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CARICA PAPAYA: FORMULATION AND EVALUATION OF NEW DOSAGE FORM DESIGN

Swati Patil and Priyanka Ayare *

Department of Pharmacognosy, Prin. K. M. Kundnani College of Pharmacy, University of Mumbai, Cuffe Parade, Mumbai - 400005, Maharashtra, India.

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Correspondence to Author:

Priyanka Ayare

Post-Graduate Student,
Department of Pharmacognosy,
Prin. K. M. Kundnani College of
Pharmacy, Cuffe Parade, Mumbai -
400005, Maharashtra, India.

E-mail: priyanka.v.ayare@gmail.com

ABSTRACT: Phytosomes are recently introduced drug delivery system and novel botanical formulation to produce lipophilic molecular complex to improve absorption and bioavailability of phytoconstituents. The objective of the present study was to formulate and evaluate tablets of *Carica papaya* phytosomes. Solvent injection method was used for the preparation of phytosomes. *Carica papaya* phytosomes were characterized by particle size, Zeta potential, Scanning electron microscopy, Fourier Transform Infrared Spectroscopy, Differential scanning calorimetry, and *in-vitro* drug release. The results showed that the average particle size and zeta potential of the optimized phytosomes formulation were 135.8 nm and -36.7 mV. *In-vitro* drug release studies revealed that the cumulative % drug release of tablets of *Carica papaya* phytosomes was found to be 85.32%. Cytotoxic effect of aqueous extracts and phytosomes on human leukemia cell line K-562 was evaluated by performing Sulforhodamine B (SRB) assay. The GI_{50} value of aqueous extract and F2 was found to be $75.2 \mu\text{g/mL}$ and $48.4 \mu\text{g/mL}$ respectively. The result showed that the phytosomes exhibited better anticancer activity than *Carica papaya* aqueous extract. Hence it was concluded that *Carica papaya* phytosomes serve as useful novel drug delivery system and provide more bioavailability than conventional formulations.

INTRODUCTION: Most of the biologically active constituents of plants are water soluble molecules. However, these are mainly hydrophilic molecules due to that they are limited in their effectiveness and are poorly absorbed either due to their larger molecular size which cannot be absorbed by passive diffusion and due to their poor lipid solubility limiting its ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine resulting poor bioavailability of drugs ¹.

Therefore, a larger dose is usually required for dosage regimens. The effectiveness of many herbal drugs is mainly based upon delivering an effective level of the active phytoconstituents present in it ². Phytosome is cell-like structure “Phyto” means plant while “Some” means cell-like the structure; it’s a novel approach to drug delivery system. Phytosome is a vesicular drug delivery system in which phytoconstituents of herbal extracts bound by lipids ³.

When a stoichiometric amount of the phospholipid was made to react with one mole of herbal extract in an aprotic solvent, phytosomes were formed ⁴. Phytosome protect valuable component of extract from destruction by digestive secretion and gut bacteria and because of which they show better absorption which produces better bioavailability

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and improved pharmacological and therapeutic profiles than conventional herbal extract⁴.

The project was aimed at improving the release characteristics of *Carica papaya* extract by formulating *Carica papaya* phytosomes tablet. *Carica papaya* Linn. belongs to family Caricaceae. *Carica papaya* leaves contain various phyto-constituents like saponins, L-tocopherol, ascorbic acid, flavonoids, alkaloids, cardiac glycoside, tannins. Alkaloids include carpaine, pseudocarpaine, and dehydrocarpaine I and II. The *Carica papaya* leaf extract has a wide variety of pharmacological properties including anticancer, antioxidant, anti-inflammatory, antibacterial, hepatoprotective, hypoglycemic and hypolipidemic effects and increases platelet count⁵. In this study, a complex of *Carica papaya* aqueous extract and lipids were prepared, and the physiochemical properties and cytotoxicity studies of the complex were investigated⁴.

MATERIALS AND METHODS:

Materials: Hydrogenated soya phosphatidylcholine (Phospholipon 90H) was obtained as a gift sample from Lipoid GmbH (Ludwigshafen, Germany), cholesterol from Himedia Lab. Ltd. All the other chemicals and reagents used in this study were of analytical grade.

Methods:

Extraction of Leaves: Fresh leaves of *Carica papaya* were collected during July. Fresh leaves (plant authentication specimen number P 06010717) were collected, washed with water and wiped with a clean cloth to remove dust. Leaves were shade dried at room temperature and powdered using a mixer grinder. 30 g of powdered plant material was extracted with 300 ml water in an Ultrasonicator at 37 °C for 2 h. The extract thus obtained was concentrated and evaporated to dryness on a water bath maintaining the temperature at 70 °C.

Determination of λ_{max} : Concentration of 120 µg/mL of *Carica papaya* aqueous extract dissolved in 0.1N HCl and phosphate buffer pH 7.4 separately scanned over a wavelength range of 200-800 nm.

Preparation of Standard Calibration Curve of *Carica papaya* Aqueous Extract: 10 mg of *Carica*

papaya aqueous extract was dissolved in 10 ml of 0.1N HCl and phosphate buffer pH 7.4 separately to give a stock solution of 1000 µg/mL. From the stock solution, the standard solutions with concentrations ranging from 30-180 µg/mL were obtained. The absorbance of these solutions was observed at 268 nm, in triplicate against 0.1N HCl and phosphate buffer pH 7.4 separately as blank. These absorbance values were used to prepare the standard plot.

Preparation of Phytosomes Containing *Carica papaya* Aqueous Extract: Phytosomes of *Carica papaya* aqueous extract was prepared by solvent injection method. The required amount of lipids, i.e. Phospholipon 90H and cholesterol (in different ratios) were dissolved in ethanol. In another beaker, the aqueous extract of *Carica papaya* was dissolved in phosphate buffer pH 7.4. To this aqueous phase, the lipid phase was added by injection at one jet. The mixture was continued stirring for 2 h at 1200 rpm using a magnetic stirrer to allow the solvent to evaporate and to obtain uniform vesicular dispersion. The phytosomes were homogenized in a high-speed homogenizer to form small uniform size vesicles. The final formulation was freeze-dried using 10% w/v D-(+)-Trehalose dihydrate as a cryoprotectant⁶.

Characterization of *Carica papaya* Phytosomes: Measurement of Particle Size Zeta Potential Analysis: The average particle size, polydispersity index, and Zeta potential of phytosomal formulation were analyzed by Horiba Scientific SZ-100. For the measurement, the formulation was diluted with an appropriate volume of phosphate buffer pH 7.4.⁴

Determination of Entrapment Efficiency: This parameter was calculated to know the amount of aqueous extract entrapped in the phytosomes. The untrapped aqueous extract present in the supernatant was quantified by centrifugation at 12,000 rpm for 45 min⁴. After centrifugation supernatant was analyzed by UV-Visible spectrophotometer at 268 nm. The entrapment efficiency was calculated according to the following formula.

Entrapment Efficiency (%) = $\frac{\text{Weight of total drug} - \text{Weight of free drug}}{\text{Weight of total drug}}$

Differential Scanning Calorimetry (DSC): *Carica papaya* aqueous extract, Phospholipon 90H, cholesterol, and the phytosomes complex was weighed accurately into a standard aluminum pan, hermetically sealed and heated from 25 °C - 350 °C at a constant rate of 10 °C/min under constant purging with nitrogen at 20 ml/min. (Mettler Toledo DSC 60 using data recording software STAR@SW 9.20). Peak transition onset temperatures were recorded using an analyzer⁷.

Fourier Transform Infra-Red Spectroscopy (FTIR): FTIR (Shimadzu, Japan) spectral data were taken to ascertain the structure and chemical stability of *Carica papaya* aqueous extract, Phospholipon 90H, cholesterol, and phytosomes complex. Samples were crushed with KBr to get pellets at 600 kg/cm² pressure. Spectral scanning was done in the range between 4000- 400 cm⁻¹.⁷

Scanning Electron Microscopy (SEM): SEM was used to determine particle size distribution and surface morphology of the complex. Samples were studied using a JEOL JSM-6701F scanning microscope. Then the particle size of the formulation was viewed and photographed using a Scanning electron microscope (Sigma, Carl Zeiss)^{7, 8}.

In-vitro Release Studies: *In-vitro* release studies were carried out by using dialysis method (Dialysis membrane-50 with a molecular weight cut off 12000 to 14000 Da from Hi-Media Laboratories Pvt. Ltd.) using phosphate buffer pH 7.4. The prepared phytosomes (3 ml) was filled in the dialysis membrane, and both the end closed with clips and suspended in the medium. The contents were stirred at 100 rpm at 37 °C ± 0.5 °C. The aliquots of 3 ml were withdrawn at a different time interval. Fresh medium was used to replenished with an equal volume of the sample withdrawn. The aliquots were analyzed at 268 nm in UV-Visible spectrophotometer and the amount of drug released at different time intervals was calculated^{9, 10}.

Stability Studies: The optimized phytosomes formulations were stored at different temperature ranges 4°C ± 2°C, 25°C ± 2°C and physical stability of prepared phytosomes were evaluated for 3 months and studied for drug entrapment⁴.

In-vitro Cytotoxicity Activity: Cytotoxic effect of *Carica papaya* aqueous extract and phytosomes on human leukemia cell line K 562 by Sulforhodamine B (SRB) assay.

Method: The cell lines were inoculated into 96 well microtiter plates containing 10% fetal bovine serum and 2 mM L-glutamine. After cell inoculation, the microtiter plates were incubated at 37 °C, 5 % CO₂, 95% air and 100% relative humidity for 24 h. After 24 h 10, 20, 40, 80 µg/mL of different test compound concentration were added to the microtiter plates. After compound addition, plates were incubated at standard conditions for 48 h and assay was terminated by the addition of cold TCA. Cells were fixed *in-situ* by the gentle addition of 50 µl of cold 30% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 min at 4 °C. The supernatant was discarded; the plates were washed five times with tap water and air dried. The air-dried plates were stained with Sulforhodamine B (SRB) solution (50 µl), and plates were incubated for 20 min at room temperature. The unbound dye was removed by rapidly washing four times with 1% acetic acid. The bound stain was subsequently eluted with 10mM trizama base, and the absorbance was measured using a microplate reader at a wavelength of 540 nm with 690 nm reference wavelength. The percentage of growth inhibition was calculated^{11, 12}.

$$Ti / C \times 100\%$$

Where C= Control growth and Ti= Test growth in the presence of drug at the four concentration levels

Preparation of Powder Blend for Tablet: *Carica papaya* aqueous extract phytosomal complex tablets were prepared by direct compression technique. All the ingredients were thoroughly mixed. Then the powder was passed through sieve mesh 40# to get the uniform size of particle¹³.

Pre-compression Parameter of Blended Powder: Pre-compression parameters of blended powder were carried out. These included bulk density, tap density, Carr's index, Hausner's ratio, the angle of repose¹³.

Formulation *Carica papaya* Phytosomes Tablet: *Carica papaya* aqueous extract phytosomal

complex tablets were prepared by direct compression technique. All the ingredients were thoroughly mixed. Then the powder was passed through sieve mesh 40# to get the uniform size of the particle.

TABLE 1: COMPOSITION OF CARICA PAPAYA PHYTOSOMES TABLETS

Ingredients	Quantity (%)
<i>Carica papaya</i> phytosomes	29
Avicel PH 102	45
Anhydrous lactose	23
Aerosil 200	0.8
Talc	0.8
Total (mg)	340

Talc was finally added as glidant and lubricant respectively. The powders were compressed using the tablet compression machine¹³.

Evaluation of *C. papaya* Phytosomes Tablets:¹³⁻¹⁷

Weight Variation: The weight variation test was carried out for 20 tablets randomly by weighing each tablet individually, and their average weight was calculated.

Thickness and Diameter: Thickness and diameter of the tablet were determined using Vernier Callipers and expressed in mm.

Hardness Test: Hardness of the tablet was determined by using the Monsanto hardness tester and expressed in kg/cm².

Friability Test: Tablet strength was tested by using Roche Friabilator. The percentage of weight loss was calculated by weighing the tablets again. The % friability was then calculated by

$$\% \text{ Friability} = [(W1-W2)/W1] \times 100$$

Where, W1= weight of tablets before the test, W2 = weight of tablets after the test.

Disintegration Time: The disintegration test was carried out using the disintegration test apparatus. This test was carried out at 37 °C ± 2 °C in 900 ml distilled water. Six tablets were placed individually in each tube of the disintegration test apparatus, and discs were placed over each tablet to prevent them from floating. The time taken for each tablet to disintegrate completely was recorded.

In-vitro Dissolution Study of Phytosome Tablet:

In-vitro dissolution studies for the prepared phytosomal complex tablet formulations were carried out using type-II apparatus at 50 rpm. The dissolution media used was 900 ml of 0.1N HCl, and phosphate buffer pH 7.4 media were used as dissolution media for first two hours and the next 24 h respectively and maintained at 37 °C ± 0.5 °C. 5 ml aliquots were withdrawn at the specified time intervals. An equal volume of fresh media was replenished after each sampling to maintain the constant volume of the medium. The samples were analyzed at 268 nm using UV-visible spectrophotometer.

RESULTS AND DISCUSSION:

Determination of λ_{\max} : The concentration 120 µg/mL of *Carica papaya* aqueous extract in 0.1N HCl and phosphate buffer pH 7.4 was found to be 268 nm.

Standard Calibration Curve of *Carica papaya* Aqueous Extract in UV Spectrophotometer: The UV absorbance of *Carica papaya* aqueous extract standard solution in the range of 30-180 µg/mL in 0.1N HCl and phosphate buffer pH 7.4 showed linearity at λ_{\max} 268 nm. The linearity was plotted for absorbance against concentration with R² value 0.998 for 0.1N HCl and 0.998 for phosphate buffer pH 7.4.

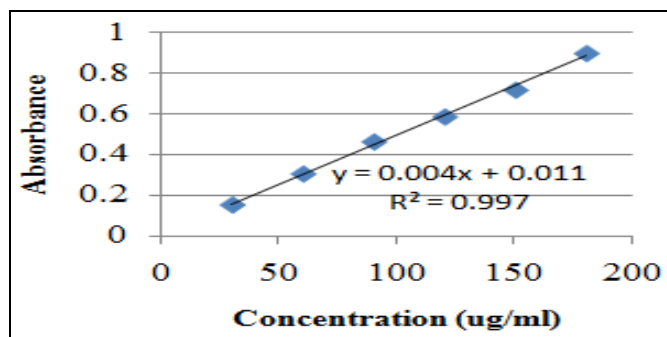


FIG. 1: CALIBRATION CURVE OF CARICA PAPAYA AQUEOUS EXTRACT IN 0.1N HCl

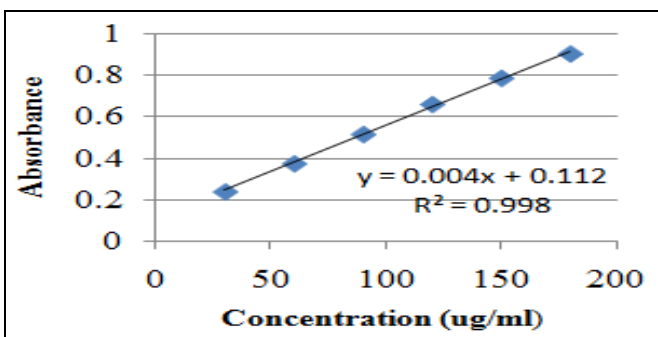


FIG. 2 CALIBRATION CURVE OF CARICA PAPAYA AQUEOUS EXTRACT IN PHOSPHATE BUFFER pH 7.4

Preparation of Phytosomes Containing *Carica papaya* Aqueous Extract: Phytosomes of *Carica papaya* aqueous extract was successfully prepared by solvent injection method in the ratios of 1:1, 1:2, 1:3, 1:4, 2:1, 2:2. The formulation compositions were given in **Table 2**. Phytosomes of *Carica*

papaya aqueous extract were optimized based on the effective concentration of aqueous extract and phospholipids, cholesterol ratios⁴. After freeze-drying using 10% w/v D-(+)-Trehalose dihydrate as a cryoprotectant phytosomes were found to be as free-flowing powder.

TABLE 2: FORMULATION COMPOSITIONS OF *CARICA PAPAYA* LEAVES EXTRACT PHYTOSOMES

Formulation code	Ingredients		
	Aqueous extract: Lipid: Cholesterol ratios	Phosphate buffer pH 7.4 (ml)	Ethanol (ml)
F1	1:1:0.3	14	6
F2	1:2:0.3	14	6
F3	1:3:0.3	14	6
F4	1:4:0.3	14	6
F5	2:1:0.3	14	6
F6	2:2:0.3	14	6

Characterization of *Carica papaya* Phytosomes: Measurement of Particle Size and Zeta Potential: The average particle size of *Carica papaya* aqueous extract phytosomes with Phospholipon 90H and cholesterol ratio of 1:2:0.3

formulation (F2) was found to be 135.8 nm, and the polydispersity index value was 0.540 and Zeta potential value was found to be -36.7 mv indicating good stability of the formulation. The results were graphically represented in **Fig. 3** and **4**.

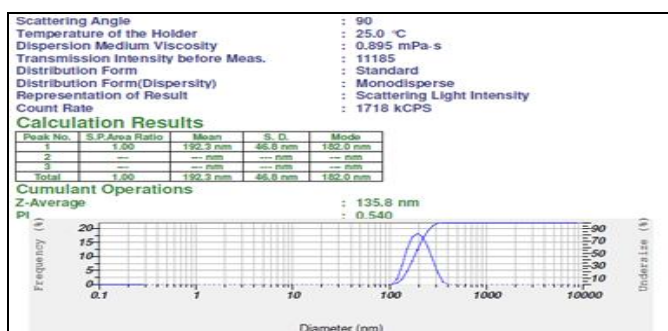


FIG. 3: PARTICLE SIZE PREPARED OF *CARICA PAPAYA* PHYTOSOMES

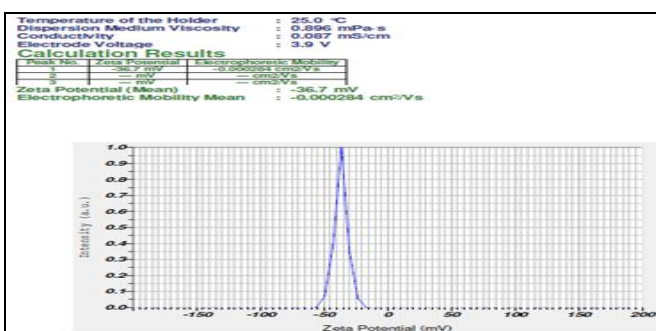


FIG. 4: ZETA POTENTIAL OF *CARICA PAPAYA* PHYTOSOMES

Entrapment Efficiency: The maximum drug entrapment was shown by F2. The entrapment efficiency of all formulations was graphically represented in **Fig. 5**.

of *Carica papaya* aqueous extract phytosomes. With further increase in the lipid concentration, the entrapment efficiency decreased indicating that the lipid concentration did not help in entrapping the drug into the matrix⁴.

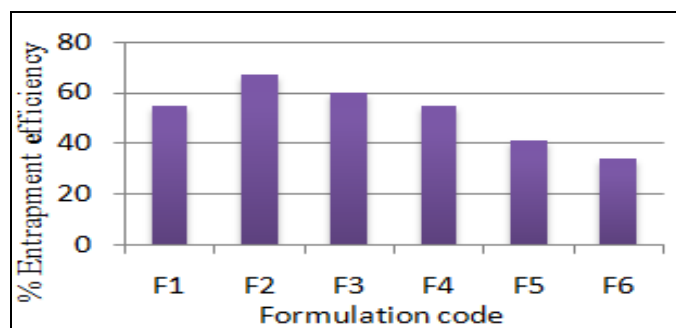


FIG. 5: GRAPHICAL REPRESENTATION OF ENTRAPMENT EFFICIENCY OF *CARICA PAPAYA* PHYTOSOMES

The formulation F2 showed highest release entrapment efficiency of 67% indicating the optimum amount of lipid required for the formation

Differential Scanning Calorimetry: The DSC thermograms of *Carica papaya* aqueous extract, Phospholipon 90H, cholesterol, and the prepared *Carica papaya* aqueous extract phytosomes were displayed in **Fig. 6**. The *Carica papaya* aqueous extract revealed two peaks, endothermic peak around 79.7 °C and at 212.8 °C. This is associated with second-order phase transition such as glass transition¹⁸. Phospholipon 90H showed two sharp endothermic peaks at 125.2 °C and 182.5 °C, respectively. The first peak at 125.2°C is likely due to the melting of phospholipid. The second peak at 182.5 °C appears to be due to the phase-transition from gel to a liquid-crystalline state, and the

carbon-chain in the phospholipid may have perhaps undergone other isomeric or crystal changes¹⁹. Cholesterol showed sharp endothermic peaks at 153.21 °C, indicating its melting point²⁰. In the phytosome formulation, two peaks are observed at

117.6 °C and 125.9 °C. This may be due to the melting of the lipid component and their interaction with aqueous extract. This suggests that the aqueous extract has been entrapped into the lipid vesicles.

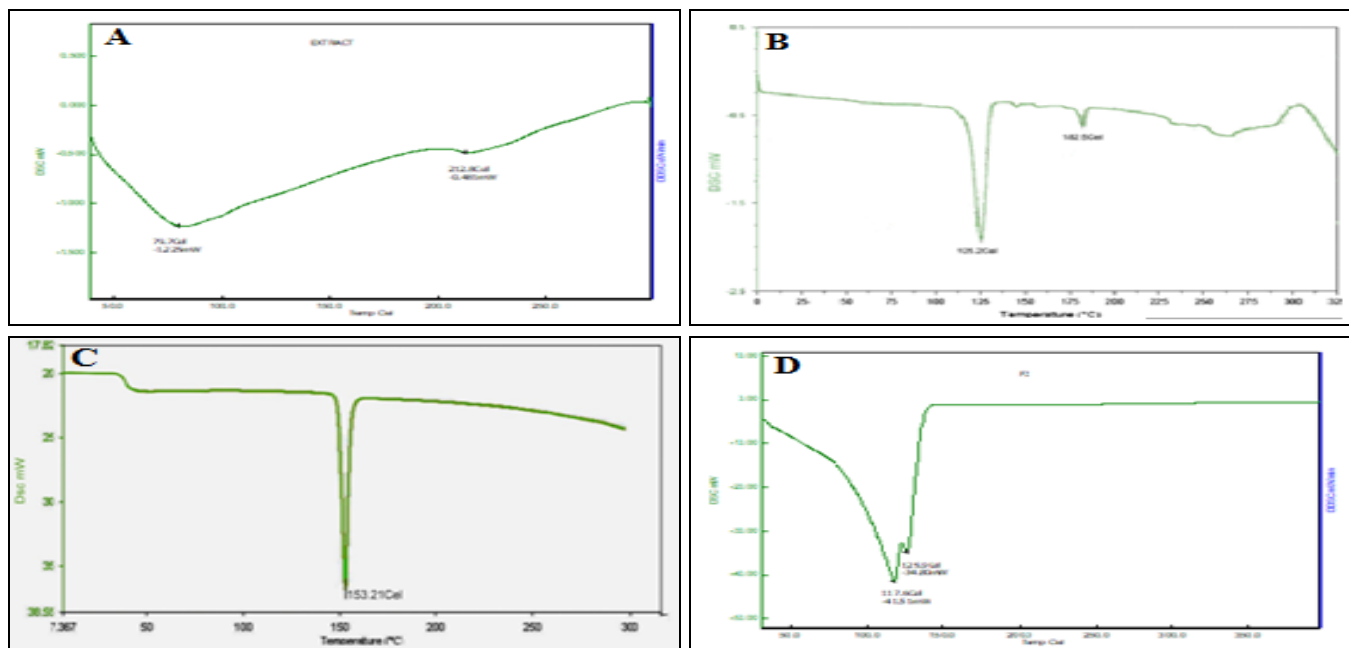


FIG. 6: DSC THERMOGRAM OF A) *CARICA PAPAYA* AQUEOUS EXTRACTS B) PHOSPHOLIPON 90 H C) CHOLESTEROL D) *CARICA PAPAYA* AQUEOUS EXTRACT PHYTOSOMES

Fourier Transform Infra Red Spectroscopy: FTIR spectrum of *Carica papaya* aqueous extract, phospholipon 90H, cholesterol, and the prepared phytosomes are shown in Fig. 7. In FTIR spectroscopy the peaks were found in the *Carica*

papaya aqueous extract, phospholipon 90H, cholesterol remained consistent in the phytosomes which confirmed the absence of any chemical interaction between the aqueous extract and lipids⁴.

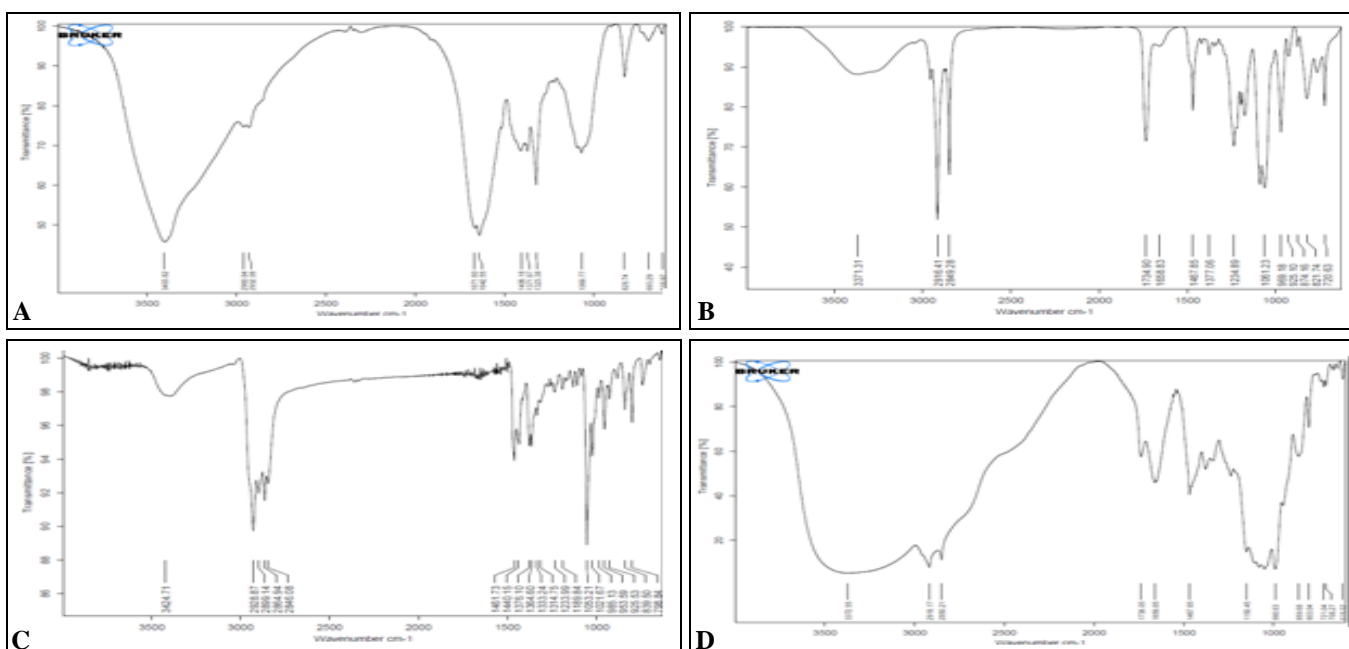


FIG. 7: FTIR SPECTRA OF A) *CARICA PAPAYA* AQUEOUS EXTRACT B) PHOSPHOLIPON 90 H C) CHOLESTEROL D) *CARICA PAPAYA* AQUEOUS EXTRACT PHYTOSOMES

Scanning Electron Microscopy (SEM): The surface morphology, shape, and structure of the phytosome complex of *Carica papaya* aqueous extract are shown in Fig. 8. ⁷ The results indicated that the particles were round and homogeneous with a rough surface.

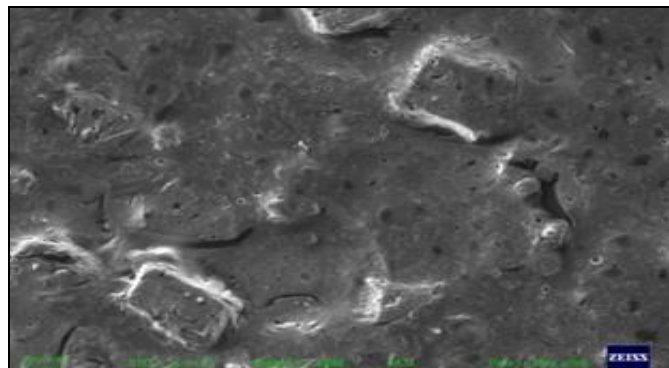


FIG. 8: SEM IMAGE OF CARICA PAPAYA PHYTOSOMES

In-vitro Release Studies: The % cumulative release of all batches was 62.57-86.34% which is shown in Fig. 9. The cholesterol and phospholipid concentration affects the drug release. The formulation F2 with 6 mg cholesterol and 20mg phospholipid showed the highest release, i.e. 86.34% as shown in Fig. 9. This highest release pattern of formulation F2 is due lowest particle size. The release from F2 and *Carica papaya* aqueous extract was found to be 86.34% and 45.98% respectively at the end of 24 h study.

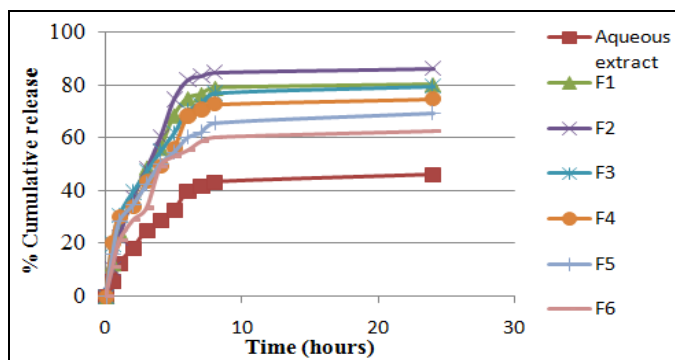


FIG. 9: IN-VITRO RELEASE FROM PHYTOSOMES FORMULATION AND CARICA PAPAYA AQUEOUS EXTRACT

Stability Studies: *Carica papaya* aqueous extract phytosomal formulations (F2) were stored at room temperature and refrigerated temperature for 3 months and entrapment efficiency was determined. At the temperature of 4 °C ± 2 °C, there was no significant change in the entrapment efficiency of phytosomal formulation. There was a decrease in entrapment at 25 °C ± 2 °C after 1 month. Thus, it can be stated that F2 showed good storage stability at 4 °C ± 2 °C.

In-vitro Cytotoxicity Activity: *Carica papaya* aqueous extract and phytosomes formulation were evaluated and compared for anticancer activity. GI50 value of aqueous extract and F2 was found to be 75.2 µg/mL and 48.4 µg/mL resp. when compared with standard anticancer drug Adriamycin having GI₅₀ value of <10 µg/mL.

Hydrogenated phosphatidylcholine being a constituent in the phospholipid taken for study acts as a selective carrier allows the molecule to have both an improved crossing through the gastrointestinal mucosal layer and with better permeability into the cells leading to increased cellular uptake. Due to the surfactant properties of phospholipid, the product is better adhered to the mucosal surface and makes it easy for the complex product to better interact with cell structure ¹⁹.

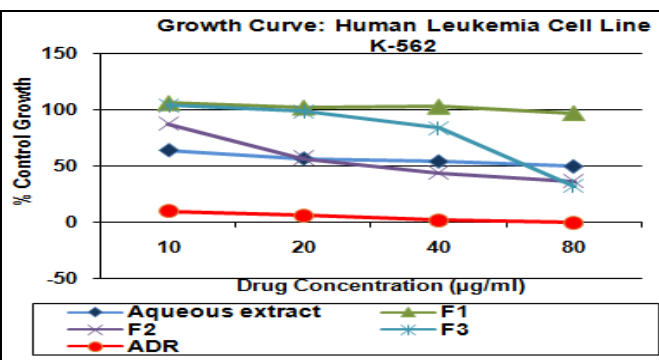


FIG. 10: COMPARATIVE % CONTROL GROWTH BY AQUEOUS EXTRACT OF CARICA PAPAYA AND ITS PHYTOSOMES FORMULATIONS

TABLE 3: RESULT FOR % CONTROL GROWTH OF HUMAN LEUKEMIA CELL LINE K-562 BY AQUEOUS EXTRACT AND PHYTOSOMES FORMULATION

	Human Leukemia Cell Line K-562															
	% Control Growth															
	Drug Concentrations (µg/ml)															
	Experiment 1				Experiment 2				Experiment 3				Experiment 4			
	10	20	40	80	10	20	40	80	10	20	40	80	10	20	40	80
Aq.ext	66.1	54.6	55.2	59.4	57.3	50.2	49.7	45.5	69.5	66.4	58.6	45.7	64.3	57	54.5	50.2
F1	110.3	105.8	104.7	105.7	97.2	93.4	98.2	88.6	111.1	107.2	106.4	97.1	106.2	102.1	103.1	97.2

F2	93.6	61.7	50.7	50.7	81.6	39.5	31.7	22.6	87.7	70.9	51.2	37.2	87.6	57.4	44.5	36.8
F3	104.6	100.4	93.6	39.5	98.6	89.3	75.3	26.7	109.2	107.2	83.1	31.2	104.1	99.0	84	32.4
ADR	11.0	9.3	46.2	4.3	5.7	-7.0	-10.6	-8.8	13.9	16.0	8.0	3.4	10.2	6.1	2.2	-0.4

In-vitro cytotoxicity results indicate that F2 was found to be more potent than aqueous extract showing less GI₅₀ value. This further strengthens the fact that phytosomes are the herbal products wherein the individual components of herbal extracts bind to phosphatidylcholine matrix and produce a dosage form which shows better anticancer activity and bioavailability as compared to *Carica papaya* aqueous extract²¹.

Pre-compression Parameter of Blended Powder and Evaluation of Tablet: The results of the angle of repose, Carr's index and Hausner's ratio indicated that the powder mixtures possess good flow properties and better compressibility of the blend and also suited for the compression process. The physical property of the tablet was determined, and the results of the uniformity of weight, hardness, drug content and friability of the tablets are given in **Table 4**. Tablets pass the weight variation test and uniformity in content as per the limits prescribed in IP. Disintegration time indicates that the tablets are having sufficient strength to withstand physical abrasion¹³.

TABLE 4: PHYSICAL PARAMETERS OF *CARICA PAPAYA* PHYTOSOMES TABLETS

Evaluation parameter	Formulation
Weight variation (mg)	340
Diameter (mm)	9 ± 0.01
Thickness (mm)	3 ± 0.02
Hardness (kg/cm ²)	5.50 ± 0.50
Friability (%)	0.3 ± 0.12
Disintegration (sec)	330

TABLE 5: PRE-COMPRESSION PARAMETERS OF POWDER

S. no.	Parameters	Results	Inference
1	Bulk density (g/cm ³)	0.55	Pass
2	Tapped density(g/cm ³)	0.607	Pass
3	Carr's index (%)	10.36	Excellent
4	Hausner's ratio	1.10	Poor
5	The angle of repose (θ)	24.55	Good

***In-vitro* Dissolution Study of Phytosome Tablet:**

In-vitro dissolution study was carried out as mentioned in the procedure discussed above in 0.1N HCl and phosphate buffer pH 7.4. The phytosomes complex tablets showed 21% release in 2 h in 0.1N HCl while the marketed tablets showed 81% release in 2 h in simulated stomach pH media.

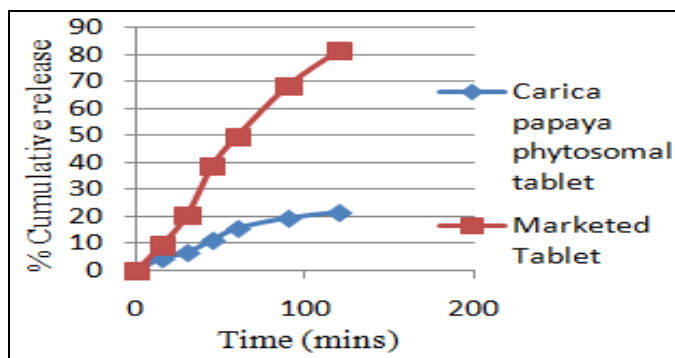


FIG. 11: IN-VITRO RELEASE FROM PHYTOSOMES COMPLEX TABLETS, MARKETED TABLET IN 0.1N HCl

In the physiological conditions simulated by phosphate buffer pH 7.4, phytosomes complex tablets showed 85.32% release in 24 h in while the marketed tablets showed 97.3% release in 6 h. The *Carica papaya* phytosomal tablet was found to release the drug in a sustained manner compared to a conventional marketed tablet which contains only *Carica papaya* aqueous extract.

CONCLUSION: *Carica papaya* extract was formulated as phytosomes. The best formulation

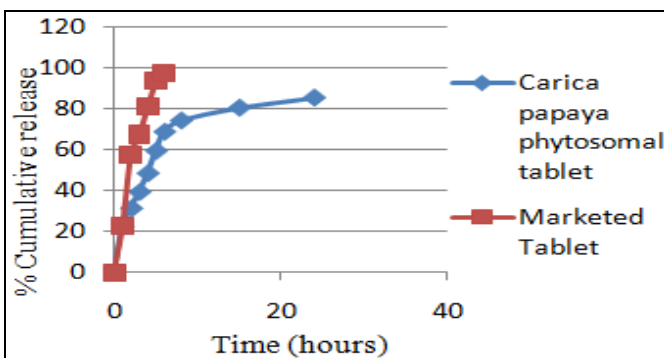


FIG. 12: IN-VITRO RELEASE FROM PHYTOSOMES COMPLEX TABLETS, MARKETED TABLET IN PHOSPHATE BUFFER pH 7.4

selected ratio 1:2 for the final formulation. These phytosomes were formulated into a tablet. The new formulation showed maximum drug release when compared to existing marketed tablet formulation. The phytosomes exhibited better anticancer activity than the extract.

Hence, it may be concluded that the phytosome tablet may show increased potency in dengue fever treatment due to increase bioavailability.

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CONFLICT OF INTEREST: None of the authors has any conflict of interest in the context of this work.

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