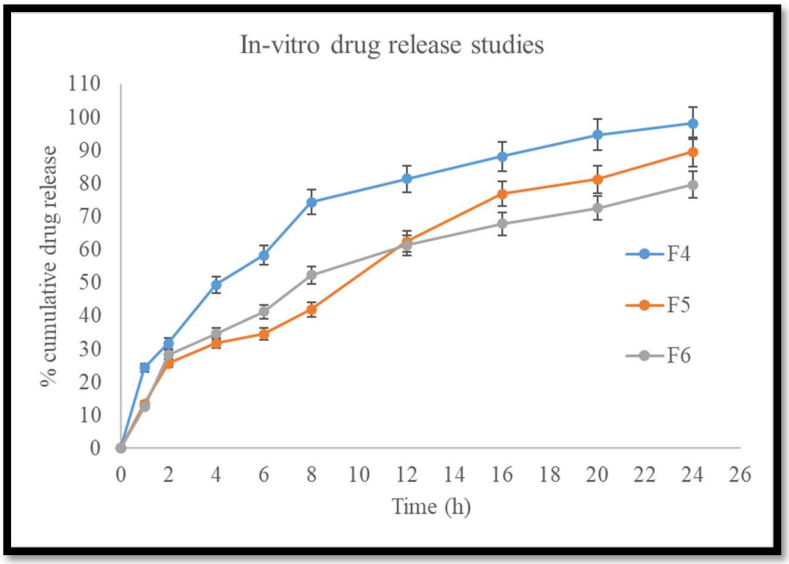


Fig 11: Invitro drug release studies of formulation F4-F6

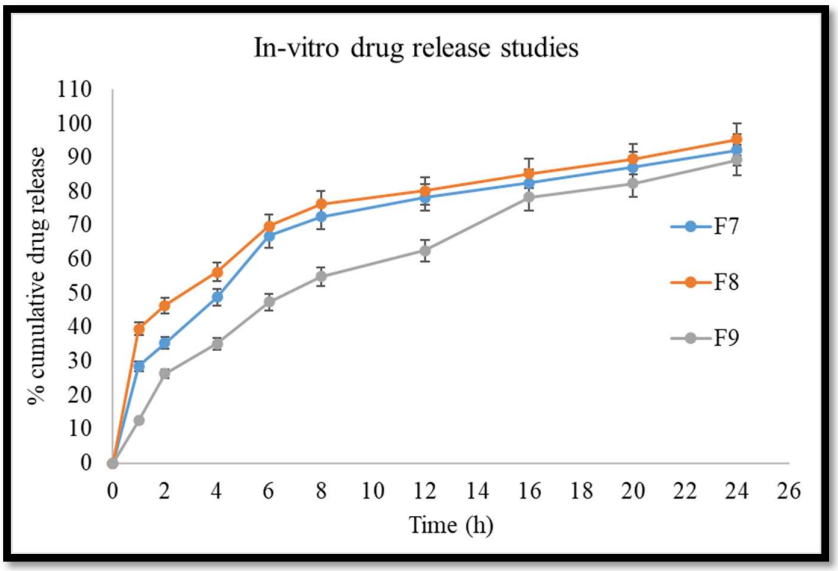


Fig 12: Invitro drug release studies of formulation F1-F3

CONCLUSION

A variety of people worldwide are afflicted with epilepsy, a neurological condition. Thirty percent of the patients still experience seizures even after using antiepileptic medications. The discovery of contemporary medications has benefited greatly from the use of natural products from folk remedies, which may also serve as a substitute source for the development of antiepileptic medications with novel structures and improved safety and efficacy profiles. In convulsion models generated by MES and PTZ, the chloroform extract of Soymida febrifuga delayed the onset and decreased the duration of convulsions. It can be utilized as an adjuvant therapy against cognitive deficiency in convulsions.

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