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Antiparkinson's Activity of Curcumin Extract Loaded Phytosomal Intranasal Gel

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KEYWORDS

Curcumin extract, Phytosome, Intranasal gel, Curcuma longa

Abstract

Purpose

Curcumin is a Phytoconstituents obtained from Curcuma longa rhizome. Curcumin is having anti-inflammatory and anti-oxidant properties. The extract would show antiparkinson's activity Oral use of this drug has some limitations like less solubility, Low bioavailability, High first pass Metabolism. The aim of the present investigation was to formulate Curcumin extract loaded Phytosomal gel for improved delivery and to target brain

Method

Phytosomal formulations were prepared using different methods like solvent evaporation method, salting out anti solvent precipitation method, direct egg yolk method and egg lipid method. Phytosome were characterized by using Scanning Electron Microscopy, Particle size, FTIR, XRD etc. Optimized batch was further transferred into gel formulation and further evaluated for various physical parameters. The final batch was subjected for different animal study Antiparkinson's activity,

Result

Phytosome were characterized by using Scanning Electron Microscopy, Particle size, FTIR, XRD etc. salting out Phytosome prepared by anti-solvent precipitation method showed best results. Further Full Factorial Design: A 3^2 randomized full factorial design was used in this study. In that batch F5 showed 56±1.029 % CDR, and entrapment efficiency of **81**±1.53%. Depending upon variable concentration of Cholesterol and Phosphatidylcholine. Different batches of Phytosomal gel formulation were prepared using Carbopol as gelling base and further evaluated. Out of three batches F5G1, F5G2 and F5G3 the batch F5G2 showed better result for Spreadability (**24.30 ± 0.25**), Viscosity (**5421**cps at 100rpm) Drug Content (**67.63 ±1.07**%), and Extrudability (**78.84±0.52**) as compared with other batches. *In-vitro* drug diffusion study showed that diffusion of drug was enhanced across the membrane due to having Phytosomal formulation. *Curcuma longa* Phytosome gel (Batch F5G2) was found to follow Higuchi's kinetic. Antiparkinsonian activity of test nasal gel formulation showed improvement in behavioral pattern.

Conclusion:

The phytosomal gel formulation administered through nasal route would be best choice for better treatment of Parkinson's disease.

Introduction

Herbal medicine is one of the oldest and most universal systems of health care system. The advancement in the field of herbal drug delivery started

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recently with the aim to manage human diseases efficiently. Natural origin drugs are important and constitute valuable segments of modern medicines. Medicinal plants are used by various Traditional medical practitioners and scientists for curing aliments such as inflammation, rheumatoid arthritis, cancer, diabetes, and many more because of the of the fact that they possess lesser side effects because of its natural origin. For the ease of administration these products are formulated into different formulations. The novel herbal formulations are reported to have incredible advantages over conventional formulations of plants actives and extracts which include improvement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue, macrophages distribution, sustained delivery, and protection from physical and chemical degradation.

Phytosome: The effectiveness of any herbal medication is dependent on the delivery of effective level of the therapeutically active compound. Severe limitation exists in their bioavailability when administered orally or topically. Phytosome are recently introduced herbal formulations that are better absorbed than extracts. The term "Phyto" means plant, while "some" means cell-like (Vandana et al 2013). Over the past century; phytochemical and Phyto-pharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Most of the biologically active constituents of plants are polar or water-soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, glycosidic aglycones etc) are poorly absorbed either due to their large molecular size which cannot absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability **(**Jagruti Patel et al 2009**,**Bhupen Kalita1 et al 2013, Mahmood Barani et al 2021) .

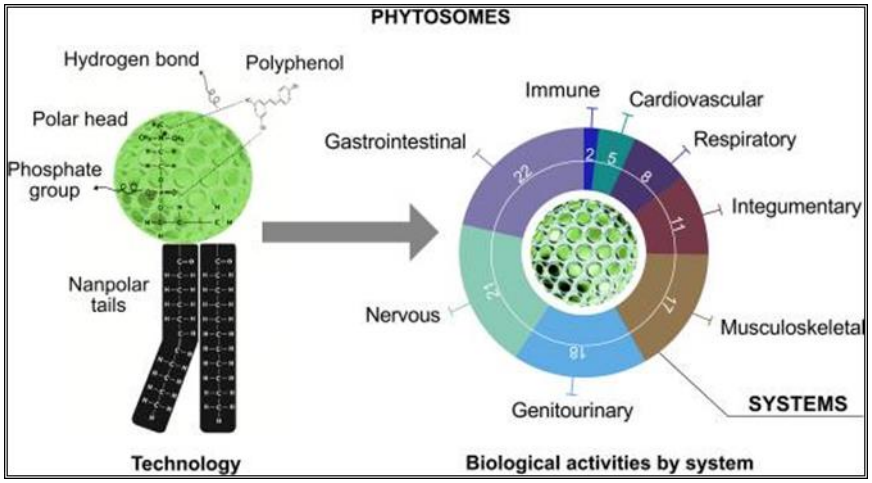

Fig.No. 01 Structure of Phytosome and its applications (Mahmood Barani et al 2021)

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Parkinson's disease:

Parkinson's disease is a brain disorder that causes unintended or uncontrollable movements, such as shaking, stiffness, and difficulty with balance and coordination. Symptoms usually begin gradually and worsen over time. As the disease progresses, people may have difficulty walking and talking (Yih-Ru Wu et al 2018). They may also have mental and behavioral changes, sleep problems, depression, memory difficulties, and fatigue. The most prominent signs and symptoms of Parkinson's disease occur when nerve cells in the basal ganglia, an area of the brain that controls movement, become impaired and/or die. Normally, these nerve cells, or neurons, produce an important brain chemical known as dopamine. When the neurons die or become impaired, they produce less dopamine, which causes the movement problems associated with the disease (K.D.Tripathi 2003).

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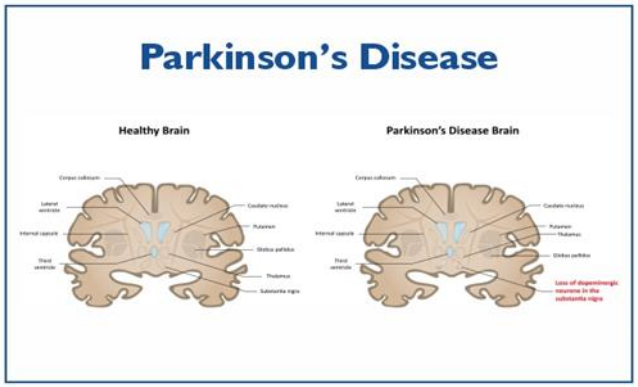

Fig.No. 02 Comparison of healthy brain and Parkinson's disease brain (Terina Martinez et **al 2020)**

Treatment

Parkinson's disease has no known cure; however, medicines can help individuals manage their symptoms (Yih-Ru Wu et al 2018). Medicines can help treat the symptoms of Parkinson's by:

- Increasing the level of dopamine in the brain
- Having an effect on other brain chemicals, such as neurotransmitters, which transfer information between brain cells
- Helping control non-movement symptoms

Curcumin

The main cause of neurodegeneration is disturbed balance between reactive species of oxygen and cellular activity showing antioxidation effect (Bingjing Zheng et al 2020). It includes Alzheimer's disease (AD) and Parkinson's disease (PD). We can explore antioxidants for the treatment of the same. In Parkinson's disease there is loss of dopaminergic neurons in the part of brain known as substantia nigra with the formation of Lewy bodies.

Currently herbs containing antioxidants have been tried for the treatment of the neurodegenerative disorders (Muthian G et al (2015). It includes turmeric (*Curcuma longa*). It is been used in the food and as traditional medicine.

Donation of proton to reactive species of oxygen is said to be useful for the treatment of the neurodegenerative disorders through its antioxidant property. It is helpful to the patient suffering from Parkinson's disease by protecting brain against α-synuclein aggregation and monoamine oxidase B. curcumin has showing protective role in damage of nerve cell responsible for release of dopamine.

Curcumin is lipophilic compound which is responsible for decrease in rate and extent of absorption **(**Hamed Mirzaei et al 2017**)**. So here attempt has been made to enhance solubility of curcumin to improve its bioavailability by incorporating it in phytosomal formulation.

The presence of curcumin in the test samples was confirmed by comparing the TLC pattern of testing extract and the standard curcumin using optimized solvent system. TLC of the recrystallized curcumin was performed on pre-coated silica gel G plates (Stationary Phase) using mixture of in the ratio 97:3 (Dichloromethane: Methanol) as solvent system (Mobile Phase).

The plate was sprayed with reagent and retention factor values were calculated and compared with standard value.

2.0 Methods:

2.1 Chemicals

Phosphatidylcholine, Cholesterol, curcumin was purchased from Ozone International Mumbai. India. Carbopol was purchased from Research-Lab Fine Chem Mumbai. Ethanol was purchased from Pallav Chemicals & Solvents Pvt.Ltd.

2.2. Plant Material

Curcuma longa Rhizome was purchased from local area market of Lonavala (Pune) which was further authenticated from Agharkar Research Institute, Pune. The Rhizome was cleaned thoroughly; and allowed to shade dry. The dried rhizomes were pulverized into a fine powder and stored in an airtight container for further studies.

2.3 Extraction of Curcuma longa Rhizome

Accurately weighed turmeric powder (50 gm) is extracted with n-Hexane (200 ml) for 2 hrs then with acetone (100 ml) for 2 Hrs. Solvents were separated by using rotary evaporator (Harsha Mainum et al 2014).

2.4 Preliminary phytochemical investigation

The extracts were concentrated and subjected to

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phytochemical screening using standard procedures. Alkaloids, glycosides, flavonoids, tannins, proteins, carbohydrates, amino acids and steroid are the preliminary phytoconstituents that were analyzed.

2.5 Solubility analysis:

Solubility analysis of the extract was carried out in different solvent system and buffer of various pH. This analysis helps in selection of suitable solvent system for the further studies.

2.6 Confirmation of identity by TLC:

The presence of curcumin in the test samples was confirmed by comparing the TLC pattern of testing extract and the standard curcumin using optimized solvent system. TLC of the recrystallized curcumin was performed on pre-coated silica gel G plates (Stationary Phase) using mixture of in the ratio 97:3 (Dichloromethane: Methanol) as solvent system (Mobile Phase) Ratna Wulandari et al 2018).

The plate was sprayed with reagent and retention factor values were calculated and compared with standard value.

2.7 Estimation of Curcumin in the extract samples by HPLC analysis

Extracts and standards were analyzed by Agilent's 1100 series quaternary HPLC system equipped with auto sampler under the following conditions:

HPLC conditions:

Mobile phase: A: Methanol, B: 0.05 % Acetic acid and C: Acetonitrile

HPLC analyses were carried out by applying the gradient conditions with and Detector: UV detector at 425 nm (Bruno Fonseca-Santos et al 2017)

2.8 Identification and Estimation of Curcumin by (HPTLC)

A Camag high performance thin layer chromate-graphic (HPTLC) system equipped with linomat V automatic sample applicator, a CAMAG glass twin trough chamber (20 × 10 cm), TLC Scanner 3 and integrated WinCATS Software 4.03 was used for the analysis. (Sharad Kharat et al 2017)

2.9 Development of Curcumin extract loaded Phytosome

Method 01 Solvent evaporation method (Sanjay Saha et al 2013, Vishal Gaurav et al 2021)**:**

Molar concentration of Curcumin extract (100 mg), Phosphatidylcholine (100 mg) (1:1) and 0.25% Cholesterol mixed with 50 ml organic solvent for 2 hours, then dried using vacuum till solvent was evaporated. Complex washed with another solvent with continuous stirring. The Extract–phospholipids complex was precipitated and the precipitate was filtered and dried under vacuum to remove traces of solvents.

Method 02 Salting out anti solvent precipitation method:

Molar concentration of Curcumin extract (100 mg), Phosphatidylcholine (100 mg) (1:1) and 0.25% Cholesterol were taken in the beaker 50 ml methanol was the mixture is refluxed at (65^0C.) for two Hrs with continues stirring. The solution is later concentrated and anti-solvent is (25 ml) is added (Vishal Gaurav et al 2021).

Method 03 Direct egg yolk method:

Egg yolk was separated from egg. The extract was heated and to it egg yolk (5:1) was added with homogenization for not less than 20 min. The filtration of formed precipitate was done.

Method 04 Egg Lipid method:

20 ml of egg yolk was added into 50 ml of ethanol and 30 ml of ethyl ether. The mixture was stirred continuously. Then 10 ml of extract was added into it with homogenization for 20 min. The filtration of formed precipitate was done.

2.10 Characterization

2.10.1 Morphological Analysis: The surface morphology of the Curcumin Extract Phytosome was investigated by Scanning Electron Microscopy.

2.10.2 Entrapment efficiency

Mechanical spinning technique was used. The vesicles were separated. Amount of drug in the sediment was determined by lysing the vesicles using solvent. It was further diluted and quantified. From this, the entrapment efficiency was determined by the following equation,

$$EE\% = \frac{\text{(Total drug) - (free drug) X 100}}{\text{Total drug}}$$

Method two Salting out anti solvent precipitation method was further selected based on Surface morphology study and Entrapment efficiency results.

2.11 Salting out anti solvent precipitation method

2.11.1. Optimization of Temperature

Molar concentration of Curcumin extract (100 mg), Phosphatidylcholine (100 mg) (1:1) and 0.25% Cholesterol were taken in the beaker 50 ml methanol was the mixture is refluxed at (below 60^0C, at 60^0C and above 75^0C) for two Hrs with continues stirring Five

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hundred Rotation/min. The solution is later concentrated and anti-solvent is (25 ml) is added. The effect of different temperatures (below 60^0C, at 60^0C and above 75^0C) was seen on the formation of Phytosomal vesicles.

2.11.2. Optimization of Rotating Speed

Molar concentration of Curcumin extract (100 mg), Phosphatidylcholine (100 mg) (1:1) and 0.25% Cholesterol were taken in the beaker 50 ml methanol was the mixture is refluxed at (65^0C.) for two Hrs with continues stirring (at 100 rpm, at 250 rpm and at 500 rpm). The solution is later concentrated and anti-solvent is (25 ml) is added. The effect of different Rotating Speed condition was seen on the formation of Phytosomal vesicles.

Three batches of Curcumin Extract were prepared using various concentration ratios of Extract and Phosphotidylcholine as mentioned below with temperature of 60^0C and speed of 500 rpm.

Table 1. Composition of different Phytosomal Formulation of Curcumin Extract

Phytosomal Formulation	Lecithin (Soya Lecithin %)	Methanol	Drug(ml) %)	Cholestrol (%)
CF1	0.5	20 ml	1.0	0.25
CF2	1.0	20 ml	1.0	0.25
CF3	2.0	20 ml	1.0	0.25

2.12 Characterization of Phytosome

2.12.1. Surface morphology

The morphology of Phytosome was determined using scanning electron microscopy (Hitachi S-3700N). SEM gives a three-dimensional image of the vesicles.

2.12.2. Zeta potential

Zeta potential was determined using zeta sizer (HORIBA SZ-100). Measurements were performed for the samples prepared.

2.12.3. Particle size Determination

The mean size of the Phytosome colloidal suspensions was determined by photon correlation spectroscopy.

2.11.4. XRD (X Ray Diffraction Techniques)

Samples of the prepared Phytosome were examined using Shimadzu XRD -6000 (X-Ray Diffract meter). The measurements were carried out using Cu as an anode material and operated at a voltage of 25 KV with a current of 40 mA. The samples were analyzed in the 2 Theta angle ranges of 4 to 50 degrees and a scanning speed of 1.2degree/min.2

2.11.5. Drug Entrapment Efficiency

Mechanical spinning technique was used. The vesicles were separated. Amount of drug in the sediment was determined by lysing the vesicles using solvent. It was further diluted and quantified. From this, the entrapment efficiency was determined.

2.12 Optimization

Full Factorial Design: A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations shown in table. Percentage of Phosphotidylcholine (X_1) and Percentage of Cholesterol (X_2) were selected as independent variables. Entrapment efficiency (Y1), in-vitro

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drug release (Y2), were selected as dependant variable.

Table 2 Batch code

Batch code	**Variable levels in coded form**		
	X_1	**X_2**	
F1	+1	0	
F2	-1	-1	
F3	0	-1	
F4	0	+1	
F5	+1	+1	
F6	+1	-1	
F7	-1	0	
F8	-1	+1	
F9	0	0	
Transformation of code levels in actual units			
Variable levels	**Low (-1)**	**Medium 0**	**High (+1)**
Percentage of Phosphotidylcholine (**X_1**)	1	1.5	2

BATCH	**% Phosphotidylcholine**	**Cholesterol (%)**	**Curcumin Extract (%)**	**Methanol (ml)**
F1	2	0.375	1	20
F2	1	0.25	1	20
F3	1.5	0.25	1	20
F4	1.5	0.5	1	20
F5	**2**	**0.5**	**1**	**20**
F6	2	0.25	1	20
F7	1	0.375	1	20
F8	1	0.5	1	20
F9	1.5	0.375	1	20

Percentage of Cholesterol (**X2)**	0.25	0.375	0.50

Table 03 Optimization batches

2.13 Preparation of Gels

Based on the results obtained from optimization study batch F5 was further explored for final formulation. The gels were prepared by dispersion method using Carbopol 940 in different ratios as shown in the table. The mixture was then left to swell for the entire night. Triethanolamine was added to the mixture drop by drop until it was neutralized. The gel's viscosity was then adjusted with the addition of glycerol. This gel solution is mixed with optimized phytosomal dispersion until a clear gel formed. Preservative methylparaben was added. The ready-made gels were put into glass vials and kept between 4 and 8°C.

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Table 4 Formulation of Phytosomal gel using Carbopol 940 (Curcumin extract)

Formulation Code	Phytosomal Suspension(ml	Carbopol 940 (%)	Triethanolamine (%v/v)	Methlyparaben (%)	Water (upto 30gms)
F5G1	5	1	0.5	0.01	q.s
F5G2	5	1.5	0.5	0.01	q.s
F5G3	5	2	0.5	0.01	q.s

2.15 Characterization of Phytosomal Gels

Physical Evaluation

Physical parameters such as color and appearance of the herbal gel were observed manually.

2.15.1. Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of eachformulation was done.

2.15.3. Homogeneity

After placing the generated gels in the container, each gel was visually inspected to ensure homogeneity. Their appearance and the existence of any aggregates were noted.

2.15.4. Viscosity

The Brookfield viscometer was used to measure the gel's viscosity. Three different rotation speeds for the gels were set: 0.3, 0.6, and 1.5 rpm. The matching dial reading was recorded for each speed. By multiplying the dial value by the factor specified in the Brookfield Viscometer handbook, the viscosity of the gel was determined.

2.15.5 Drug content

A spectrophotometer was used to measure the drug concentration and content in the gelled phytosome. By dissolving a known quantity of gelled phytosome in ethanol using sonication, the curcumin content of the phytosome was determined. Using a UV/VIS spectrophotometer, absorbance was measured at 425 nm following an appropriate dilution.

2.14.6. Extrudability Study of Topical Gel

In the present study, the method adopted for evaluating gel formulation for Extrudability was based upon the quantity in percentage of gel and gel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of gel in 10 seconds. More quantity extruded better was Extrudability. The measurement of Extrudability of each formulation was in triplicate and the average values are presented. The Extrudability was than calculated by using the following formula:

Extrudability = Applied weight to extrude gel from tube (in gm) / Area (in cm^2)

2.14.7. *In-vitro* Drug Diffusion Study

In- vitro release of Curcumin *Phytosomal gel* was studied using locally Franz diffusion cell (Dolphin-1366, Systronic Analytical Instrument. Ahmedabad).The effective permeation area of the diffusion cell and the receptor cell volume was 2.50cm^2 and 20ml of the pH 6.4 and was constantly stirred by magnetic stirrer at 100rpm. The nasal mucosa of sheep was placed in the diffusion chambers, facing the donor and recipient phases on the mucosal and serosal sides. Phytosomal gel formulation (equivalent to 10mg drug) was applied to the membrane.2ml sample was withdrawn through the port of the sample of the diffusion cell at predetermined time interval over 8 hours and diluted it to 10ml with methanol. The samples were analyzed spectrophotometrically at 425 nm. The receptor phase was immediately replenished with equal volume of distilled water. Sink condition was maintained though out the experiment.

2.14.8. Release Kinetics

To analyse the mechanism for the release and the release rate kinetics of the dosage form, the data obtained was fitted into zero order, first order, and higuchi matric model. In this by comparing the R-values obtained the best fit model was selected. Studies analysis by PCP disso 2.8v software.

2.15. Animal Study:

Antiparkinsonian activity of test nasal gel formulation

Experimental Animals

Healthy either sex, wistar rats (14-18 weeks old) of 350-400 gm, were divided into various groups (n=6).

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They were housed 3 animals per cage (polycarbonate cages) with normal animal house conditions as temperature 22-25 0C, 40-60 relative humidity and 12:12 light and dark cycle. Animals were fed with standard animal diet (Krishna Aggrotech Ltd, India) with water ad libitum.

Experimental Design (Sharma et al 2021).

Briefly, seven days acclimatized animals were divided into various groups

Group I was given 0.5% CMC (5 ml/kg p.o.) and sunflower oil (1 ml/kg s.c.) as a vehicle. Group I functioned as the usual control group.

Animals in Group II (disease control) received rotenone (2 mg/kg s.c. emulsified in sunflower oil at a dose of 2 mg/ml), while animals in Group III got both rotenone and intranasal levodopa gel (INL) at a dose of 2 mg/kg s.c. blended in sunflower oil at a dose of 2 mg/ml. All the drugs were administered once daily for 30 days, after 30 days post treatment various behavioral changes were studied.

Intranasal curcumin gel (INC) plus rotenone (2 mg/kg s.c. emulsified in sunflower oil at 2 mg/ml) was administered to animals in Group IV. Intranasal levodopa and curcumin gel (IN-L+C) plus rotenone (2 mg/kg s.c. emulsified in sunflower oil at 2 mg/ml) was administered to animals in Group V.

Behavioral evaluations:

All the behavioral evaluation were performed on weekly basis during the treatment regimen. Catalepsy (Bar test Verma and Nehru, 2009)]. Number of crossing behavior by open field test (Thakare et al., 2021) Muscle grip and postural instability (inclined test),

Behavioral evaluation

Catalepsy test (Verma and Nehru, 2009)

In the present study we evaluated the catalepsy condition induced by repeated rotenone administration. Catalepsy can be studied by placing an animal into an unusual posture and recording the time taken to correct this posture. In this test catalepsy was studied as duration of catalepsy behavior showed by respective animal with treatment.

The catalepsy was studied during various weeks of rotenone administration during 30 days' time period and the duration of catalepsy (time during which the mice maintained the fixed rearing posture) was measured and behaviors were recorded. The cut off time was 5 minutes.

Open field test (Freitas et al 2014, Thakare et al., 2021)

Reduction in the crossing behavior by the individual rat is considered to be reduction in the motor coordination action. Impairment in motor coordination was observed in the Parkinson's disease.

Rota rod test

Rota rod test was used to study the muscle grip strength of the rats by using Rota rod apparatus. The method outlined in the findings of Sharma et al. (2021) was used to calculate the latency to fall off time. In short, the latency to fall off time—that is, the amount of time that passed between the rat being placed on the revolving rod and its falling off—was observed after the rats were on it for two minutes. The animals were held at a maximum score of 120 seconds for the cut-off.

Biochemical estimation:

On 31st day, after the behavioral evaluation, all the animals were sacrificed by CO2 euthanasia, brain was immediately separated and uniformized. It was then poured in 15ml centrifuge tubes and rotated at (Neaution, India) at 3000 RPM at 4 0C for 30. The Supernatant was removed in Eppendorf tubes and labelled respectively. The supernatant was separated and stored at -80 0C until used.

Estimation of dopamine contents in brain homogenate

The stored supernatant allowed to kept at normal temperature 30 minutes prior to dopamine estimation, the dopamine contents were estimated by using readymade ELISA kit and procedure described in the leaflet provided in the kit.

3. Result

3.1. Pharmacognostic Characterization (Rhizome of Curcuma longa)

Morphology: It is a group of rhizomes, the central primary rhizome being conical to ovoid in shape with a number of longer secondary rhizomes or fingers attached to it laterally. Both are covered with scale leaves whose remnants are seen as transverse scars and differentiated into nodes and internodes.

Organoleptic Evaluation: Fresh rhizomes are light yellow/brown in colour externally and deep orange internally, has characteristic aromatic smell and bitter hot taste

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Table no 5 Preliminary Phytochemical analysis of the extract of Curcumin

Sr.	Test	Presence (+)/
1	Glycosides	+
2	Saponins	+
3	Oils and fats	+
4	Alkaloids	+
5	Steroids	-
6	Flavonoids	-
7	Proteins and free	+
8	Tannins and phenols	+

Fig. 01 Confirmation of identity by TLC for Curcumin

A B

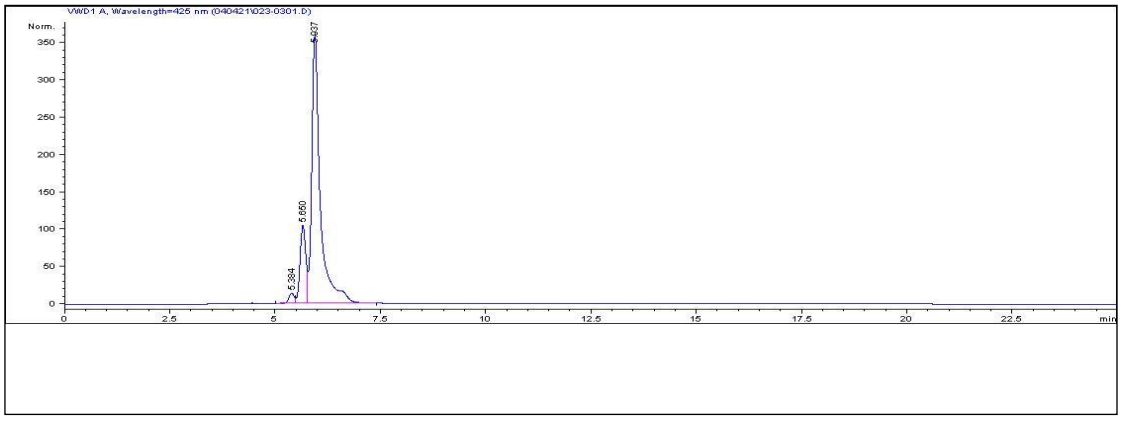
A= Extract B= STD Curcumin

Rf value calculation for levodopa -For standard =0.80 for Extract 0.80

Rf value of standard and Extract is Identitical. Compound extracted and isolated is identified as Curcumin. So, this study confirms curcumin in the rhizomes of Curcuma Longa.

3.2. Estimation of Curcumin in the extract samples by HPLC analysis Extract

Fig.2 Estimation of Curcumin in the extract samples by HPLC analysis Extract



Estimation of Curcumin from the extract samples by HPLC:

Concentration of Curcumin in % = Area of sample/area of standard x concentration of Standard

Sample C-1.7471/1.7361X0.25=2.5%

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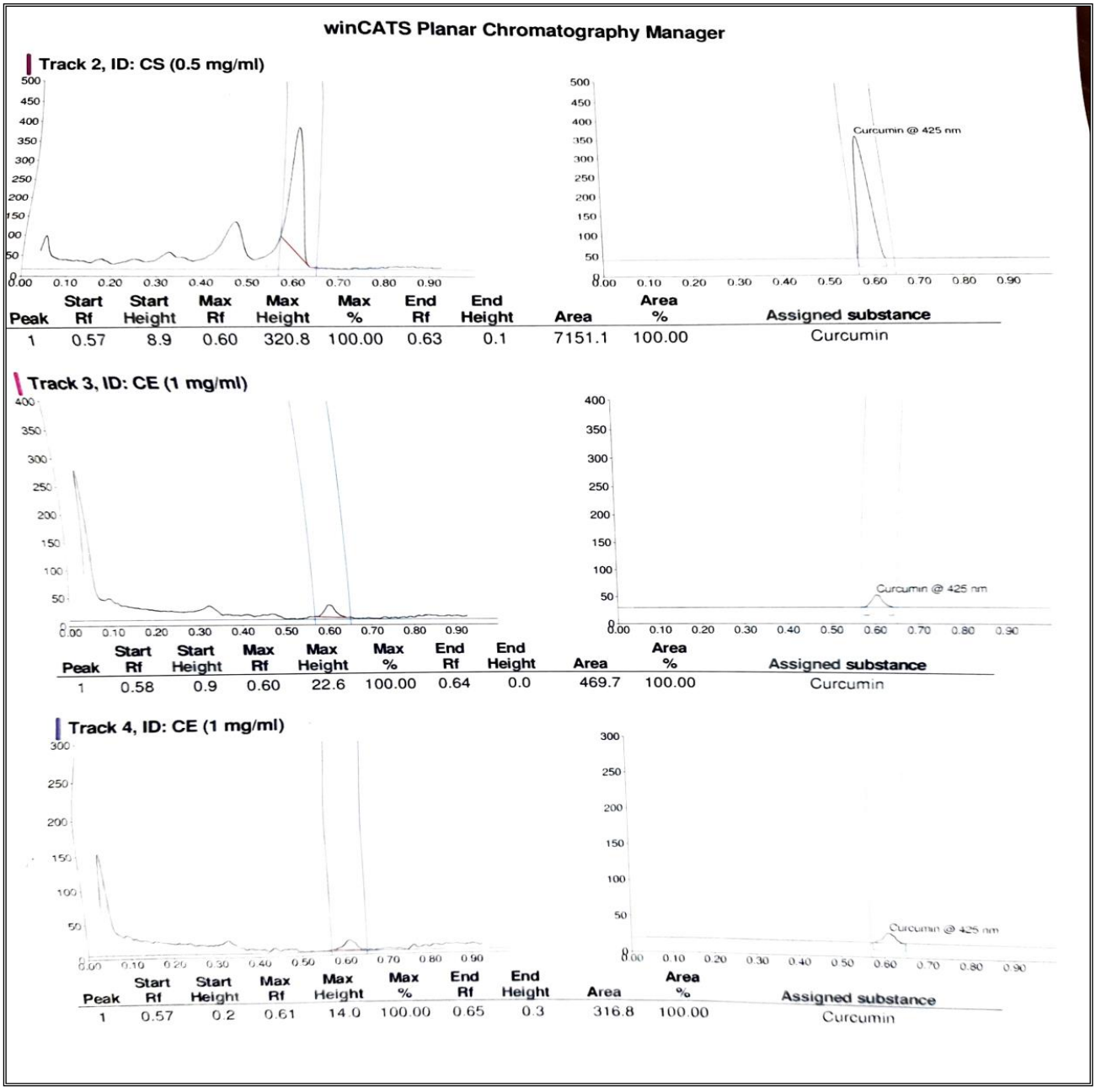
3.3. Estimation of Curcumin in the extract samples by HPTLC analysis Extract

Comparison of standard Curcumin spectra and C. Longa rhizome extract seed at peak apex and peak base is done, which confirm the method was selective

Fig. 3 Estimation of Curcumin from the extract samples by HPTLC



3.4. Scanning Electron Microscopy Results

Fig 4 Method 01 Solvent evaporation method (SEM)

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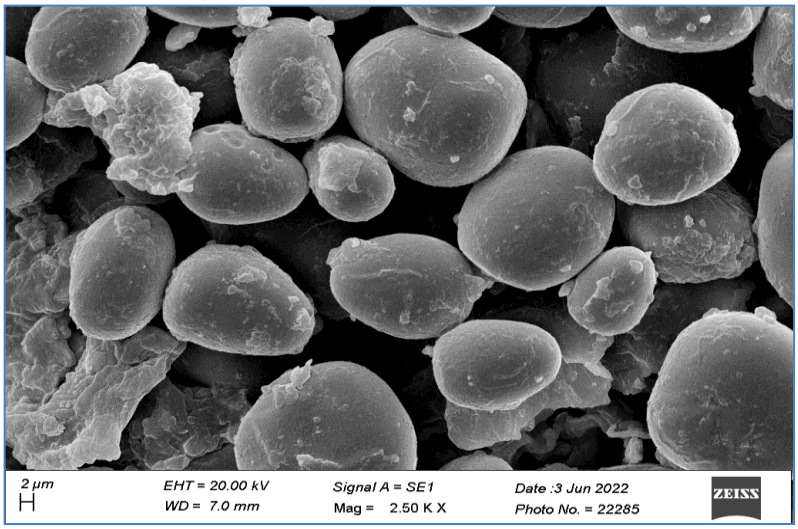

Fig. 6 Method 02 Salting out anti solvent precipitation method (SEM)

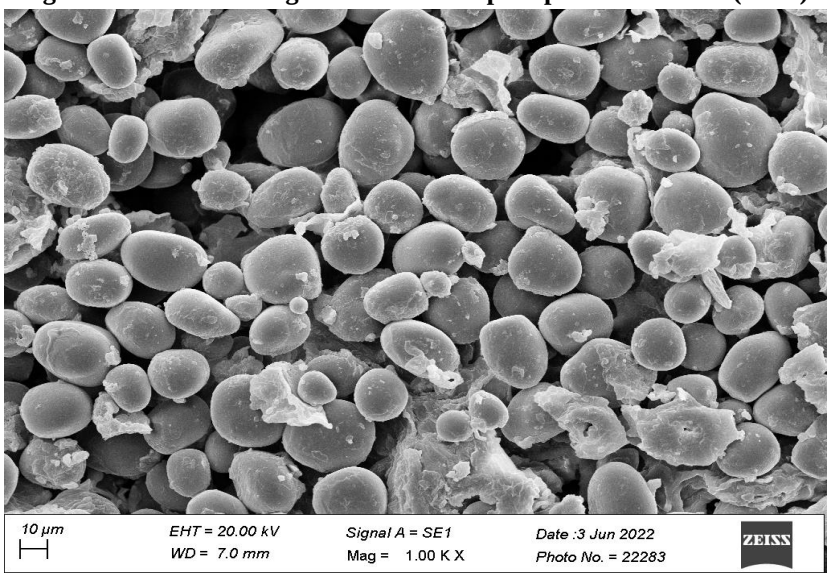

Fig 7 Method 03 Direct egg yolk method (SEM)

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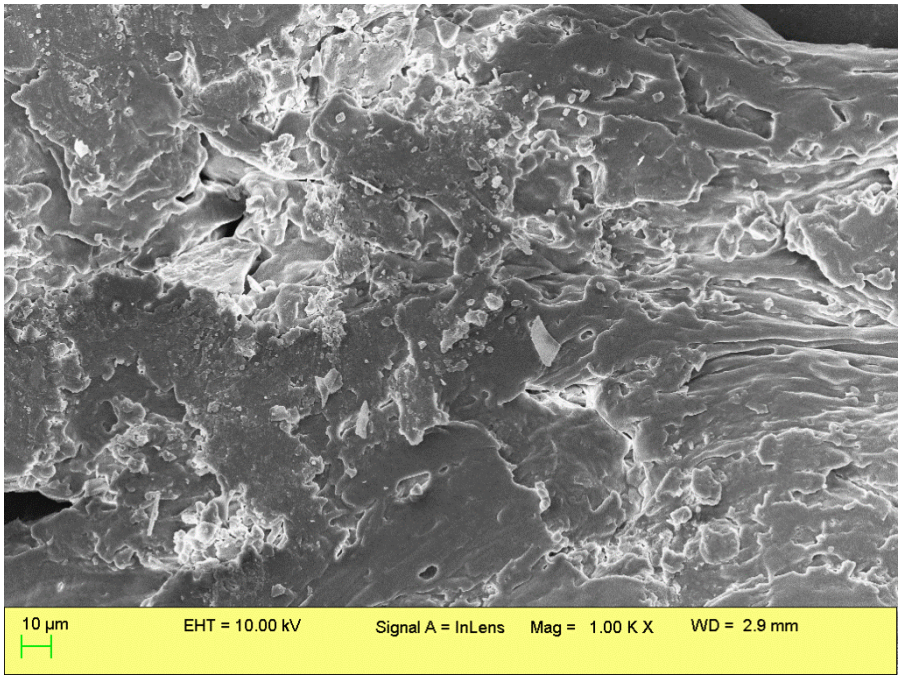
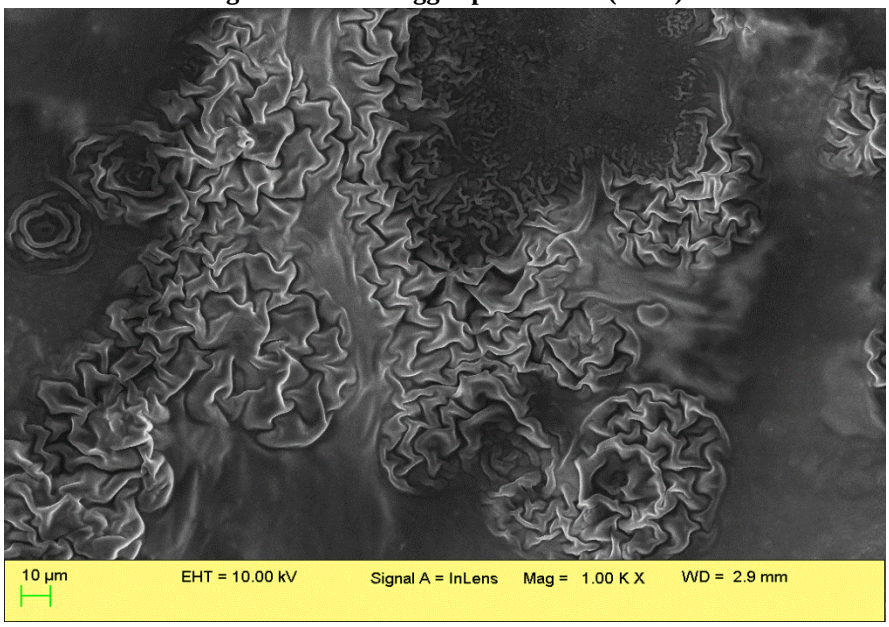


Fig 8 Method 04 Egg Lipid method (SEM)



Scanning Electron Microscopy confirmed the formation of vesicles (Phytosomes) with methods one (Solvent evaporation method) and two (Salting out anti solvent precipitation method) only.

3.5. Results of Entrapment efficiency determination

Table No. 6 Entrapment Efficiency Determination

Method	Entrapment Efficiency (%)
Solvent Evaporation Technique	59.32±0.13
Salting out and antisolvent precipitation method	65.70±0.4

The entrapment efficiency was found better in the curcumin extract Phytosome prepared by using salting out and

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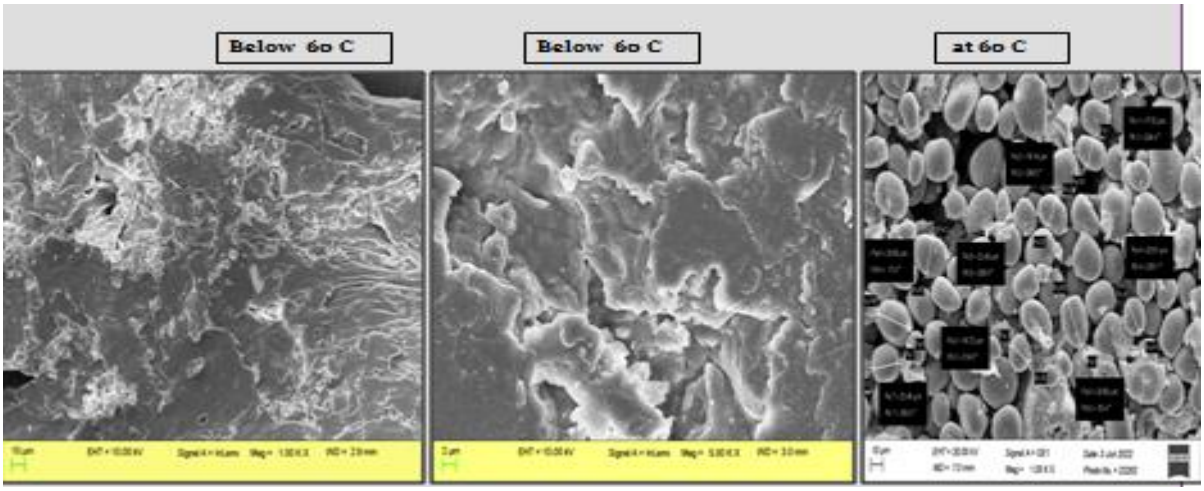
antisolvent precipitation technique

Based on this salting out and antisolvent precipitation technique was further explored for the preparation of Curcumin Extract Phytosome.

3.6. Scanning electron images of Curcumin extract Phytosome prepared by using different temperature conditions

Optimization of Temperature

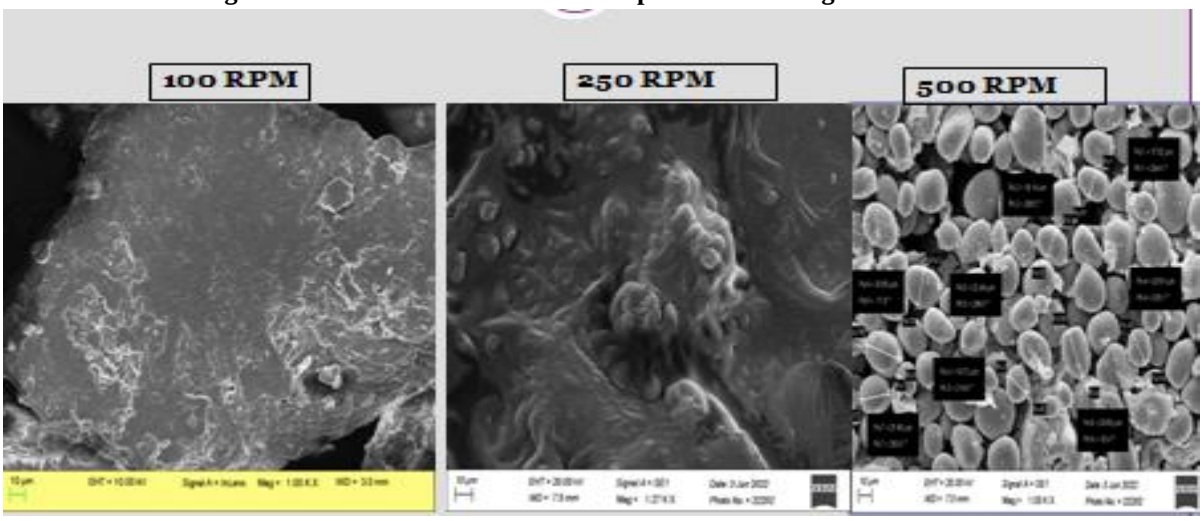
Fig 09 Based on SEM result Selected optimized temperature was 60^0 C.



3.6. Scanning electron images of Curcumin extract Phytosome prepared by using different Rotating speed conditions (RPM)

Optimization of Rotating Speed

Fig 10 Based on SEM result Selected optimized rotating was 500 RPM



Based on SEM result temperature of 60^0 C.and Magnetic stirrer rotating speed of 500RPM were selected further for the preparation of curcumin extract phytosme

3.7. Particle size determination

Particle size determination of all three batches was done

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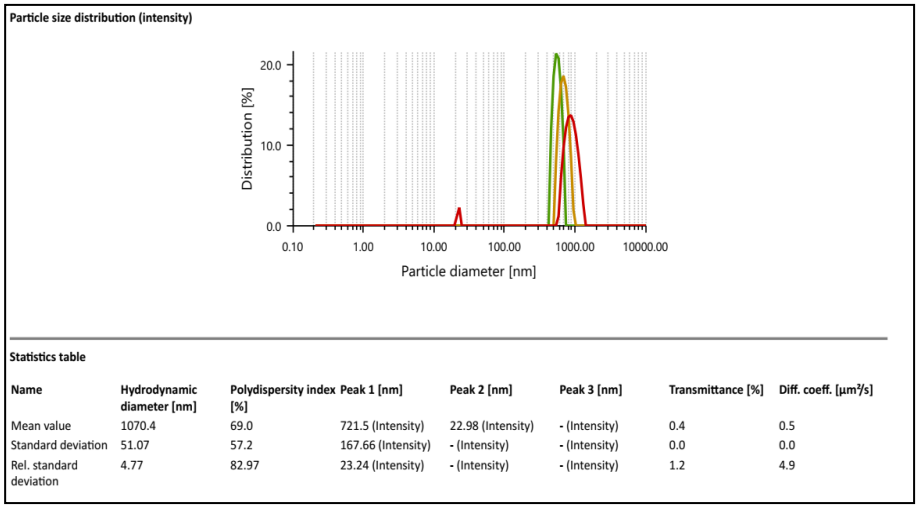
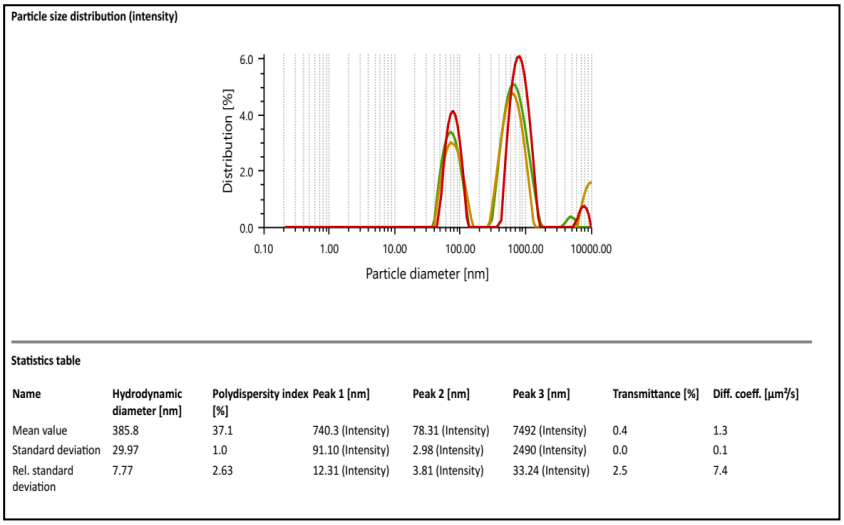
Fig 11 Batch F1 Particle Size Distribution



Statistics table

Name	Hydrodynamic diameter [nm]	Polydispersity index [%]	Peak 1 [nm]	Peak 2 [nm]	Peak 3 [nm]	Transmittance [%]	Diff. coeff. [µm²/s]
Mean value	1070.4	69.0	721.5 (Intensity)	22.98 (Intensity)	- (Intensity)	0.4	0.5
Standard deviation	51.07	57.2	167.66 (Intensity)	- (Intensity)	- (Intensity)	0.0	0.0
Rel. standard deviation	4.77	82.97	23.24 (Intensity)	- (Intensity)	- (Intensity)	1.2	4.9

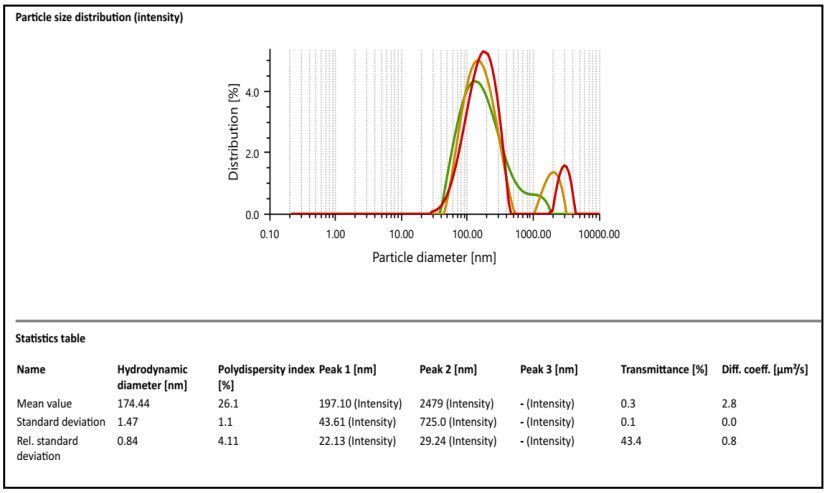
Fig 12 Batch F1 Particle Size Distribution



Statistics table

Name	Hydrodynamic diameter [nm]	Polydispersity index [%]	Peak 1 [nm]	Peak 2 [nm]	Peak 3 [nm]	Transmittance [%]	Diff. coeff. [µm²/s]
Mean value	385.8	37.1	740.3 (Intensity)	78.31 (Intensity)	7492 (Intensity)	0.4	1.3
Standard deviation	29.97	1.0	91.10 (Intensity)	2.98 (Intensity)	2490 (Intensity)	0.0	0.1
Rel. standard deviation	7.77	2.63	12.31 (Intensity)	3.81 (Intensity)	33.24 (Intensity)	2.5	7.4

Fig 13 Batch F1 Particle Size Distribution



Statistics table

Name	Hydrodynamic diameter [nm]	Polydispersity index [%]	Peak 1 [nm]	Peak 2 [nm]	Peak 3 [nm]	Transmittance [%]	Diff. coeff. [µm²/s]
Mean value	174.44	26.1	197.10 (Intensity)	2479 (Intensity)	- (Intensity)	0.3	2.8
Standard deviation	1.47	1.1	43.61 (Intensity)	725.0 (Intensity)	- (Intensity)	0.1	0.0
Rel. standard deviation	0.84	4.11	22.13 (Intensity)	29.24 (Intensity)	- (Intensity)	43.4	0.8

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Formulation F3 Showed best result with minimum average particle size of 174 Nanometer

3.8. Determination of Zeta Potential

Zeta Potential of the F3 was found to be -55.1mv in which shows good stability for the Phytosomal formulations. Zeta potential is an important parameter that affects the aggregation of vesicles and depicts the physical stability of the vesicular systems. High zeta potential prevents the aggregation between vesicles and hence, enhances its physical stability.

Fig. 14 Zeta Potential Batch F1

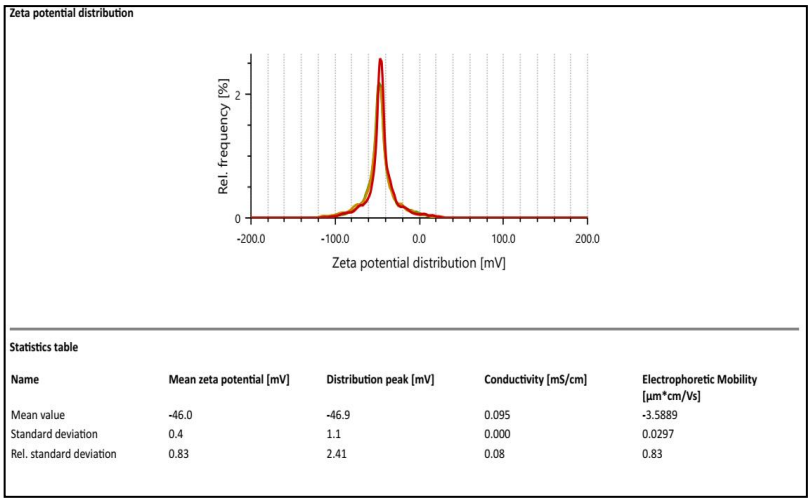

Fig. 15 Zeta Potential Batch F2

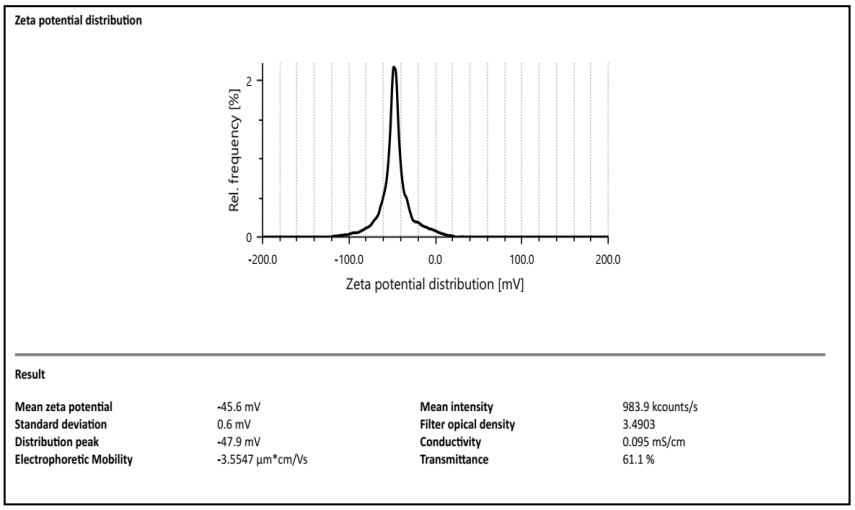

Fig. 16 Zeta Potential Batch F3

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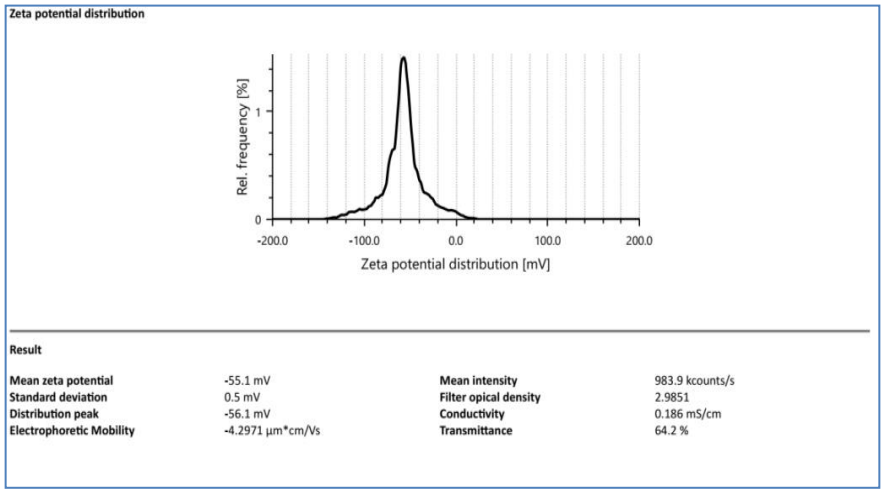

3.9. Powder X-ray diffractometry

In diffraction pattern the intense and sharp crystalline peaks at 2θ of 20 & 28 is observed. With Batch F3's crystallinity of 48.67%, it is possible that the extract is molecularly distributed in the phospholipid matrix and exists in an amorphous state.

Fig. no 17 Batch F1 XRD

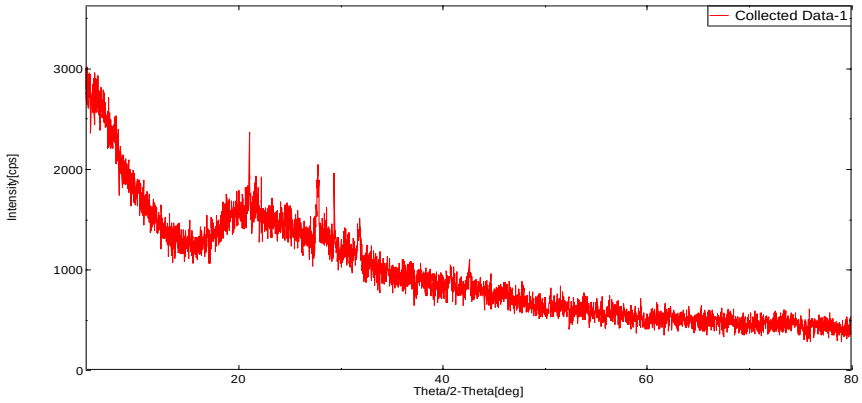

Fig. no 18 Batch F2 XRD

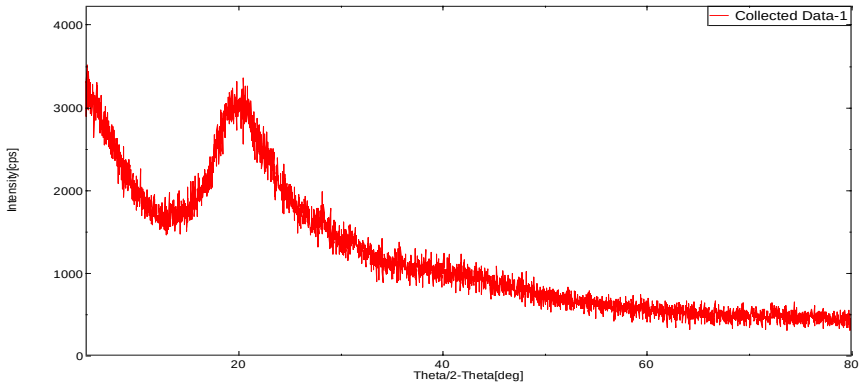

Fig. no 19 Batch F3 XRD

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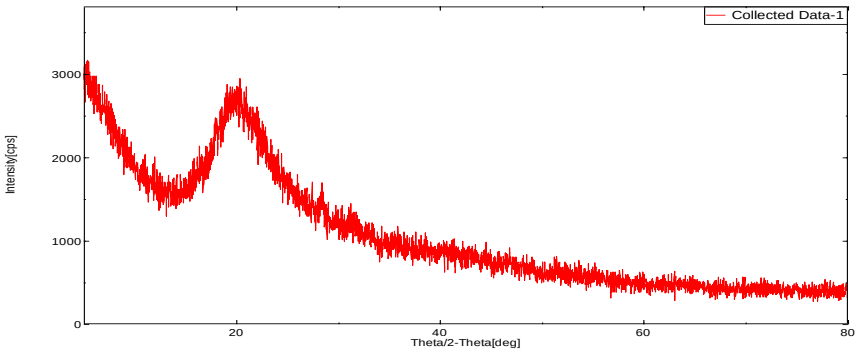

3.10. Drug Entrapment Efficiency

Table no 7 Batch Drug Efficiency of Entrapment

Formulation	Entrapment efficiency (%)
F_1	62.35±0.30
F_2	65.80±0.12
F_3	67.23±.41

As shown in the above table the maximum entrapment percentage of 67.23% was reached by using 2% (w/w) Lipid (F3). It was observed that Phytosome with higher lipid content gives better results

3.11. Optimization Study

Table no 8 Different batches (F1-F9) with results (Drug Release in 8hr and % Entrapment Efficiency)

BATCH	% Phosphotidylcholine	% Cholesterol	% Drug Release in 8hr	% Entrapment Efficiency
F1	2	0.375	**62**±0.2	72±0.01
F2	1	0.25	**78**±0.51	52±1.03
F3	1.5	0.25	**61**±1.85	69±0.53
F4	1.5	0.5	**59**±1.24	67±0.21
F5	**2**	**0.5**	**56**±1.029	**81**±1.53
F6	2	0.25	57±0.22	75±1.025
F7	1	0.375	75±3.21	59±0.22
F8	1	0.5	61±1.02	69±1.003
F9	1.5	0.375	58±0.06	61±3.52

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Fig. no 20 in vitro drug release profile Batches F1-F9

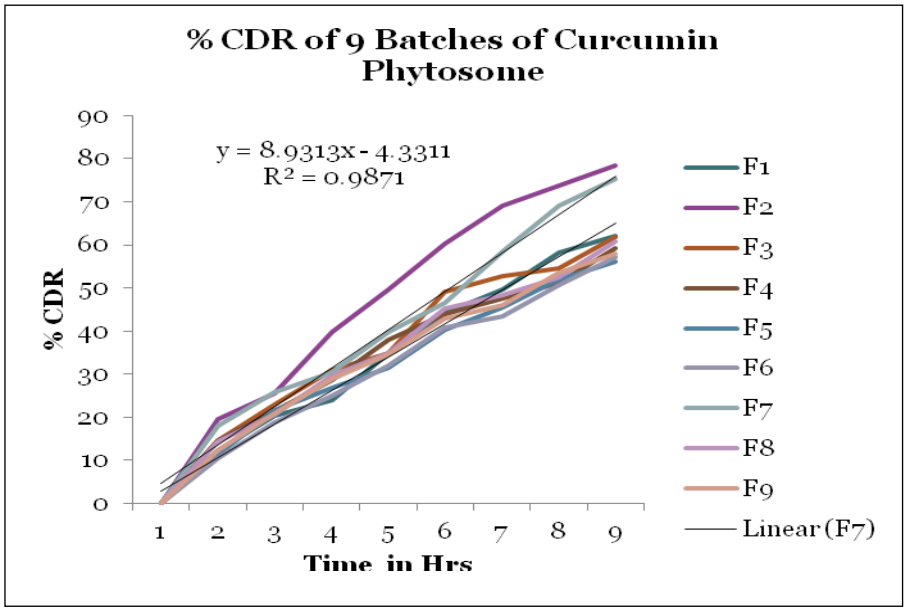

Fig. no 21 Overlay plot % drug release in 8 Hrs

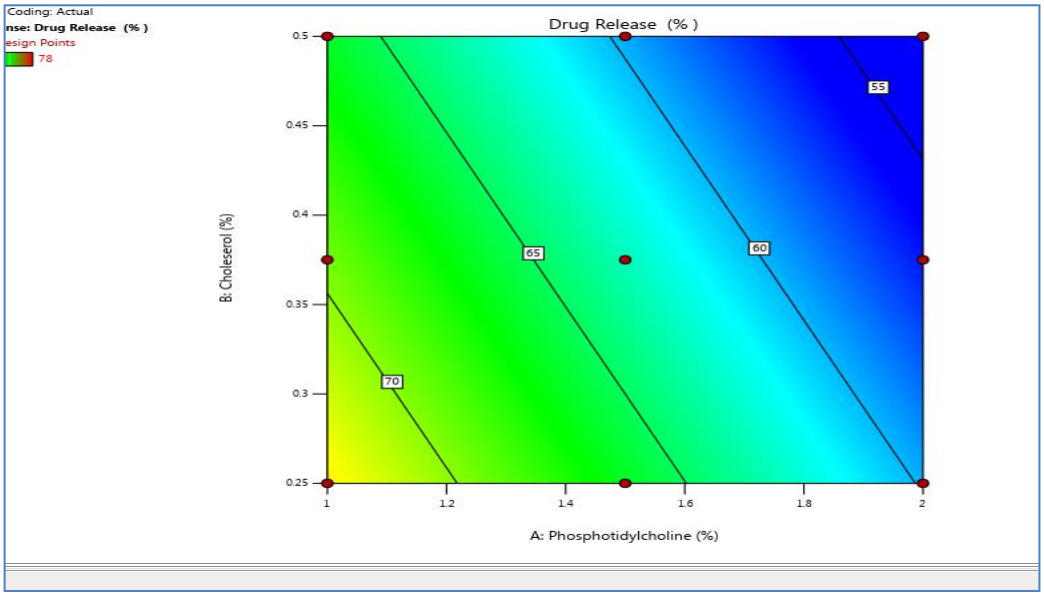

Fig. 22 3D Plot % Drug Release in 8 Hrs

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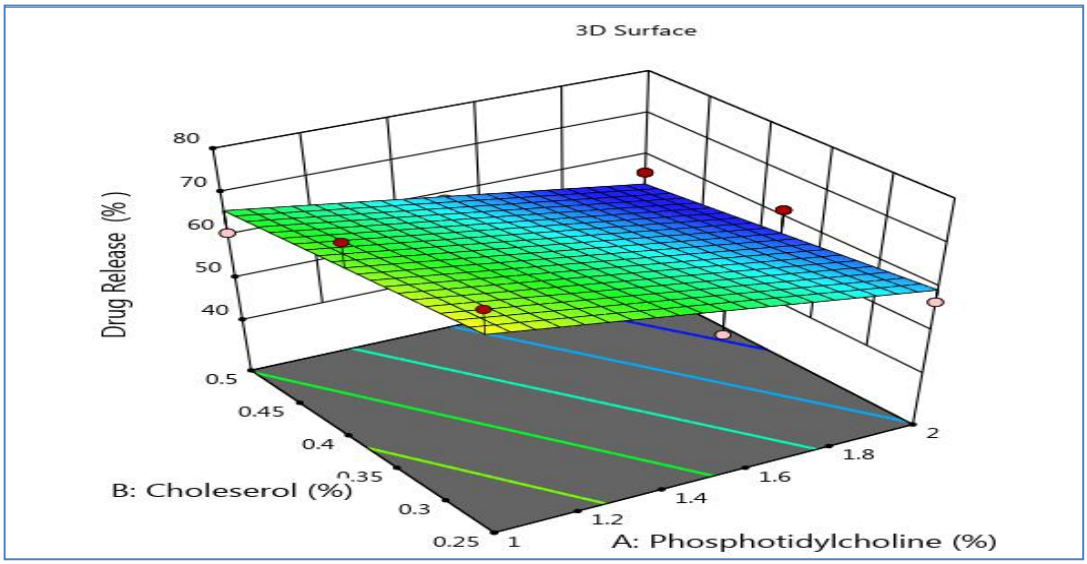

Fig.21 and 22 the plot of surface response and 3D Plot showed that with increase in concentration of Phosphatidylcholine and Cholesterol there is decrease in the release of drug at 8 hours. This may be due to increase in the bond strength (Extract and Lipid) with increase in the concentration of both excipients.

Fig. no 23 Overlay plot Entrapment Efficiency

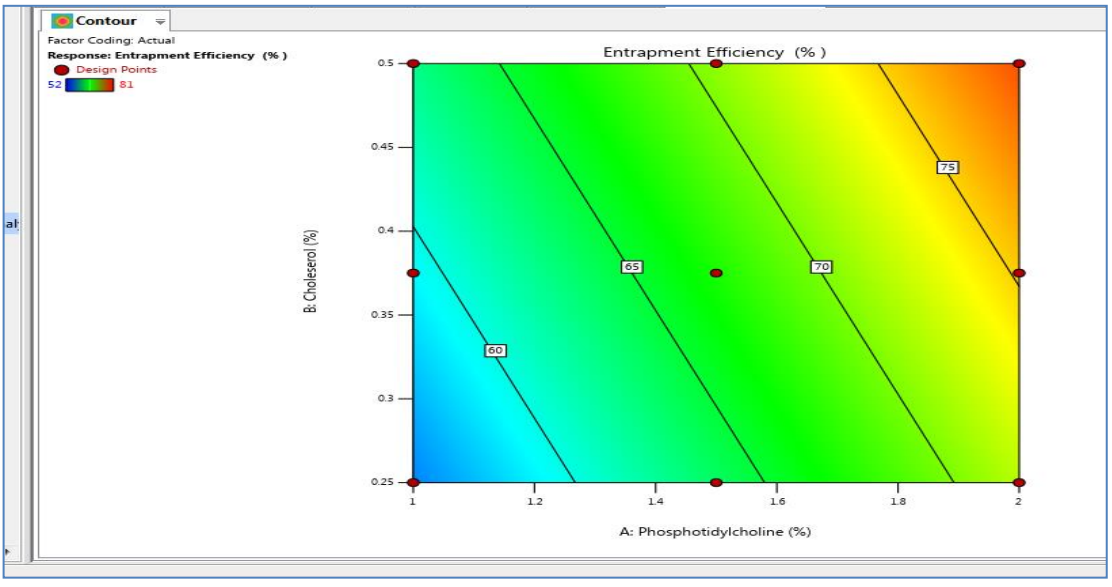

Fig. no 24 3D Plot Entrapment Efficiency

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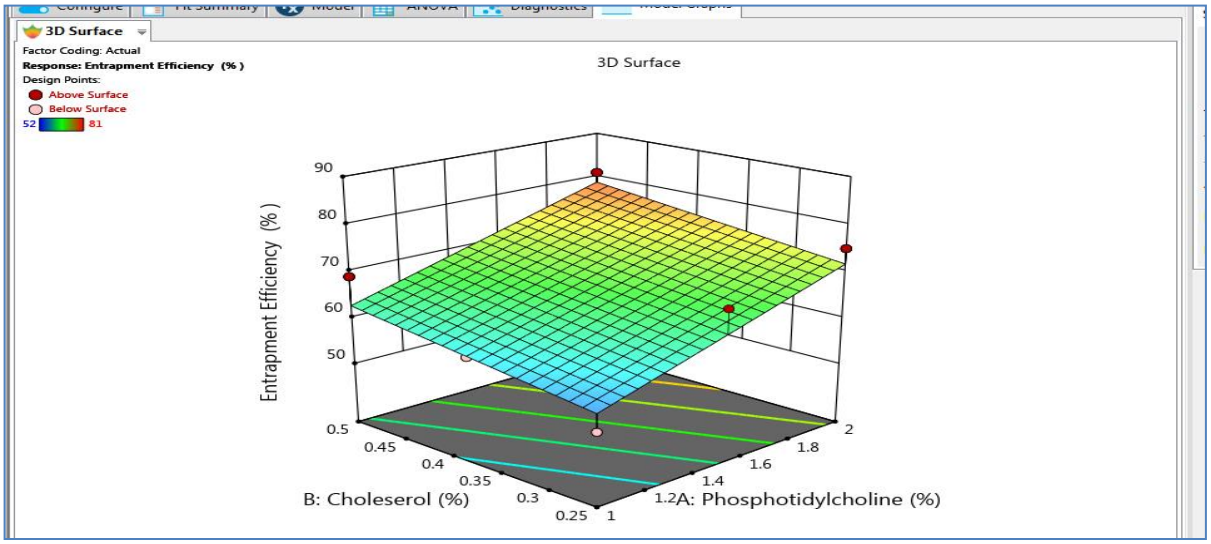

Fig.23 and 24 the plot of surface response and 3D Plot showed that with increase in concentration of Phosphatidylcholine and Cholesterol there is increase in the drug entrapment efficiency. This may be due to more availability of sites for bonding with lipid and increase in the stability due to cholesterol. Therefore formulation (Batch F5) containing 2 %w/v of Phosphotidylcholine and 0.5% w/v of Cholesterol. was selected as optimized formulation.

3.12. Preparation of gel of optimized Phytosomal formulation of curcumin extract

Table No 9 Different Batches of Phytosome Gel

Formulation Code	Phytosome Suspension (ml)	Carbopol 940 (%)	Triethanolamine (%v/v)	Methylparaben (%)	Water (upto 30gms)
F5G1	5	1	0.5	0.01	q.s
F3G2	5	1.5	0.5	0.01	q.s
F3G3	5	2	0.5	0.01	q.s

3.13. Evaluation of topical gel formulation:

3.13.1. Examination of Physical properties

The gel formulation of Curcumin extract was yellow viscous with a uniform and smooth look.

3.13.2. Measurement of pH

All the formulation was evaluated for its pH and the pH of the formulation was in range 5.4-5.9 this was acceptable to avoid the risk of irritation upon application to the nasal route

Table No 10 Different Batches of Phytosome Gel

Gellified Formulation	pH
F3G1	5.8±2.36
F3G2	**5.9±2.04**
F3G3	5.4±0.24

3.13.3. Spreadability

The spreadability of various gel formulations given in the table exhibits that the spreadability of F3 is 28.78 (g.c.m/sec).This is higher than the other formulations. The values of spreadability indicate that the gel is easily spreadable by small amount of shear as shown in the table:

Table 11 Spreadability studies

Gellified Formulation	Time

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F3G1	20.22 ± 1.20
F3G2	**24.30 ± 0.25**
F3G3	22.78 ±0.75

3.13.4. Homogeneity:

Visual Inspection of the developed formulation was done for homogeneity. The created herbal gel produced a yellowish-colored, transparent result that was well-homogeneous and lump-free.

3.13.5. Determination of Viscosity

Table 12 Viscosity Studies

Gellified formulation	**Visc osity cps**	
	Max100	**Min 50**
F3G1	5293	670
F3G2	5230	590
F3G3	**5421**	**750**

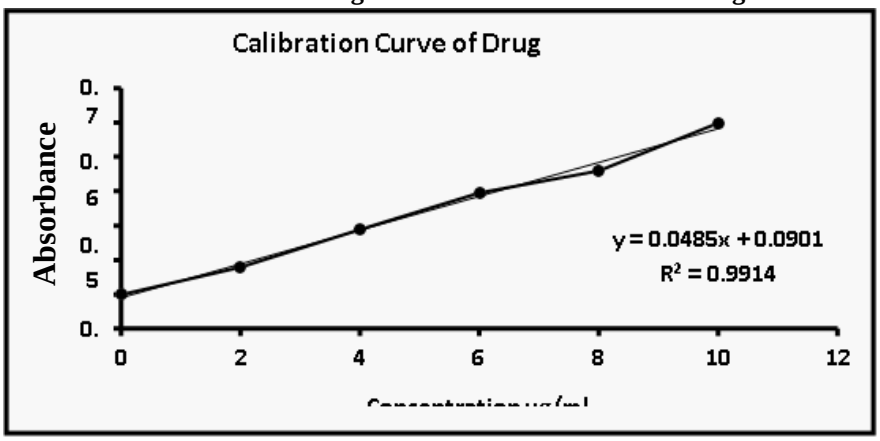
3.13.6. Determination of drug content

Determination of drug content in all herbal gel formulation spectrophotometer assays for the quantitative determination of Drug content of the herbal gel formulation was calculated by calibration curve concentration (2-10µg/ml) was confirmed by Beer's Law at 424 nm. The different concentration absorbance shown in **Table no 13**with a regression co-efficient (R2) = 0.9914. The plot has a slope (m) = 0.0485 and intercept = 0.0901. The equation of standard curve is y = 0.0485x+0.0901 (**Fig. 25**). The drug content of gel formulation shown in **Table no. 14**

Table 13 Calibration curve of the Drug

Sr. No	**Concentration(µg/ml)**	**Absorbance**
1	0	0.0988
2	2	0.1852
3	4	0.2984
4	6	0.3987
5	8	0.4580
6	10	0.5891

Fig. 25 Calibration curve of the Drug



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Calibration Curve of the Extract

Table 14 Drug content of gel formulation

Sr. No	Batch	Drug Content in percentage
1	F3G1	65.85 ±1.82
2	**F3G2**	**67.63 ±1.07**
3	F3G3	67.96 ±0.87

3.13.7 Extrudability: Low viscous gels flows quickly and have good consistency in order to extrude gels but gels having high consistency may not get easily extruded from the tube. An important parameter during topical application is the extrusion of the gel from the tube and a good patientcompliance. The value shown in the table is the measurement of Extrudability Table no: 15

Table 15 Extrudability of the gel

Formulation	% Extrudability
F3G1	80.21±2.58
F3G2	**78.84±0.52**
F3G3	74.21±1.02

Based on the results batch F3G2 was further selected for evaluation. This batch showed better results than other two batches (pH-5.9±2.04, Spreadability 24.30 ± 0.25, Viscosity 5421 at 100 rpm, Drug Content 67.63 ±1.07, Extrudability 78.84±0.52).

3.13. Drug diffusion study

The % CDD (% Cumulative Drug Diffused) of gel formulation shown in **Table no. 16** and graph shows in **Fig no. 26** It was discovered that the total quantity of drug release was55.25±3.004 and 85.21±2.01for plain and Phytosomal gel respectively after period of 12 hr which proved that Phytosomal formulation could enhance bioavailability of extract

Table no 16 Cumulative amounts of drug diffused from Phytosomal Gel

Time (Hrs)	% CDD of Plain Gel	% CDD of Phytosomal Gel
0	0	0
1	5.32±1.20	10.85±0.35
2	14.39±0.25	20.81±.87
3	27.22±0.85	38.93±073
4	34.91±2.22	48.37±1.29
5	41.88±3.87	59.33±2.007
6	48.33±4.02	68.74±1.53
7	51.87±1.25	77.8±3.1
8	55.25±3.004	85.21±2.01

Fig no. 26 *In-vitro* diffusion profile of Plain gel and Phytosomal gel

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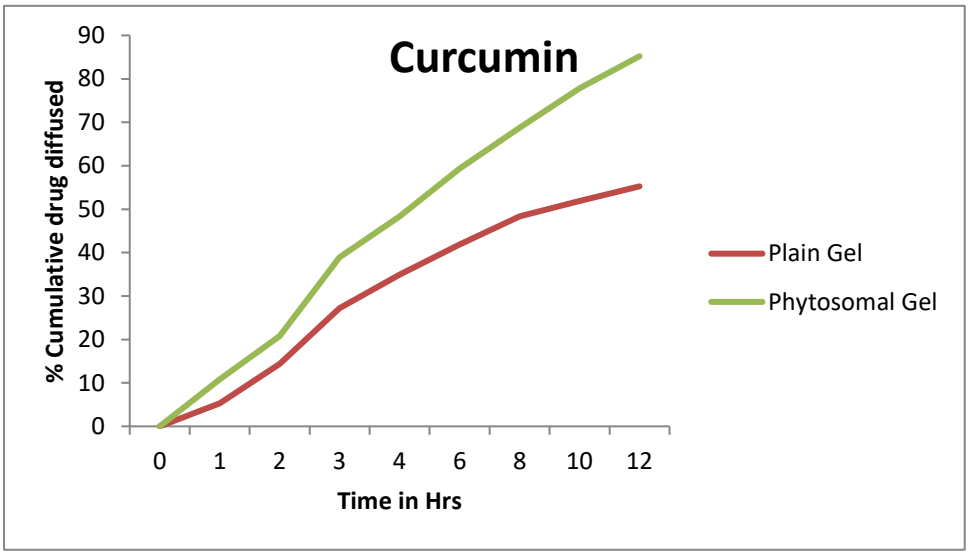

3.14. Drug release kinetic:

On comparison of the kinetic modeling and release profile data it was evident that the Phytosmes formulations were found to release the drug in accordance to Higuchi kinetics, the regression coefficient was not found to be exactly near to 1, which could be due to influence of some other factors.

Table 17 Kinetics Release studies for the best fit model

Phytosomal Formulation Code	**Zero Order Kinetics**	**First Order Kinetics**	**Higuchi Kinetics**	**Peppas Kinetics**	**Best Fit Model**
	r	**r**	**r**	**r**	
F3G2	0.9561	0.9517	**0.9717**	0.645	**Higuchi**

The study of the drug release showed that the formulation is governed by Higuchi's model. The curve was obtained after plotting the cumulative amount of the drug released from each formulation. i.*e* % CDR v/s √**t** given in the above **Table 18 and Fig 27**

Table 18 Higuchi's plot √t v/s Formulation

√**t (Hrs)**	% CDR of **Formulation (F3)**
0	0
1.00	14.31
1.41	23.80
1.73	28.33

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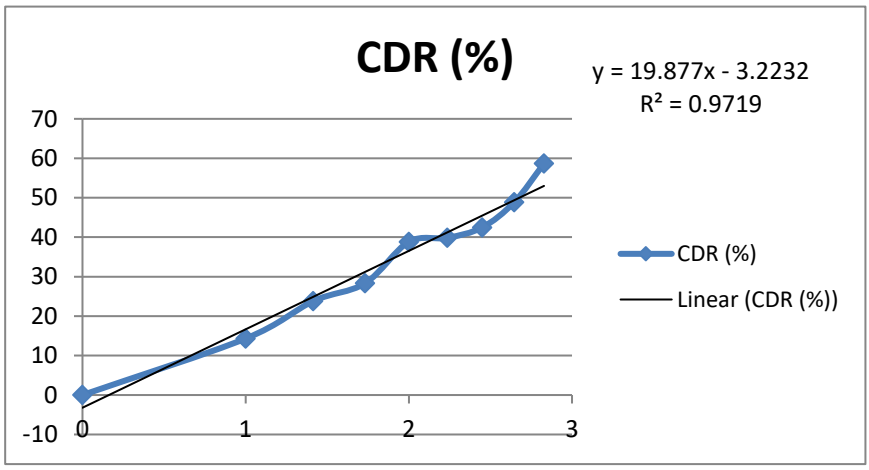
2.00	38.82
2.24	39.85
2.45	42.47
2.65	48.86
2.83	58.66

Fig 27 Higuchi's plot



3.15 Animal Study:

3.15.2 Results of antiparkinson's study

Open field test

In the present study, we demonstrated that, intranasal administration of standard levodopa alone and curcumin and their combination in rotenone induced Parkinson like symptoms in wistar rats. Our findings reveled that, the after repeated administration of rotenone for 30 days exhibited significant decrement in number of crossings in open field test from fourteenth day and remarkable ($p<0.001$) declined on twenty-eighth day when it is compared to normal control group on the respective week (Table 1 and Figure 1). Further, pretreatment with novel formulation of levodopa gel and curcumin gel elicited amelioration of crossing behavior significantly ($p<0.01$, $p<0.001$) compared to disease control group. Nevertheless, the improvement was found to be much significant ($p<0.0001$) on day 28th with the repeated administration of combination formulation of curcumin with levodopa by intranasal route. The present findings thus, suggested that combination treatment exhibited improvement in Parkinson symptom of motor coordination by reversing the crossing movement in the rats.

Table 19 Effects of intranasal administration of gel of levodopa or curcumin or their combination on number of crossing behavior in rotenone-induced Parkinson's disease in rats

Treatment and dose	**Number of crossings at various days (Numbers, Mean±SEM)**				
	0th day	7th day	14th day	21st day	28th day
Normal Control	96.33±9.2	94.01±9.1	95.92±7.9	99.67±9.3	94.12±8.2
Disease control	97.2±8.7	96.33±9.2	66.67±8.3$^{\#}$	45.33±5.3$^{\#\#}$	37.12±6.3$^{\#\#}$
Intranasal levodopa gel	94.33±8.4	91.67±8.2	94.33±8.9*	72.67±6.3*	81.23±8.4*
Intranasal curcumin gel	97.67±9.8	96.67±9.9	72.33±6.7	80.33±8.4*	78.72±7.4**

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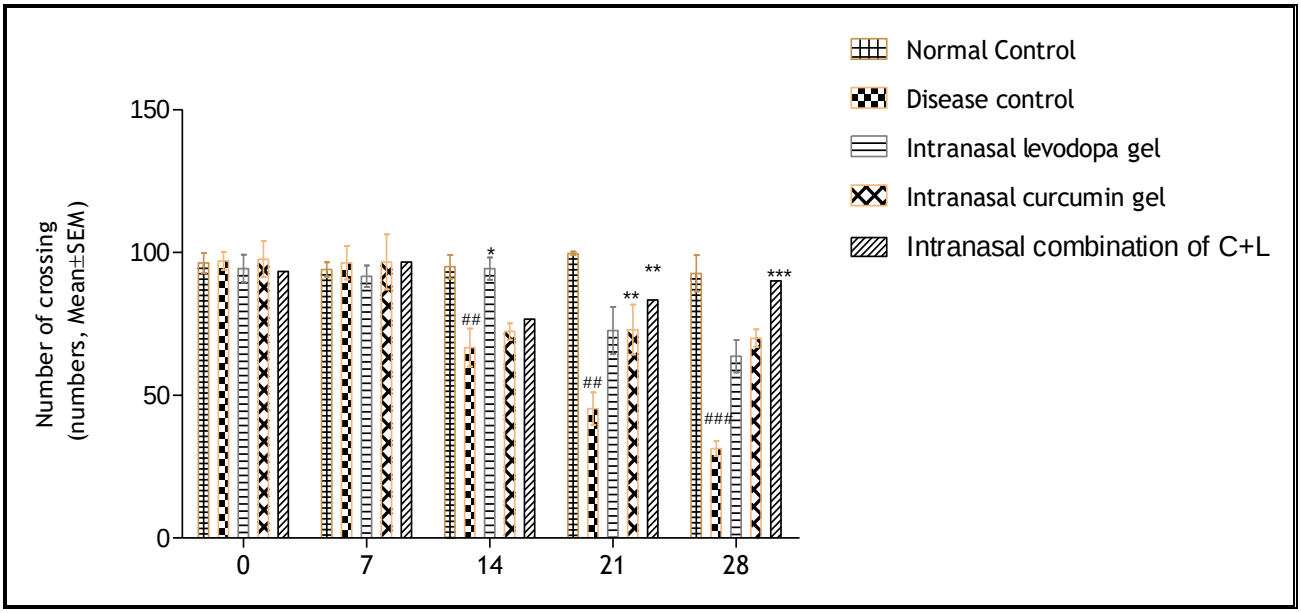
Intranasal combination of levodopa and curcumin gel	93.33±7.9	94.67±9.0	83.67±8.3*	90.33±8.4*	91.43±8.3***
##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to Disease control of respective day, one-way ANOVA followed by Bonferroni post hoc test					

Figure no. 28-Effects of intranasal administration of gel of levodopa or curcumin or their combination in on number of crossing behavior in rotenone-induced Parkinsons disease in rats ##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to Disease control of respective day, one-way ANOVA followed by Bonferroni post hoc test



Catalepsy

In the present study we evaluated the catalepsy condition induced by repeated rotenone administration.

The present experimental findings showed that, the disease control group rats exhibited remarkable (p<0.0001) increased in cataleptic behavior compared normal control group. Pretreatment with intranasal gel of levodopa and curcumin elicited significant (p<0.0001) attenuation of cataleptic behavior compared to disease control. Furthermore, combination of levodopa and curcumin gel treatment exhibited better attenuation in cataleptic behavior compared to vehicle treated disease control

Table 20: Effects of intranasal administration of gel of levodopa or curcumin or their combination in on catalepsy in rotenone-induced Parkinsons disease in rats

Treatment and dose	**Catalepsy (second) (Mean±SEM)**				
	zero day	Seventh day	Fourteenth day	Twenty first day	Twenty eighth day
Normal Control	1.33±0.2	1.67±0.2	2.33±0.3	2.67±0.4	1.67±0.3
Disease control	1.33±0.2	3.67±0.2	5.67±0.5#	15.67±2.3###	43.67±4.6###
Intranasal levodopa gel	1.33±0.2	2.0±0.2	5.33±0.6	9.67±0.8**	18.67±1.8**
Intranasal curcumin gel	1.33±0.2	2.01±0.2	7.02±0.7	14.67±1.7	28.33±2.8**
Intranasal combination of levodopa and curcumin gel	1.33±0.2	2.01±0.3	4.33±0.2	10.67±1.0*	6.67±0.7***
##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when					

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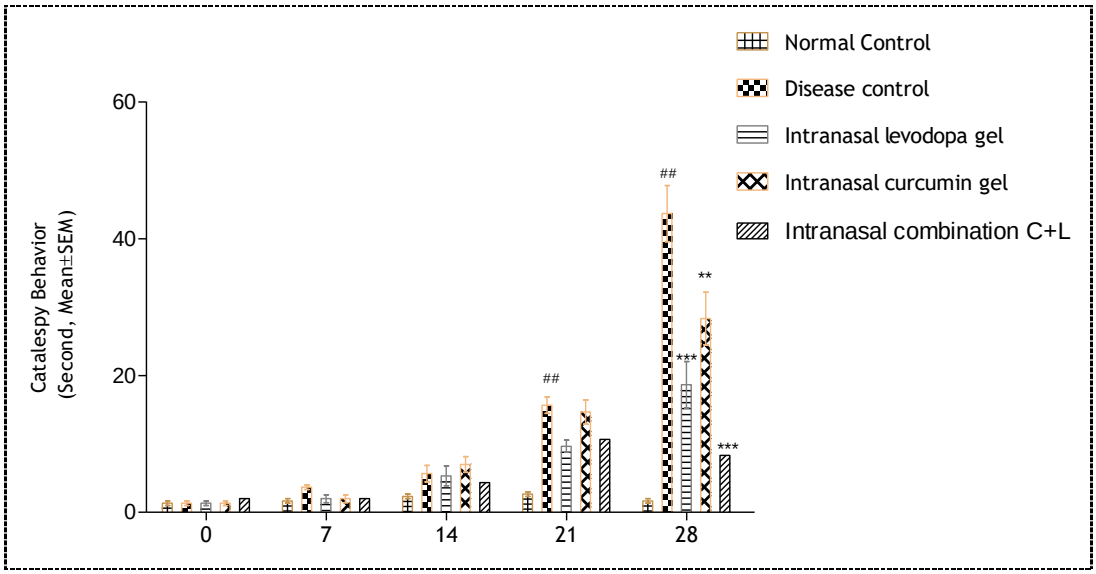
compared to Disease control of respective day, one-way ANOVA followed by Bonferroni post hoc test

Figure 29-Effects of intranasal administration of gel with of levodopa or curcumin or their combinations on catalepsy behavior in rotenone-induced Parkinsons disease in rats $^{\#\#}p<0.0001$ when compared to normal control animals of respective day; $^{***}p<0.0001$, $^{**}p<0.001$, $^{*}p<0.01$, when compared to disease control of respective day, one-way ANOVA followed by Bonferroni post hoc test.



Fall off latency by Rota rod test

In the present study, we determined the rigidity and muscle coordination and grip strength which are the major manifestations developed in Parkinsons disease. Our experimental findings revealed that, the repeated administration of rotenone showed reduction in the fall off time from 14 days and continued thereafter until the last day of treatment. Further, treatment with levodopa gel and curcumin gel alone by intranasal administration elicited significant ($p<0.01$) prevention of fall off time compared to disease control treated with vehicle at respective week. However, the degree of prevention of fall off time was much higher and significant ($p<0.001$) on 21st and 28th day in the groups treated with intranasal administration of combination of levodopa and curcumin gel Thus, the treatment of levodopa and curcumin combination exhibited better effects on muscle coordination disturbance due to repeated rotenone administration observed in the present studies.

Table 21- Effects of intranasal administration of gel with of levodopa or curcumin or their combinations on fall off latency in rotenone-induced Parkinsons disease in rats

Treatment and dose	**Fall off time (second) (Mean±SEM)**				
	zero day	Seventh day	Fourteenth day	Twenty first day	Twenty eighth day
Normal Control	196.2±20.3	184.3±18.2	200.5±19.2	195.5±17.7	205.5±22.3
Disease control	202.67±21.8	169.67±12.3	141.2±12.9$^{\#}$	109.67±9.4$^{\#\#\#}$	68.33±4.5$^{\#\#\#}$
Intranasal levodopa gel	196.7±17.6	180.33±12.4	171.2±12.4	164.33±15.2*	127.33±11.2*
Intranasal curcumin gel	196.2±16.3	171.33±18.2	162.33±17.9	144.2±13.6*	131.67±12.6**

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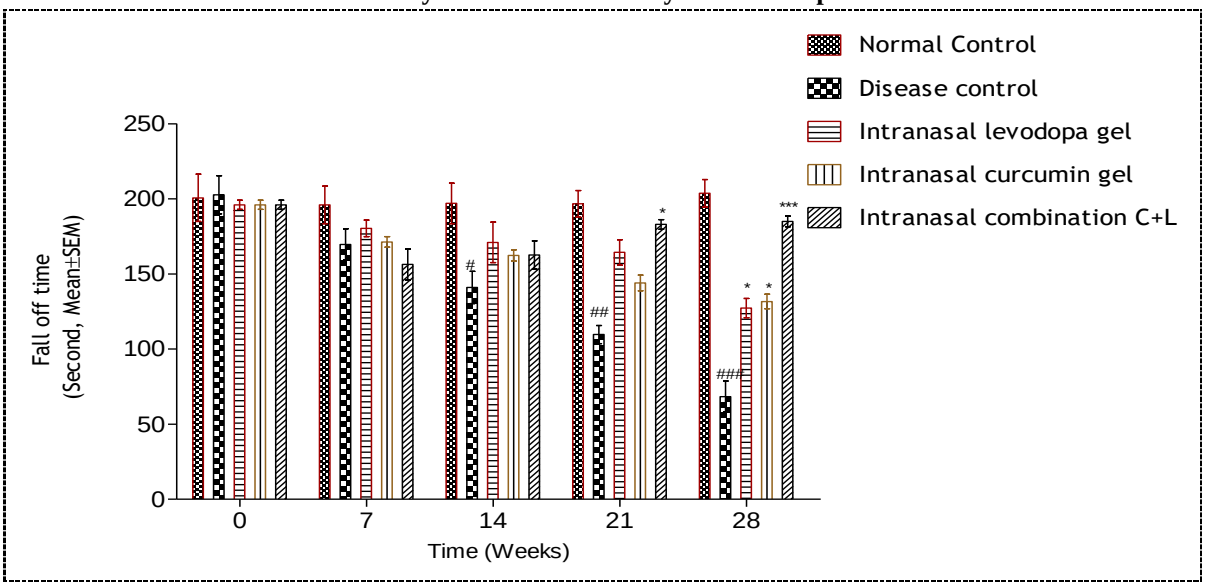
Intranasal combination of levodopa and curcumin gel	196.5±18.4	156.33±13.3	162.67±14.2	183.9±12.3**	185.3±12.9***
##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to Disease control of respective day, one-way ANOVA followed by Bonferroni post hoc test					

Figure 30-Effects of intranasal administration of gel with of levodopa or curcumin or their combinations on fall off latency in rotenone-induced Parkinsons disease in rats; ##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to disease control of respective day, one-way ANOVA followed by Bonferroni post hoc test



Conclusion:

The present study was to be satisfactorily attempted to formulate the Phytosome of *Curcuma Longa* extract for the nasal delivery with a view of enhancing bioavailability of the drug. The experimental result exhibits that, the Phytosome of extract of plant *Curcuma longa* prepared by using salting out method are more stable. The gel of the same formulation prepared using carbopol 940 as a base showed satisfactory release. The animal study result also showed that there is considerable enhancement of dopamine level in the brain after nasal administration of gel of Curcumin Phytosome This finding suggests that the Phytosomal gel formulation can be used to enhance bioavailability of curcumin. Phytosomal gel formulation of curcumin extract would be the best option to target brain for the treatment of Parkinson's disease.

Antiparkinsonian activity of test nasal gel formulation showed improvement in behavioral pattern.

Discussion:

Preliminary Phytochemical analysis of the extract of Curcumin revealed the presence of phenolic compound in the extract. This could be curcumin. That further identity of curcumin was confirmed by TLC, HPLC and HPTLC analysis study. HPLC study also confirmed the amount of curcumin present in the extract i.e. 2.5%.

The different batches of *Curcuma longa* phytosmes were prepared by different methods but salting out methods gave better result that is confirmed by SEM study and with good entrapment efficiency (67.04±0.4). The prepared Phytosome were characterized for their Entrapment efficiency percent, Zeta potential, Particle size, Percent Entrapment efficiency was higher in F3 formulation than that of other formulations. The particle size revealed that the F3 formulation gave particle size of 174 nanometer. Zeta potential was more towards the negative charge (55.1mv) for the F3 formulation. XR reveled the crystallinity of the Batch F3 which was found to be 48.67%. Further Full Factorial Design: A 3^2 randomized full factorial design was used in this study. In that batch F5 showed 56±1.029 % CDR, and entrapment efficiency of **81**±1.53%. The formulation of this batch was further selected for final dosage form i.e. gel formulation.

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The *Curcuma longa* Phytosome gel formulations were prepared by using carbopol 940 and they were characterized for its pH, Spreadability, Viscosity, Drug Content, Extrudability, Homogeneity and washability the result showed fairly acceptable values for all the parameters evaluated. Out of three batches F5G1, F5G2 and F5G3 The batch F5G2 showed better result as compared with other batches. *In-vitro* drug diffusion study showed that diffusion of drug was enhanced across the membrane due to having Phytosomal formulation. *Curcuma longa* Phytosome gel (Batch F5G2) was found to follow Higuchi's kinetic. Antiparkinson's study of formulation showed improvement in behavioral pattern

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