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Development And Characterization Of Capsaicin Loaded Phytosomes For Topical Used

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Abstract: Lipid binds and surrounds the plant-based components of herb extract to form phytosomes, a vesicular drug delivery mechanism.Capsaicin is hydrophobic, has a high permeability, and is less soluble.Using the rotary evaporation process, capsaicin-loaded phytosomes are generated with the goal of formulating, optimizing, and evaluating a phytosomal gel for neuropathic and anti-inflammatory activities.A 0.025% capsaicin phytosomal gel was created using the improved formulation of capsaicin phytosomes and a Carbapol 934 and HPMC K4M combo gel basis. Its drug content, pH, spreadability, viscosity, and in-vitro drug release were assessed.A maximum EE percentage of 97.28±0.25%, drug content of 96.38±0.35%, particle size of 472.1 nm, zeta potential of -40.7 mV, and spherical phytosomes were observed in the produced capsaicin phytosomes. In the phytosomal gel loaded with capsaicin, the spreadability was 18.86±0.34, the viscosity was 9661.0±0.742 cps, the pH was 5.8±0.21, and the drug content was 98.09±0.181%. It was discovered that the phytosomal gel's cumulative percentage of drug release was 94.10±0.02%. The phytosomal gel remained stable for 30 days at 40°C.For the zero order model, the improved formulation's R2 value was the greatest.This demonstrated that all formulations' drug release was governed by diffusion-controlled processes.

Keywords: Capsaicin, Phytosomes, Rotory evaporation method, Carbapol 934,HPMC K4M,Phytosomal gel

Introduction

The term "transdermal drug delivery system" (TDDS) refers to any drug formulation that is applied topically with the goal of releasing the active components into circulation. [1].For topical administration, the vesicular route is one of the most prestigious drug delivery techniques. [2] Plants' active ingredients are typically polar or soluble in water. Nonetheless, Water-soluble phytoconstituents, particularly tannins, flavonoids, and glycosidal aglycones, have low bioavailability due to their larger molecular mass, which acts as an obstacle in passive diffusion, or their poor lipid solubility. [3] The Indena Companies (the city of Milan, Italy) created the first phytosomes in the late 1980s with the intention of complexing drugs with phospholipids to boost their bioavailability.[4]

Combining the terms "phyto" and "some," which both refer to plants, yields the term "phytosomes."Phospholipid and standardized extracts of polyphenolic chemicals reacted stoichiometrically for the formation of phytosomes in an inorganic solvent, which resemble cells.Pharmacosomes and phytosomes[5] are the names given to this kind of tactic. The majority of the world's population frequently uses phytomedicine. In order to ascertain the chemical makeup of plant extracts and products and to bolster the recommendations of traditional medicine, phytochemical and phytopharmacological investigations have been carried out on them throughout the past century. The majority of a plant's active components are polar or water soluble compounds such as tannins, terpenoids and flavonoids[6].A link between convectional and novel delivery systems is provided by the phytosomes, also known as the phytolipid delivery system. [7]

Plants of the genus Capsicum, which includes chili peppers, contain capsaicin as an active ingredient. A particular kind of pain called neuralgia burning or shooting pain in the nerves can be lessened with the use of capsaicin. Capsaicin is also used to assist reduce mild pain from sprains and strains of the muscles or rheumatoid arthritis [8].

Materials and Methods

Dichloromethane was employed as a solvent, and analytical-grade capsaicin and soy lecithin were acquired from Yucca Enterprises in Mumbai and Shiva Biochem in Nandgaon Khandeshwar, respectively. HPMC K4M and Carbopol 934 are products of Colorcon in the city of Mumbai, India. Propylene glycol, methanol, and triethanolamine are supplied by S. D. Fine Chemicals in Mumbai, India. utilized were of analytical quality.

Characterization of powdered drug Capsaicin:

Organoleptic properties The organoleptic characteristics of capsaicin, such as color, solubility, and wavelength maxima, were noted.

Solubility profile of capsaicin Several solvents, including dichloromethane, ethanol, methanol, acetone, and phosphate buffer 7.4, were used to test the solubility of capsaicin

Determination of wavelength maxima

10 milligrams of capsaicin were carefully weighed and then added to a 100 milliliter volumetric flask. The drug was added in a 7.4 pH buffer with 5% methanol to make the stock solution of 100 µg/ml, and the volume was raised to 100 ml. The resulting solution was tested between 200 and 400 nm in a dual beam UV-visible spectrophotometer.

Compatibility Studies

Any chemical and physical interactions between capsaicin and soy lecithin in a formulation can be examined and predicted using FTIR spectroscopy. As a result, it can be used to choose appropriate excipients that are chemically compatible. The purpose of this investigation was to determine whether carriers and drugs interact in any way.[9-10]

Preparation of Capsaicin Phytosomes by Rotary Evaporation Method

A quantity of capsaicin and the lecithin of soy were mixed with dichloromethane in a rotating round-bottom flask, and the mixture was swirled for an hour at an average temperature below 40 degrees Celsius. A phosphate buffer pH 6.8 was incorporated to the the sample's thin sheet obtain after n- hexane was added and spun often until a single film of phospholipid developed. The resulting phytosomal solution was then collected and stored in a desiccator in an amber-colored glass bottle for use later on.[11]

Table No:1 Formulation of Capsaicin Loaded Phytosomes

Sr.no	Capsaicin (mg)	Soy lecithin (mg)	DCM	n-Hexane (ml)	Phosphate Buffer 6.8 pH(ml)
1	25	250	20 ml	15 ml	5
2	50	250	20 ml	15 ml	5
3	75	250	20 ml	15 ml	5
4	100	250	20 ml	15 ml	5

Evaluation of phytosomes

Microscopy

Under a microscope, phytosome vesicles were examined at a 40x magnification.

Drug entrapment efficiency

Calculating the amount of entrapped capsaicin in the phytosomes allowed for the determination of the entrapment effectiveness of the phytosomes.Capsaicin's entrapment efficiency in phytosomes was assessed by transferring a suitable volume of dispersion into a culture tube.At 1500 rpm, the dispersion was centrifuged for 15 minutes.Centrifugation was followed by the collection of the supernant, and

spectrophotometric analysis at ʎmax279 nm was used to quantify the percentage drug entrapment quantity of free capsaicin. This equation has been used to calculate the entrapment efficiency.

$$EE\ \% = \frac{Wa\ (Added\ drug) - Wb\ (free\ drug)}{Wa\ (Added\ drug)} \times 100$$

Where Wa (added drug) is the quantity of drug introduced during the phytosome manufacturing process and Wf (free drug) is the quantity of free drug in the lower chamber of the culture tube after centrifugation.

Drug content

The drug content was calculated. The drug concentration of the loaded phytosomes can be ascertained by dissolving precisely weighed 100 mg of the phytosome in 10 ml of methanol. Following the proper dilution, absorbance can be measured using a UV Spectrophotometer ʎmax 279 nm.Calculations were made to determine the drug content.

Particle size and zeta potential analysis

The vesicle properties, its particle diameter, and zeta potential were assessed at room temperature via a zeta potential or particle size analyzer. To measure the size of the particles and zeta potential of the phytosome formulations, saline with phosphate buffer pH 7.4 was utilized to dilute them.[12]

Scanning electron microscopy

The phytosomes were studied under a scanning electron microscopy, Double-sided sticky tape was used to attach them directly onto the SEM sample tube, and a 200 nm-thick gold layer was applied at a low pressure of 0.001 mmHg. Images were captured at an appropriate magnification.

DSC

Using DSC (Pyris, Diamond Perkins Elmer, Osaka, Japan), investigations of capsaicin, soy lecithin, and phytosome formulations (1:5) were conducted.heated in a nitrogen environment at a rate of 10°/min from 30 to 300° (flow rate: 20 ml/min). [13]

Preparation of Phytosomal Gel

Using distilled water, the gel base (Carbapol 934 and HPMC K4M or Carbapol 940 and HPMC K4M) was created independently.After letting the base stand for 20 minutes, it was stirred and a neutralizing base, TEA, was added to the gel base. Once the gel base had formed, capsaicin phytosome suspension was added, and it was stirred until it was homogenous. Next, methyl and propyl paraben, which had previously been dissolved in some propylene glycol, were added, and it was all stirred until it was homogenous [14].

Table No:2 Preparation of Phytosomal Gel

Batches	Carbapol 934(mg)	HPMC K4M (mg)	TEA (ml)	Propylene glycol (ml)	Methyl paraben (gm)	Propyl Paraben (gm)	Water (ml)	Equivalent Capsaicin Phytosome (1:5)
F1	500	100	1.2	0.5	0.05	0.02	q.s to 100 ml	25 mg
F2	400	500	1.2	0.5	0.05	0.02	q.s to 100 ml	25 mg
	Carbapol 940	HPMC K4M						
F3	500	100	1.2	0.5	0.05	0.02	q.s to 100 ml	25 mg
F4	400	500	1.2	0.5	0.05	0.02	q.s to 100 ml	25 mg

Evaluation of Phytosomal Gel

Organoleptic Characteristics

Following gel preparation, the compositions' appearance, homogeneity, consistency, and phase separation were assessed visually.

Measurement of pH

The pH value was measured using a digital pH meter after one gram of gel was dissolved in twenty milliliters of pure water.

Spreadability

There were two glass slides that measured twenty centimeters by 20 cm. There was a small amount of sample between both glass slides. The upper slide had a 50 g weight placed on it to form an extremely thin film of gel across the two slides. The gel's spreading time was measured using a stop clock and weight attached to the upper plate. It is a parallel-plate approach that is most commonly used to determine and quantify the ability to distribute of semisolid preparations. This method's relative price and user-friendliness are advantages. This was done using the following formula.

$S = m \times L/T$

Where S - Spreadability

m - Weight tied to the upper slide L- Length of the glass,T - Time taken in seconds.

Figure 5.3: Spredability study

Drug content

For dissolving 1 g of gel, a hundred milliliters of a buffer containing phosphate with a pH value of 7.4 was employed. Spectrophotometric analysis was used to ascertain the drug concentration of the resultant solution after it had been filtered.

Viscosity

Using Brookfield Viscometer (DV-E Model), the sample's viscosity was measured. A tiny volume holding was utilized to hold the necessary amount of gel, and the spindle, LV4-64, rotated at 30 revolutions per minute (rpm). The appropriate viscosity measurement was recorded in centipoises (cp).

Washability

After weighing out one gram of gel, it was applied to the hand and rinsed for one minute under running water.

In vitro release study

Phosphate buffer with a pH of 7.4 served as the diffusion medium. The diffusion cell for in vitro diffusion experiments was assembled. The magnetic stirrers were set on top of the diffusion cells. The pH 7.4 phosphate buffer was added to the receptor compartment. After that, the dialysis membrane-70 (which was prepared by boiling it with phosphate buffer 7.4 pH) was carefully placed on the cell to prevent air bubbles from becoming trapped beneath it. Gel was applied to a membrane in the donar compartment after the membrane's intimate contact with the receptor fluid was confirmed To maintain sink condition, 0.5 ml of sample was taken using a micropipette and then taken from the receptor compartment's sampling port every hour. The same volume was then refilled with receptor fluid solution. A UV spectrophotometer was used to detect the absorbance at 279 nm after the samples had been suitably diluted.

Determination of permeation coefficient,flux and Lag time

The permeation studies were conducted utilizing a modified Franz diffusion cell and an optimized phytosomal gel batch, F1.The dialysis membrane was placed on the Franz diffusion cells with the donor compartment facing the membrane and the gel being studied near to the membrane. Twenty milliliters of 7.4 pH saline phosphate were introduced into the receptor compartment.

The receptor compartment's contents were stirred at 500 rpm using a magnetic bead, and the assembly was kept at 37±1 ºC on a magnetic stirrer. A corresponding volume of saline with phosphate buffer (pH 7.4) was used in place of each sample (0.5 mL) at different intervals. With a pH 7.4 phosphate buffer, the resulting samples were analyzed at 279 nm using a UV-visible spectrophotometer. The average amount of permeate per cm2 vs. time during the ex vivo permeate research was displayed in order to assess the data. We calculated several parameters, such as the permeability factor (Kp) across the membrane, also called lag time (T lag), a steady state drug flow (Jss), and a straight line inside the membrane that was interpreted as a medication flux (Jss) and its X-intersect as lag period (T lag).

In vitro drug release kinetic study

Ascertaining the process by which drugs release and analyzing the differences in release patterns across phytosomal gel formulations were done using the data collected from the amount and time of medication released. Drug release kinetics were studied using mathematical models, including the Korsmeyer-Peppas model, Higuchi , Hixson Crowell, Zero order, and First order. The release characteristics of a drug from the matrix have been explained by a variety of kinetic models available. Three parameters were used to analyze the release mechanism: the rate at which release occurs constant (k), correlation value (R), and releasing exponent (n). The model that matched the optimal formulation was selected.

Stability studies

Stability of a drug refers to a formulation's ability to retain its physical, chemical, medicinal, and toxicological characteristics in a particular container. A medication formulation is deemed stable if it meets the following requirements:By showing how the effectiveness of a medicinal product or drug ingredient

varies over time under the impact of several environmental elements including temperature, humidity, and light, stability testing aids in the determination of appropriate conditions for storage, retest periods, and self-live.The capsaicin phytosomal gel stability study was conducted at room temperature (30°C), cold temperature (4°C), and 45°C/RH, per ICH.The physical properties of the samples and their drug content were assessed after ten, twenty, and thirty days.[15-25]

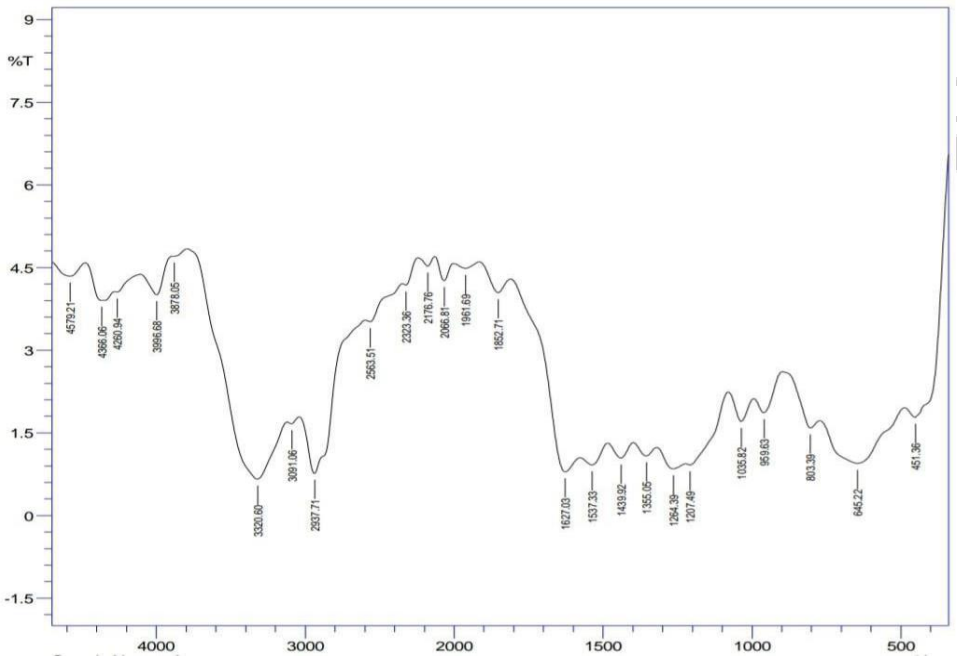
Results and discussions

Conformation of Pure Drug

Capsaicin is a crystalline substance with a strong, pungent flavor.Solubility: It dissolves in organic solvents such as dichloromethane, methanol, ethanol, acetone, and chloroform.Melting point determination: The capillary tube method was used to measure the melting point. Capsaicin's melting point was determined to be between 62 and 650 degrees Celsius. Study on the compatibility of drugs and soy lecithin.

Fourier Transform Infrared Spectroscopy for Analysis of Drug and Excipients

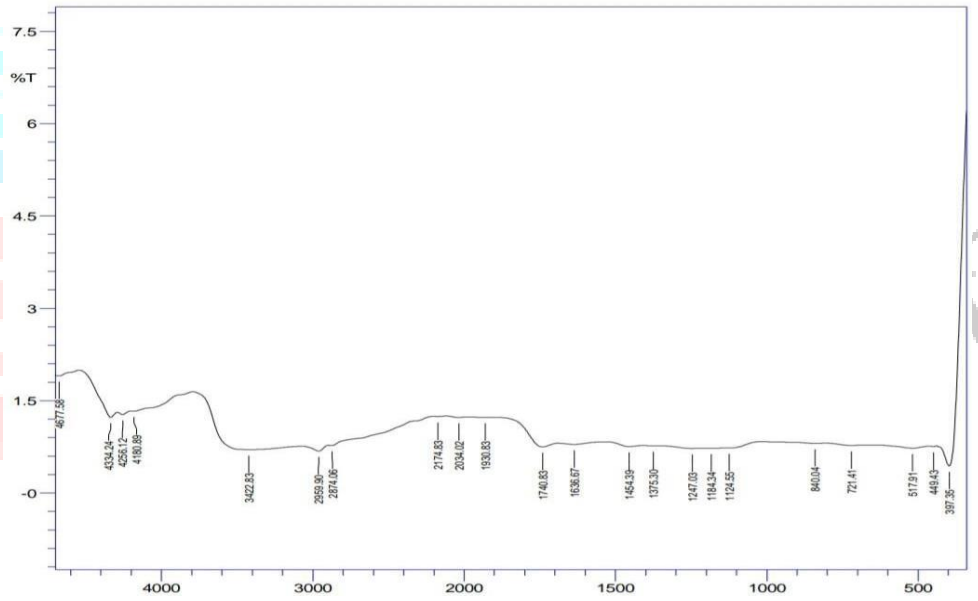
A study was conducted on the drug's compatibility with soy lecithin. All of capsaicin's characteristic peaks were seen in the and soy lecithin physical mixture spectra, indicating the absence of any chemical or physical interactions. Thus, soy lecithin with drugs are compatible.Results observed can be seen in Graph 1 and 2 and 3



Graph 1 : FTIR Spectrum of Pure API (Capsaicin)

Table No.3 :FTIR spectral interpretation of Capsaicin

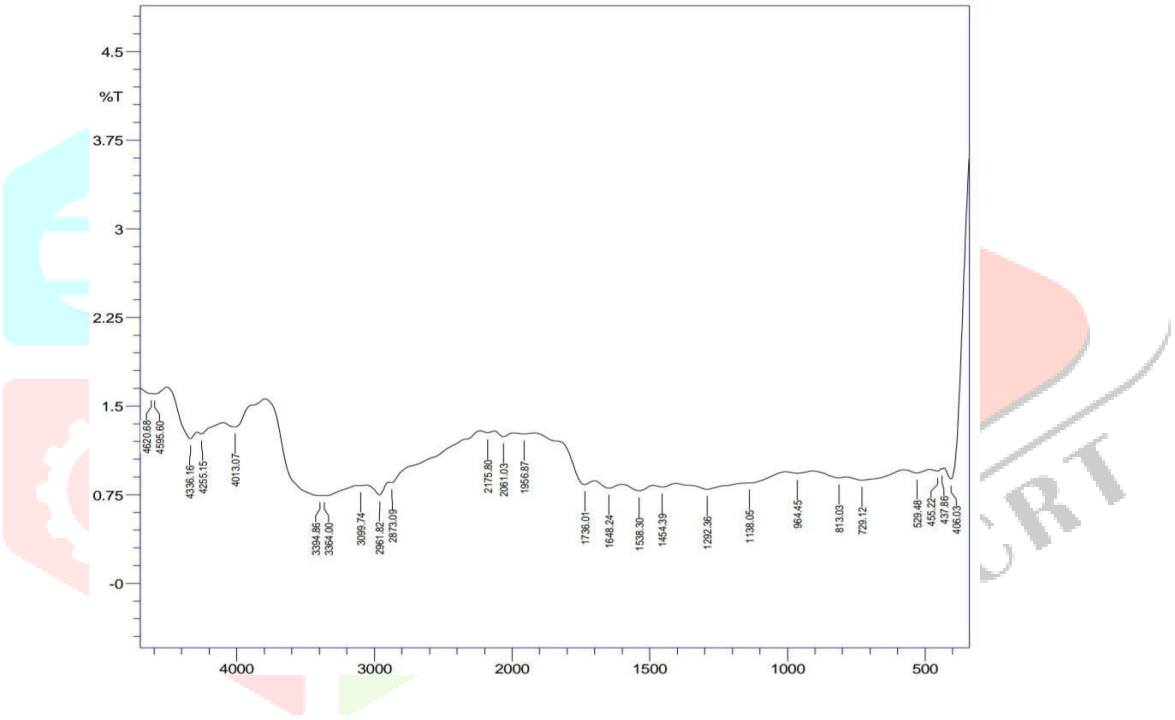
Functional groups	Reported Groups (cm-1)	Observed Groups (cm-1)
N-H	3000-3300	3091.06
O-H	1310-1390	1355.05
C-N	1200-1350	1207.49
C-H	2840-3000	2937.71
C=O	1600-16700	1627.03
O-H	3200-3700	3320.60
C-O	1000-1300	1035.82



Graph 2: FTIR Spectrum of Soy lecithin

Table No 4 :FTIR spectral interpretation of Soy lecithin

Functional groups	Reported Groups (cm-1)	Observed Groups (cm-1)
-CH2	2850-3000	2959.9
-CH	2850-3000	2874.06
O-H	3200-3700	3422.83
C=O	1600-16700	1740.83
P=O	1100-1275	1247.03
P-O-C	1100-1275	1124.55

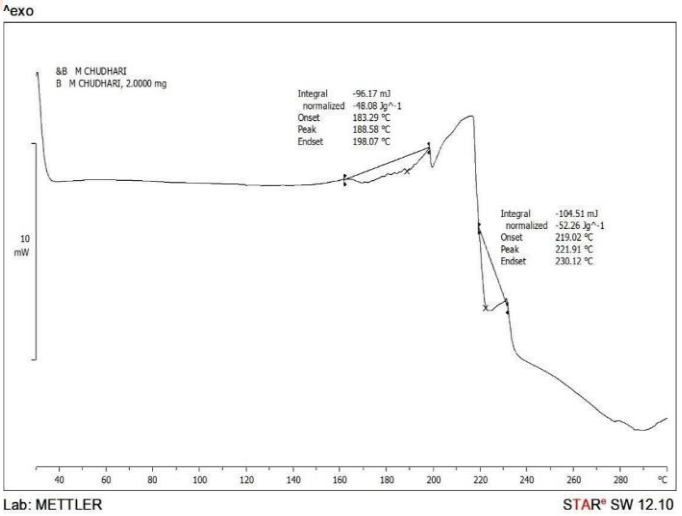


Graph 3: FTIR Spectrum of Soy lecithin and Capsaicin (Physical mixture)

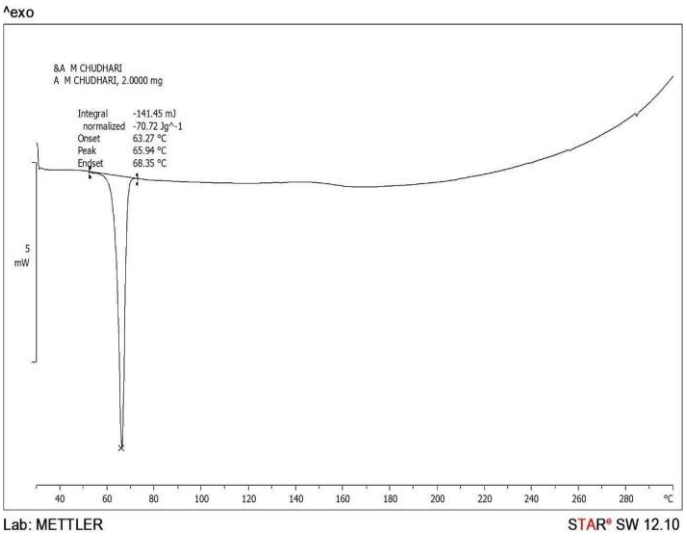
Table No 5 :FTIR spectral interpretation of Soy lecithin and Capsaicin

Functional groups	Reported Groups (cm-1)	Observed Groups (cm-1)
C=O	1600-16700	1648.24
N-H	3000-3300	3364
C-N	1200-1350	1292.36
-CH3	2850-3000	3099.74
-CH2	2850-3000	2961.82
C-H	2850-3000	2873.09
P=O	1100-1275	1292.36
P-O-C	1100-1275	1138.05
O-H	3200-3700	3394.86

Differential Scanning Calorimetry (DSC) Drugs and polymers were characterized in their solid state using DSC investigations. Additionally, by monitoring the thermal behavior of substances, such as elimination or the emergence of an endothermic or exothermic peak, the compatibility between the medicine and excipients can be assessed. The results of the DSC show that a pronounced endothermic peak occurs at 65.94˚C.which is in range of its melting point of capsaicin and depicted in the graph 4. The Graph 5 exhibits a sharp endothermic peak at 221.91ºC. is in range of its melting pointand depicted in the graph 5.



Graph 4: DSC of Drug

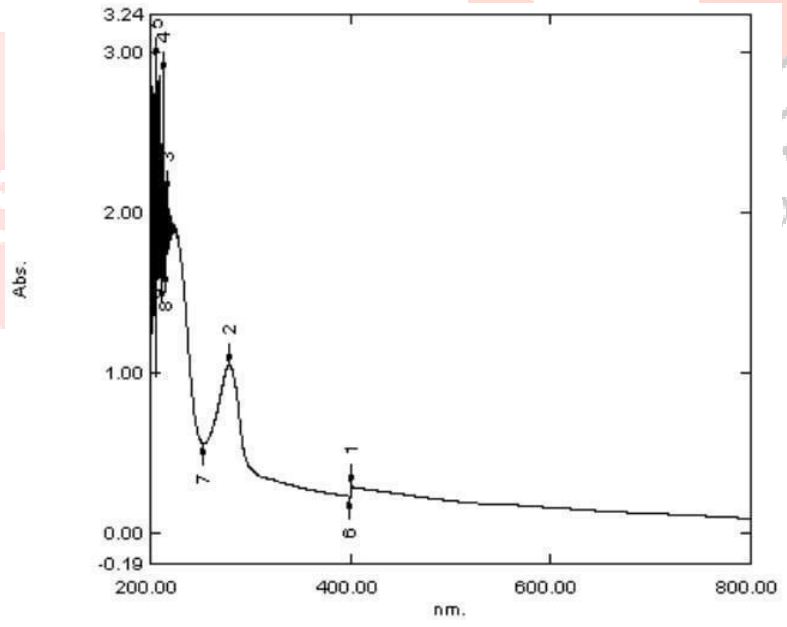


Graph 5 : DSC of soya lecithin

Spectrophotometric method for the estimation of Capsaicin

Determination of λ max of capsaicin in Phosphate buffer pH 7.4 with 5%Methanol

According to Graph 6, the maximum absorbance of capsaicin was determined to be 279 nm. Therefore, 279 nm was chosen as the wavelength for drug content estimate and drug analysis in dissolving media.



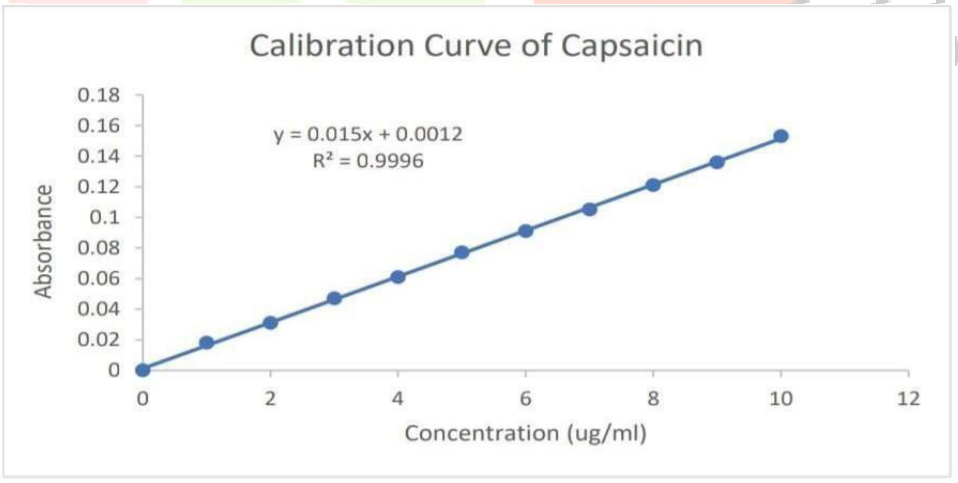
Graph 6: UV spectrum of capsaicin

Standard Calibration curve of Capsaicin in Phosphate buffer pH 7.4 with 5%Methanol at 279 nm:

To evaluate capsaicin, the UV-visible spectrophotometric technique was employed. The drug's absorbance at 279 nm in phosphate buffer pH 7.4 with 5% methanol was determined. The findings are displayed in Table 6. The Capsaicin Calibration Curve was displayed in Graph 7.

Table No. 6 : Calibration Data of Capsaicin in Phosphate buffer pH 7.4 with 5% Methanol at 279 nm

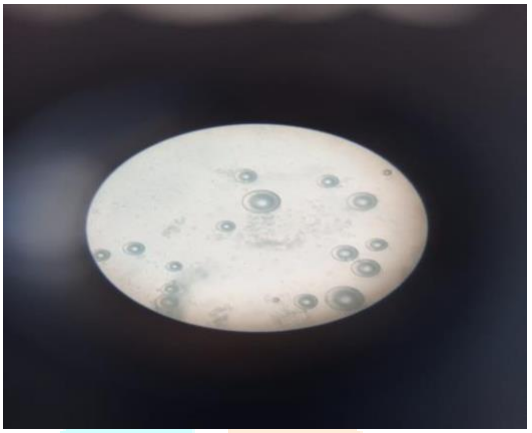
Concentration (ug/ml)	Absorbance ± SD
0	0±0.0
10	0.018±0.01
20	0.031±0.03
30	0.047±0.05
40	0.061±0.06
50	0.077±0.07
60	0.091±0.08
70	0.105±0.09
80	0.121±0.08
90	0.136±0.07
100	0.153±0.05



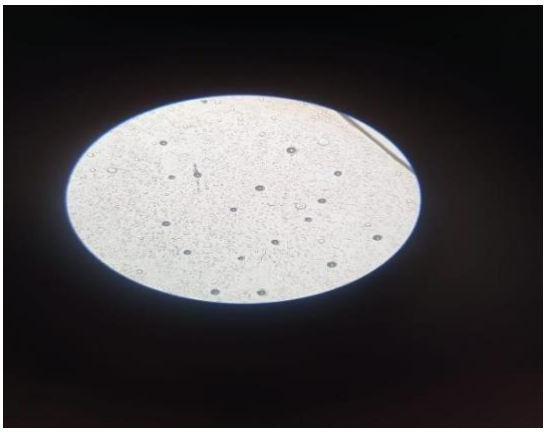
Graph 7: Calibration Data of Capsaicin in Phosphate buffer pH 7.4 with 5% Methanol at 279 nm.

Optical Microscopy

Using an optical microscope with a 40X magnification, phytosomes were examined. The observed phytosomes have a spherical form.



Before probe sonication



After probe sonications

Drug Entrapment Efficiency

The results of drug entrapment efficiency are shown in table below

Table No 7 Results of Entrapment Efficiency of Phytosomal suspension

Batch no	Entrapment efficiency (%)
F1	95±0.14%
F2	97.28±0.25%
F3	93.33%±0.37%
F4	92.5%±0.72%

In the Entrapment efficiency study , the entrapment efficiency was calculated and observation were made as for formulation F1=95±0.14%,F2=97.28±0.25%,F3=93.33%±0.37%, F4=92.5± 0.72% respectively.it can be concluded that as F2 batch show more entrapment efficiency than other batches so F2 batch is best and optimized batch.

Drug content

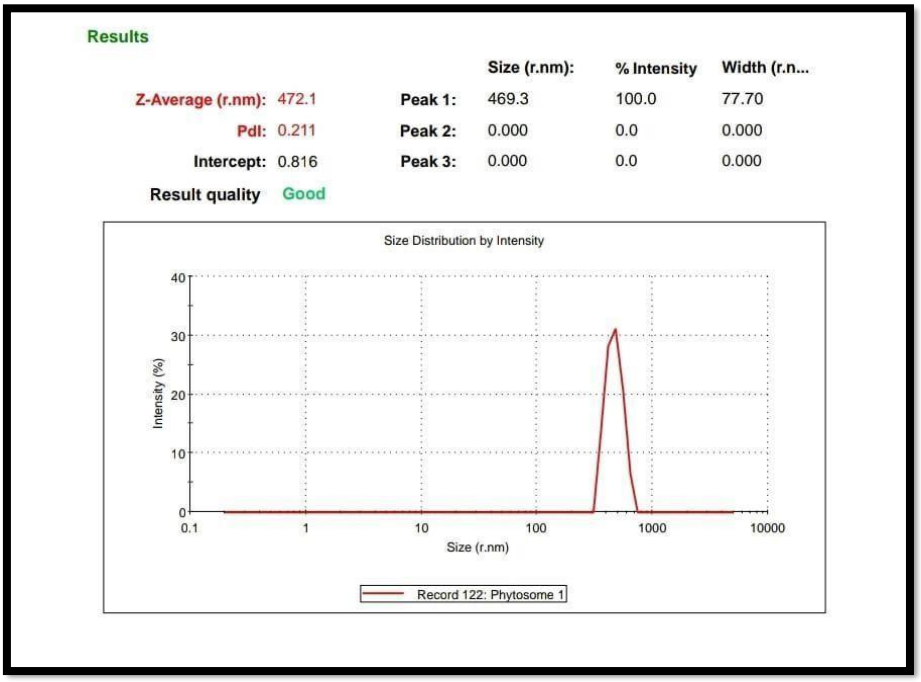
Table No 8: Results of Drug Content of Phytosomal suspension

Batch no	Drug content (%)
F1	86.85±0.13%
F2	96.38±0.35%
F3	93.42±0.19%
F4	94.47±0.52%

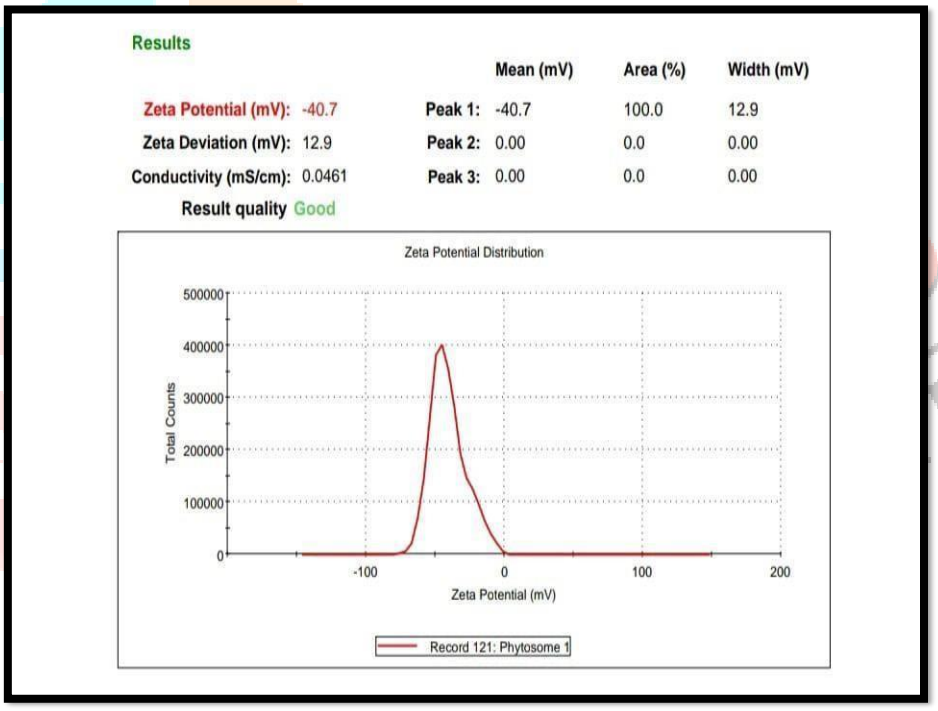
In the Drug content study , the drug content was calculated and observation were made as for formulation,F1=86.85±0.13%,F2=96.38±0.35%,F3=93.42±0.19%,F4=94.47±0.52%,respectively.it can be concluded that as F2 batch show more drug content than other batches so F2 batch is best and optimized batch.

Particle size and zeta potential analysis

The Nano Zetasizer from Malvern The zeta potential, particle size diameter, and vesicle characteristics were measured at room temperature using a Zeta Potential analyser from a dynamic light scattering apparatus. The potential for zeta and size of particles of the phytosome preparations were measured by diluting them with saline solution containing phosphate buffer (pH 7.4).The optimum 1:5 phytosome particle size is 472.1 nm, and the formulation's monodispersed nature is shown by a polydispersity index of 0.211, which is less than 1. This dispersion medium has a viscosity of 0.8872 cP. At -40.7 mV, the Zeta potential exhibits good physical stability.Both conductivity and zeta deviation were 0.0461 mS/cm and 12.9 mV, respectively.



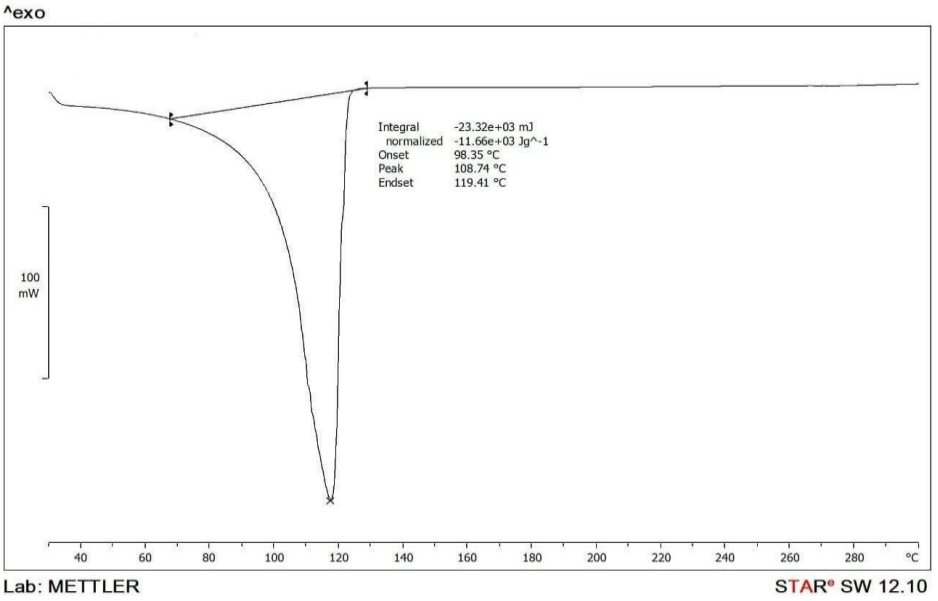
Graph No 8: Particle size of optimized phytosomes



Graph 9 : Zeta potential of optimized formulation

DSC

Studies of phytosome formulations (1:5) utilizing DSC (Pyris, Diamond Perkins Elmer, Osaka, Japan) heated with a 10 o/min heating rate from 30 to 300 o in a nitrogen atmosphere (flow rate, 20 ml/min) were conducted.Drug-specific peaks were visible in Graph 6.10 phytosomes (1:5), demonstrating the drug's physicochemical compatibility with soy lecithin.



Graph No 10: DSC of Phytosomes (1:5)

Scanning electron microscopy

In the nanoscale size range, a spherical and closed vesicular structure was shown by the SEM study. The study employed Scanning Electron Microscopy to examine the phytosomes morphology. The phytosomes is spherical in shape, distinct with strong borders, and had a big internal aqueous area, according to the SEM pictures. In Figure 1, phytosome SEM pictures were displayed. It was discovered from the SEM pictures that the spherical vesicles were in the nano range.The optimal batch (1:5) surface morphology of capsaicin phytosomes by SEM at magnifications of a) 47x, b) 850x, c) 250Xx, and d) 3000x.

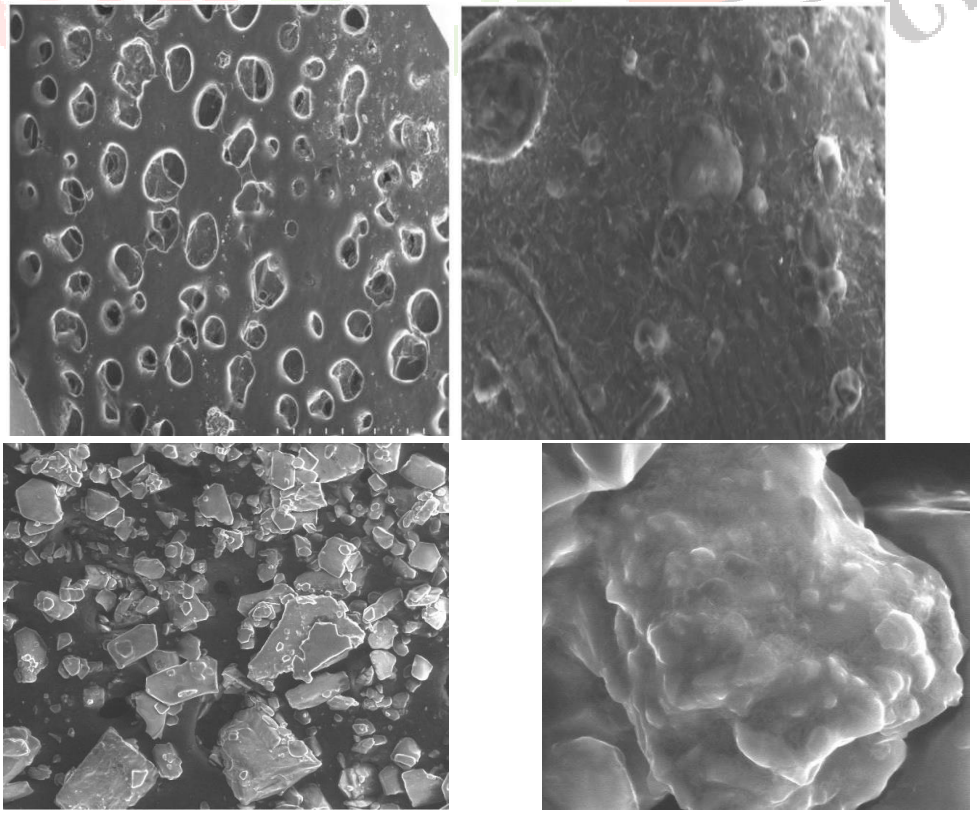


Figure No 1: SEM Image of optimised phytosomes

Evaluation of Phytosomal gel

Organoleptic Characteristics

Table No 9 : Organoleptic Characteristics of Phytosomal gel

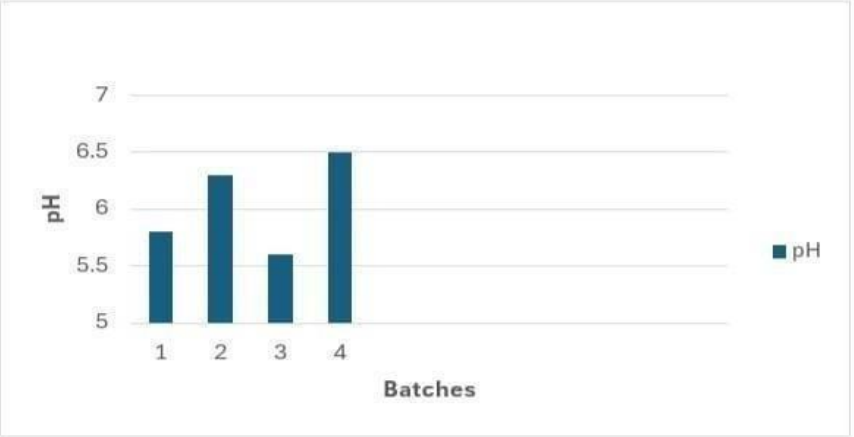
Batches	Color	Homogeneity	Consistency	Phase separation
F1	Transparent	Homogeneous	Smooth	-
F2	Transparent	Homogeneous	Smooth	-
F3	Transparent	Homogeneous	Smooth	-
F4	Transparent	Homogeneous	Smooth	-

Measurement of pH

Table No: 10 Results of pH

Formulation Batch	Measured pH
F1	5.8±0.21
F2	6.3±0.54
F3	5.6±0.35
F4	6.5±0.76

The pH of the prepared Capsaicin phytosomal gel are listed in table 6.23.their pH ranges for F1 is 5.8±0.21,F2 is 6.3±0.54,F3 is 5.6±0.35and F4 is 6.5± 0.76, all 4 batches showing similar pH as that of the skin.comparision of pH in batches is shown in graph no:6.9



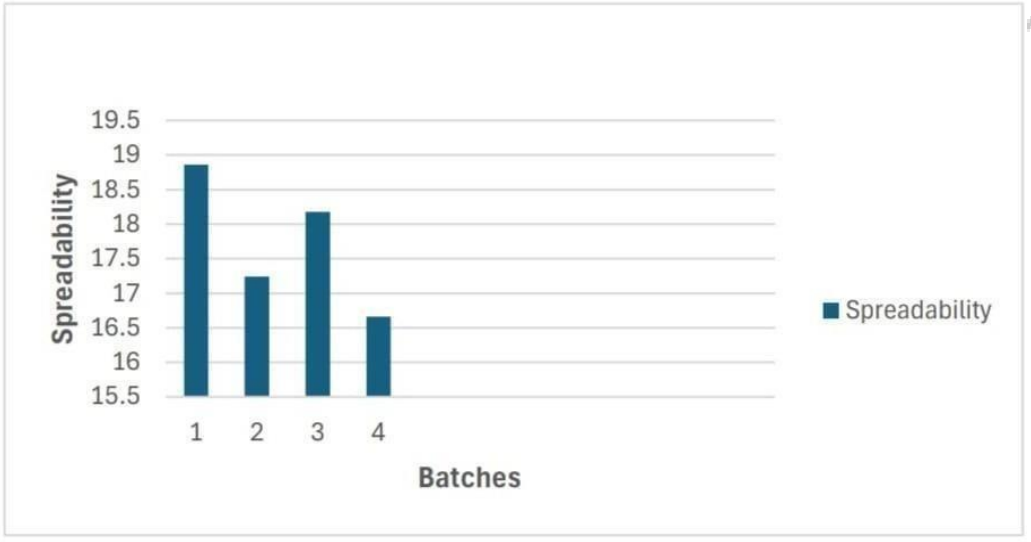
Graph 11: pH of different formulation of phytosomal gel

Spreadability

Table No 11 Result of Spreadability

Batch	Load applied (gm)	Initial radius covered by phytosomal gel	Final radius covered by phytosomal gel	Distance of spreading of phytosomal Gel	Time taken (sec)	Spreadability (g.cm/s)
F1	50	1	4.2	3.2	53	18.86±0.34
F2	50	1	4.6	3.6	58	17.24± 0.56
F3	50	1	5.2	4.2	55	18.18±0.47
F4	50	1	5.5	4.5	60	16.66±0.31

From the above study, Spreadability of phytosomal gel was studied. The Spreadability of F1 batch show good and satisfied results of spreadability as compared to other batches. The results are shown in table no : 11



Graph 12: Spreadability of batches of gel

The Spreadability of Formulation of phytosomal F1is 18.86±0.34,F2 is17.24±0.56,F3 is18.18±0.47,and F4 is 16.6±0.31.and F1 show more Spreadability 3.6 than the other batches it means the formulation easily it will spread on the skin.

Drug Content

In the drug content study ,the content of drug F1 is 98.09±0.181 %,F2 is 96.19 ±0.587 %,F3 is 95.04 ±0.852 % and F4 is 97.14±0.746 %,F1 shows more drug content than the other batches. So Batch F1 was the best optimized batch the results are shown in the table No 6.25

Table No: 12 Results of Drug Content of gel

Sr.no	Batches	%Drug Content
1	F1	98.09±0.181 %
2	F2	96.19±0.587 %
3	F3	95.04±0.852 %
4	F4	97.14±0.746 %

Viscosity determination

Table no:13 Results of Viscosity determination of phytosomal gel

Batches	RPM	Viscosity (cps)
F1	30	9661.0±0.742
F2	30	9789.1±0.542
F3	30	9760.3±0.657
F4	30	9934.2±0.620

In the viscosity determination study ,the viscosity of phytosomal gel F1 is 9661.0 cps,F2 is 9789.1cps,F3 is 9760.3 cps and F4 is 9943.2 cps,F1 shows proper and required Viscosity range according to topical drug delivery system.So the F1 batch is best and optimized batch. The results are shown in table no: 13

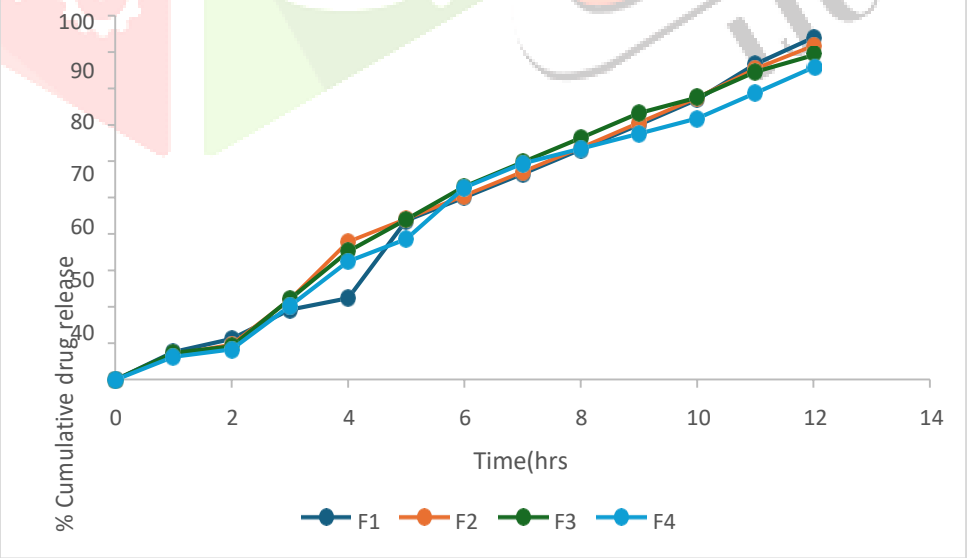
In- vitro release study

The cumulative percent drug release of formulation F1is was found to be 94.10±0.02 %, F2 was found to be 91.82±0.01% , F3 was found to be 89.30±0.01 %, F4 was found to be 85.87±0.04% after 8 hrs. Batch F1 shows 94.10±0.02 % highest drug release as as compared to other batches after 8 hrs. Thus Batch F1 is optimized batch.

Results of % CDR of different batches of phytosomal gel

Table No 14: % Cumulative Drug Release (each reading is a mean of consecative of 3 reading)

Time(hrs)	F1	F2	F3	F4
0	0	0	0	0
1	7.68±0.02	6.88±0.03	7.41±0.03	6.34±0.04
2	11.33±0.03	9.71±0.01	9.19±0.02	8.37±0.03
3	19.35±0.05	21.95±0.02	22.22±0.01	20.31±0.05
4	22.46±0.03	37.96±0.08	35.30±0.08	32.54±0.09
5	43.82±0.06	44.22±0.07	44.16±0.06	38.66±0.01
6	50.21±0.09	50.61±0.06	53.21±0.05	52.92±0.03
7	56.67±0.06	57.13±0.03	59.81±0.03	59.51±0.04
8	63.40±0.05	63.79±0.02	66.53±0.01	63.57±0.02
9	70.19±0.01	70.58±0.03	73.39±0.03	67.70±0.01
10	77.11±0.03	77.51±0.01	77.71±0.06	71.89±0.02
11	86.84±0.02	85.51±0.02	84.77±0.03	78.81±0.02
12	94.10±0.02	91.82±0.01	89.30±0.01	85.87±0.04



Graph no:13 Cumulative drug release Vs Time(hrs)

Determination of permeation coefficient, Flux and Lag time

Table No: 15 Determination of permeation coefficient, Flux and Lag time

Time(hrs)	Abs	Conc. (ug/ml)	Dilution factor	Conc.in receptor compartment(20 ml)	Cumulative amount permeated (mg)	Cumulative amount permeated per cm2
0	0	0	0	0	0	0
1	0.030	2	20	0.4	0.26	0.14
2	0.043	2.86	28.66	0.57	0.97	0.55
3	0.072	4.8	48	0.96	1.53	0.87
4	0.082	5.46	54.66	1.09	2.05	1.16
5	0.16	10.66	106.66	2.13	3.22	1.83
6	0.18	12	120	2.4	4.53	2.57
7	0.20	13.33	133.33	2.66	5.06	2.87
8	0.22	14.66	146.66	2.93	5.6	3.18
9	0.24	16	160	3.2	6.13	3.48
10	0.26	17.33	173.33	3.46	6.66	3.78
11	0.29	19.33	193.33	3.86	7.33	4.16
12	0.31	20.66	206.66	4.13	8	4.54

Area of frans diffusion cell is = 1.76 cm2 , Slope=0.015

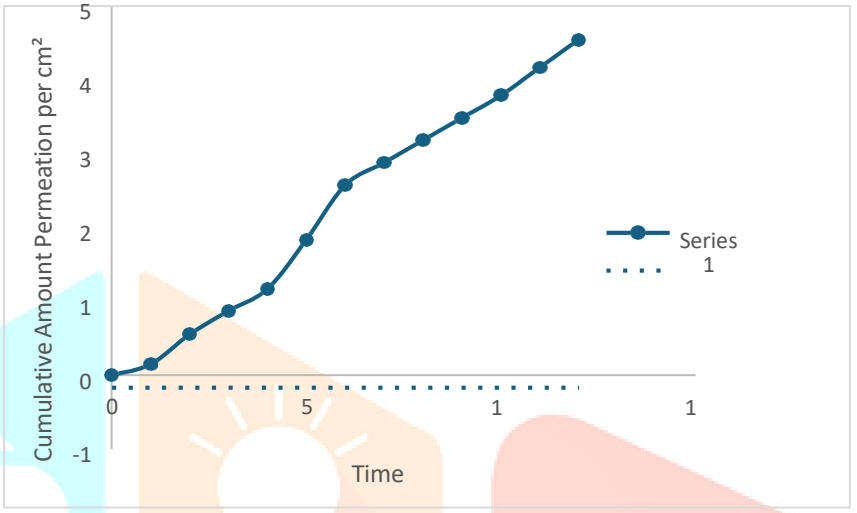
Flux (J_{SS}) = JSS is the steady state slope of line and the slope of graph cumulative amount permeation per cm2 Vs time(hrs) = 0.303 µg / cm²/min

Permeation coefficient (K_P) = JSS/CS , flux/concentration = 0.303/0.5 = 0.606 cm/min

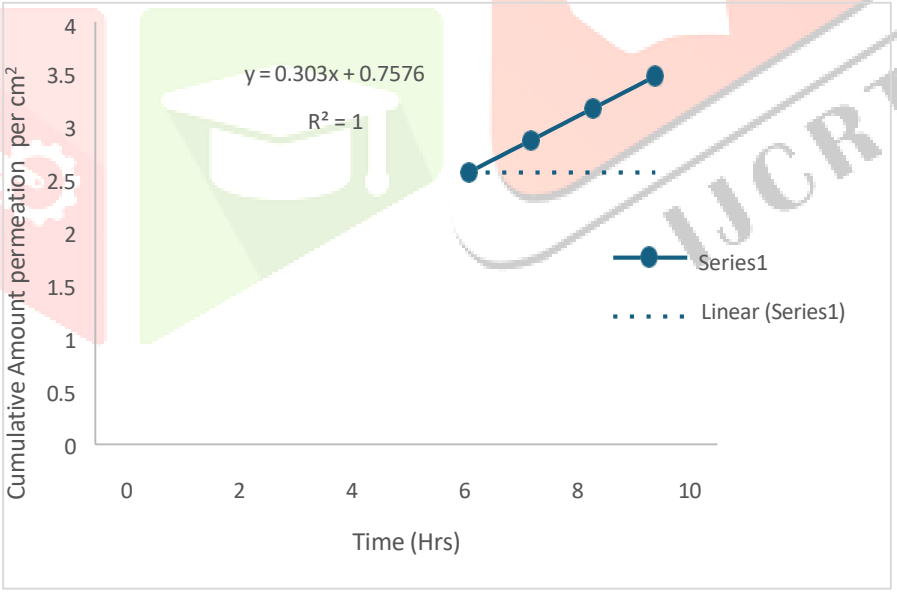
Lag time (T_{Lag}) = 60 min (1 hrs)

Table No : 16 Value of permeation coefficient flux and lag time:

Flux (J_{SS})	Permeation coefficient (K_P)	Lag time (T_{Lag})
0.303µg/ cm²/min	0.606 cm/min	120 min (2 hr)



Graph No 14 : Cumulative amount permeation per cm2 Vs time



Graph No 15 : Cumulative amount permeation per cm2 Vs time to obtained Flux Kinetics of drug release

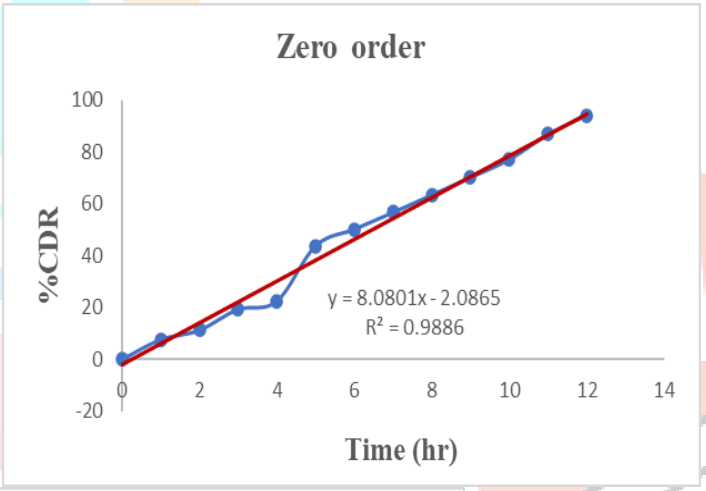
Table No 17 : Kinetics of In- vitro drug release of optimized F1 batch.

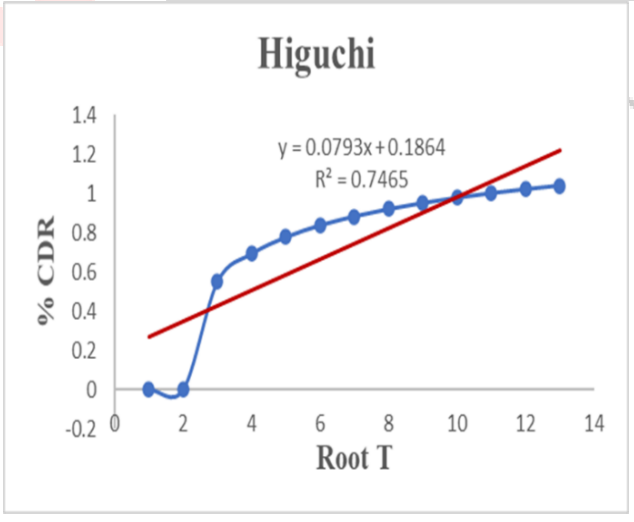
Time (hours)	Log T	Sq.rt.of T	%Cum.Drug Release	Log of % Cum.Drug Release	% Cum. Drug Retained	Log% Cum.Drug Retained	Cube root of % Cum.Drug Retained
0	0	0	0	0	100	2	4.64
1	0	0	7.68	0.8853	92.32	1.9652	4.51
2	0.3010	0.5486	11.33	1.0542	88.67	1.9477	4.45
3	0.4771	0.6907	19.35	1.286	80.65	1.9066	4.32
4	0.6020	0.7759	22.46	1.3514	77.54	1.8895	4.26
5	0.6989	0.836	43.82	1.6416	56.18	1.7495	3.82
6	0.7781	0.8821	50.21	1.700	49.79	1.6971	3.67
7	0.8450	0.9192	56.67	1.7533	43.33	1.6367	3.51
8	0.9030	0.9504	63.40	1.8020	36.6	1.5634	3.32
9	0.9542	0.9768	70.19	1.8462	29.81	1.4743	3.10
10	1	1	77.11	1.8871	22.89	1.3596	2.83
11	1.0413	1.0204	86.84	1.9387	13.16	1.1192	2.36
12	1.0791	1.0388	94.10	1.9735	5.9	0.7708	1.80

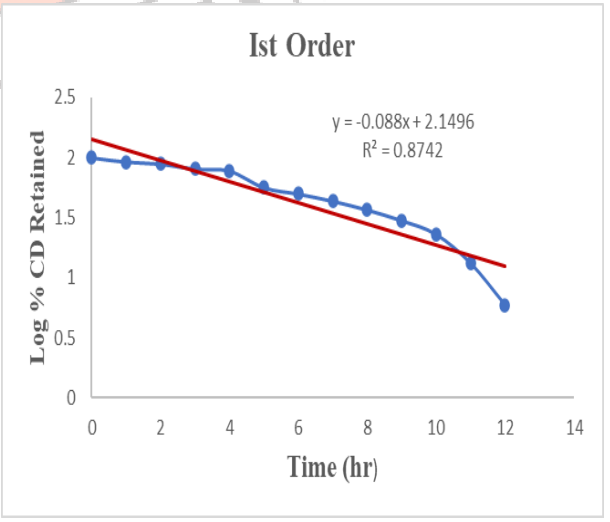
Kinetics of drug release of F1 Formulation

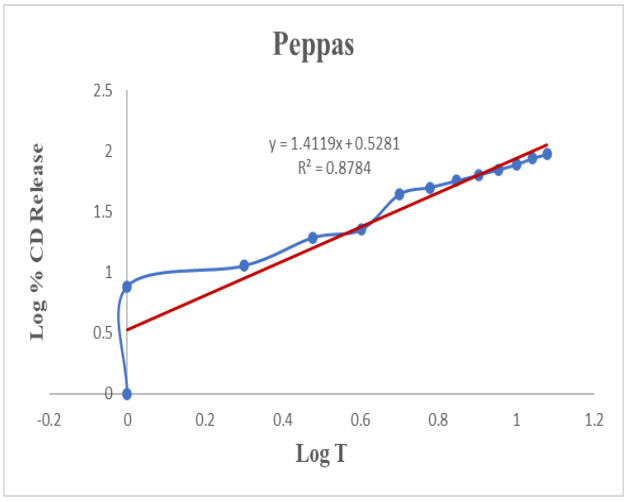
Table No 18 Kinetics of drug release of F1 Formulation

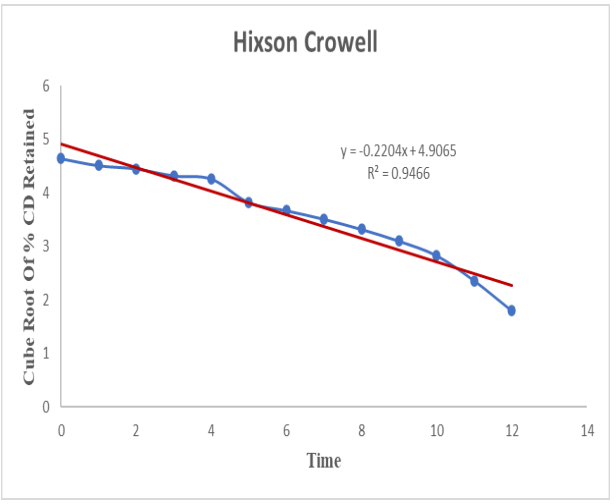
Best fit Model	Formulation code F1
Korsmeyers peppas	n 1.09 R2 0.8784
Zero-order	R2 0.9886
First order	R2 0.8742
Higuchi	R2 0.7465
Hixon crowel	R2 0.9466











Graph No 6.17 : The zero order, first order, Higuchi,Hixson crowel,and Korsmeyer peppas Release models.

For the first order, Higuchi, Hixson Crowel, zero order and Korsmeyer Peppas Release models, the data acquired for in vitro release was fitted into an equation. Depend on the value of the derived coefficients of regression, R2, the data were interpreted. Given the plots' maximum linearity and regression coefficients R square 0.9886, it was determined that zero order kinetics best explains the in vitro drug release. Using Korsmeyer-Peppas equation to analyze the release data, the release exponent and diffusion coefficients for a 'n' are 1.09. It is known that the system exhibits non-fickian diffusion when the n value is bigger than 0.45.

Stability study

Visual appearance

Throughout the whole trial period, no drug precipitation was seen under any storage circumstances, and Phytosomal Gel appeared as a clear, transparent, homogeneous gel.

Drug content

Table No 19 : Drug Content of phytosomal gel at different storage conditions

Storage conditions	Initial	10 th day drug content %	20 th day drug content %	30 th day drug content (%)
4oC	98.09±0.181	98.07±0.01	98.05±0.03	98.05±0.02
Room temperature	98.09±.181	98.06±0.03	97.05±0.09	95.0±0.04
45oC/75%RH	98.09±.181	98.03±0.03	98.00±0.02	97.01±0.03

According to the aforementioned study, the drug concentration of phytosomal gel drops between days 0 and 30 at 4°C, room temperature, 45°C, and 75% relative humidity.The table displays the findings. A one-month stability research of phytosomal gel was carried out to determine the phytosomes' capacity to hold onto an entrapped medication under specific storage conditions, such as refrigeration (4°C).at 30°C room temperature and 45°C/75% relative humidity.When stored in a refrigerator, phytosome gel remained comparatively stable.

At 4°C, the percentage of drug leakage captured in ethosomes is very low (<5%), and there is no discernible change one month later compared to right after preparation. Higher temperatures cause more medication leakage, according to the findings of drug retention studies.The influence Temperature effects on the lipid bilayers' gel to a liquid transition and possible chemical phospholipid breakdown, which leads to mistakes in membrane packing, may be the cause of drug loss from vesicles maintained at high temperatures. According to storage stability tests, the phytosomal product should be kept refrigerated because higher temperatures accelerate drug leakage.

Conclusion

Capsaicin-containing phytosomes were made using the rotary evaporation method. Discrete and spherical in shape, the phytosomes made using the rotary evaporation method were discovered. Drug absorption is enhanced by the improved particle size of the phytosomes made using the rotary evaporation process. More than -40 mV was discovered for the zeta potential, indicating improved stability. With higher polymer concentrations, the entrapment effectiveness of prepared phytosomes rises.Based on a number of factors, including drug content, entrapped efficiency, size of particles, surface shape, zeta potential, and the Rotary evaporating process, the optimal approach was determined. In vitro drug release was shown to be good, and phytosomal gel entrapped efficiency, drug content, viscosity, and spreadability were found to be higher. Stability studies for the chosen formulations were conducted; the findings indicated that the maximum drug content for them was determined to be 4˚C, and that the drug content declined at increasing ambient temperature (less than 5%) and 45°C/75% relative humidity. This indicates that phytosomal gel is more stable when kept at 4°C. Thus, the phytosomal gel loaded with capsaicin successfully controlled the release of the medication.

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