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# Formulation and evaluation of curcumin phytosomes

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## ABSTRACT

**Aim:** The aim of the present study was an attempt to prepare and evaluate Curcumin phytosomes by using Soya lecithin as a polymer for treating the Cancer potentially.

**Methodology:** The formulation FA1 to FA5 were prepared by Reflux method and the formulation FB1 to FB5 were prepared by Rotary evaporation methods, by varying theconcentration of polymer, which were significantly affect the *in vitro* drug release. The *in vitro* drug release studies were carried out by using phosphate buffer pH 6.8.

**Results:** Drug and physical mixture were characterized by FTIR, the result of FTIR study showed that no interaction between drug and polymer. The *in vitro* drug release and release kinetics of formulations showed controlled release. The other formulation parameters of formulated Phytosomes were evaluated which showed better results.

**Conclusion:** It was concluded that the formed Phytosomes showed prolonged drug release. Curcumin Phytosomes promote a fast and effective action against the Cancer. From the *in vitro* drug release and release kinetics studies it can be concluded that the formulation FB5 prepared by Rotary evaporation method has better potential of controldrug release than Reflux method.

**Keywords:** Curcumin, Phytosomes, controlled drug delivery, Soya lecithin.

## INTRODUCTION

Cancer is a disease of the cells, which are the body's basic building blocks. Thebody constantly makes new cells to help us grow, replace worn-out tissue and heal injuries. Normally, cells multiply and die in an orderly way. Some times cells don't grow, divide and die in the usual way. This may cause blood or lymph fluid in the body to become abnormal, or form a lump called a tumor. Atumor can be benign or malignant:

### Principle of Phytosome Technology

The phytochemical constituents (flavonoids and terpenoides) of the extracts provide them for the direct complexation with Phosphatidylcholine. Phytosome results from the reaction of a stoichiometric amount of the phospholipid with the standardized extract or polyphenolic constituents in a non-polar solvent. The Phosphatidylcholine is a bi-functional compound composed of lipophilic phosphatidyl moiety and the hydrophilic choline moiety. The choline head of phosphatidylcholine molecule binds to phytocomponent while the lipid soluble phosphatidyl portion comprises the body andtail which then envelops the choline bound material. Hence, the Phytoconstituents build up a lipid compatible molecular complex with phospholipid also called as phyto-phospholipid complex.[1]

### Properties of Phytosomes

Following are some of the important properties of phytosomes

### Physico-chemical properties

Phytosome are prepared by reaction of stoichiometric amount of phospholipid with the standardized plant extracts as substrate. The spectroscopic data revealsthat the phospholipid substrate interaction is due to the formation of hydrogen bond between the polar head (i.e., phosphate and ammonium group) and the polar functionalities of the substrate. [2] The size of Phytosome varies from 50 nm to a few hundred µm. [3] Phytosome when treated with water assumes a micellar shape resembling liposome and photon correlation spectroscopy (PCS) reveals this liposomal structures acquired by phytosome.[4] The complexes are often freely soluble in aprotic

solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol. But the phytosomesof certain lipophilic phytoconstituents like curcumin has shown increase in watersolubility upon complexation with phospholipid. [5]

### Biological properties

Phytosome are novel complexes which are better absorbed and utilized; hence theyproduce more bioavailability and better result than the conventional herbal extract or non-complex extracts, which has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects.[5] A phytosome is a complex of a natural active ingredient and a phospholipid mostly lecithin. It is claimed that phytosome increases absorption of "conventional herbal extracts" or isolated active principles both topically as well as orally. The phytosome beneficially alter the absorption of a drug, thus enhancing its bioavailability.[6]

Curcumin is a potent herbal medicine found in turmeric rhizomes and used for the treatment of cancer, and it has become a leading component in combined chemotherapy commonly referred as highly active anticancer therapy. Keeping in mindthe promise of Curcumin as a therapeutically active agent and its poor oral absorption due to its limited aqueous solubility and extensive presystemic metabolism, it is necessary to develop a new formulation of curcumin that could augment its oral absorption and enhance its therapeutic activity.[7]

Phospholipids are lipids that contain phosphorus, a polar and nonpolar part in their structure. Phospholipids can be divided into glycerol phospholipids and sphingomyelins according to the phospholipids alcohols, the phospholipids mostly selected for phytosome preparations are selected from group consisting of soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidyiserine.[8]

Hence in the present work, an attempt is made to provide phytosome containingCurcumin using lecithin phospholipids by using different methods having the followingadvantages.

- Improve the permeability of the drug.
- Prolonged therapeutic effect.
- Decreased frequency of drug administration.
- Patient compliance can be improved.

## METHODOLOGY

### PREFORMULATION STUDIES

### Melting point determination

Capillary method was used for the determination of melting point of Curcumin.A few crystals of compound are placed in a thin walled capillary tube of about 10-15 cm long and 1 mm inside diameter and closed at one end. The capillary which containsthe sample and a thermometer are then suspended in to an oil bath containing liquid paraffin. So they can be heated slowly and evenly. The temperature range over which the sample is observed to melt is taken as the melting point.

### Solubility analysis

Solubility analysis was carried out in 10 mg of Curcumin was dissolved in 10 ml of water. Solubility was determined on the basis of physical appearance.

### Drug-Excipients interactions studies by FTIR.

Drug-excipients compatibility studies were carried out using FT-IR. Infrared spectrum of pure drug (Curcumin), Soya lecithin and physical mixture of Curcumin andSoya lecithin 1:5, was recorded by using the potassium bromide (KBr) disk technique.FT-IR measurement over the range of 4000-500 $cm^{-1}$ is performed with FTIR 8400S.

### Determination of λmax

Curcumin 10 µg/ml concentration was prepared in pH 6.8. The solution was scanned from 400-800nm by UV spectrophotometer and a spectrum was observed for absorption maxima.

### Standard calibration curve of Curcumin

Calibration curve was constructed in phosphate buffer of pH 6.8. 100 mg of accurately weighed Curcumin was issolved and the volume ismade up to 100 ml with phosphate buffer pH 6.8 and used as standard stock solution. 10 ml of the above solution was diluted to 100 ml phosphate buffer pH 6.8 and used as working stock solution. From the above solution10, 20, 30, 40, 50 and 60µg/ml UV spectrophotometer at λmax 426nm. Calibration curve was plotted between concentration and absorbance and $r^2$ value of this graph was calculated to check the linearity of the absorbance against concentration.

### Evaluation of Curcumin Phytosomes

### DSC investigation of optimized formulation

Drug encapsulation study was also performed by Differential Scanning Calorimetry (DSC). Thermal characteristics of the optimized were performed byusing an automatic thermal analyzer system (Mettler DSC 823, Germany). The entire samples were run at a scanning rate of 10°C per min from 25 - 300°C.

### Percentage yield

Percentage practical yield is calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production.Practical yield was calculated as the weight of phytosomes recovered from each batchin relation to the sum of starting material. The percentage yield of prepared phytosomes was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

## Percent Drug content

The drug content in each formulation was determined by weighing phytosomesequivalent to 100mg of Curcumin and dissolving in 100 ml of 6.8 pH phosphate buffer,followed by stirring. The solution was filtered through a 0.45µ membrane filter, dilutedsuitably and the absorbance of resultant solution was measured spectrophotometricallyat 426 nm using 6.8 pH phosphate buffers as blank. The drug content of the prepared phytosomes was determined by the formula:

$$\text{Drug content (\%)} = \frac{\text{Weight of drug in phytosomes}}{\text{Weight of phytosomes}} \times 100$$

## Entrapment efficiency

The entrapment efficiency is also known as Association Efficiency. The drug loaded phytosomes were centrifuged at a high speed of 3500-4000 rpm for 30 min andthe supernatant is assayed for non-bound drug concentration by UV spectrophotometer. The percentage Drug Entrapment Efficiency (DEE) wascalculated as follows:

$$\text{\% Entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

## Particle size analysis

The particle size should be less than 1000 nm in phytosomes. It can beanalyzedby using Microtrac particle size analyzer. Particles in the size range of colloids displayconstant random thermal motion which is known as Brownian motion. This motion causes the intensity of light scattered by the particles to varywith time. The largerthe particle slower their motion and hence the smaller the variation in intensity of light scattered. Photon correlation spectroscopy uses the rate of change in the intensity to determine the size distribution of particles. The zeta analyzer has a correlator with 64 channels. Each of this channel measures changes in light fluctuation over a defined timespan.

## Zeta potential measurement

The zeta potential of phytosomes is commonly used to characterize the surface charge property of phytosomes. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Zeta potential is also an important parameter to evaluate and establish an optimum condition for stability of colloidal or dispersed systems. The surface charge on the microscope particle produced a difference in the electric potential in milli volts betweenthe surface of each particle and bulk of the suspending liquid. That differenceis called as zeta potential.A zeta potential, measure the effect of electrostatic charges; this is thebasis force that cause the repulse between adjacent particles. Net results are attraction or repulsion depends upon the magnitude of both forces. Thumb rule describes the relation between zeta potential determination responses of the suspension being tested, particularly hydrophobic colloids. The prepared phytosomes suspensions were characterized with respect to zeta potential by using zeta potential analyzer (Microtrac Zeta sizer).

**Table 1: Thumb Rule for zeta potential**

| Zeta Potential(mV) | Stability behavior of the colloid |
|---|---|
| From 0 to ± 5 | Rapid coagulation or flocculation |
| From ± 10 to ± 30 | Incipient instability |
| From ± 30 to ± 40 | Moderate stability |
| From ± 40 to ± 60 | Good stability |
| More than ± 61 | Excellent stability |

The electrophoretic mobility and zeta potential were measured using a zeta potentiometer (Microtrac Zeta sizer). To determine the zeta potential, phytosomes sample were diluted with KCl (0.1 Mm) and placed in the electrophoretic cell where anelectric field of 15.2 V/cm was applied. Each sample was analyzed in triplicate.

## Scanning electron microscopy (SEM)

Surface morphology of the specimen will be determined by using a scanningelectron microscope. The sample is dried thoroughly in vaccum desicator before mounting on brass

specimen studies, using double sided adhesive tape. Gold palladium alloy of 120°A Knees was coated on the sample sputter coating unit (Microtrac ltd) in Argon at ambient at ambient of 8-10°C with plasma voltage about 20mV. The sputtering was done for nearly 5 minutes to obtain uniform coating on the sample to enable good quality SEM images.

### *In vitro* drug release studies

The release of drug was determined by using the egg membrane mounted on theone end of open tube, containing drug equivalent to10 mg of formulation. The dialysistube was suspended in 250 ml beaker, containing 200 ml PBS (pH 6.8). The solution was stirred at 200 rpm with the help of magnetic stirrer at 37±0.5°C. Perfect sink conditions were maintained during the drug release testing. The samples were withdrawn at suitable time interval at (1,2,3,4,6,8,12). The dissolution medium was replaced with same amount of fresh PBS (pH 6.8) solution to maintain the volume 200 ml throughout the experiment. The drug content in the withdrawn samples (5ml) were estimated at 426 nm and cumulative % of drugreleased was calculated and plotted against time (t).

### Stability studies

Stability is defined as the extent to which a product remains within specified limits throughout its period of storage and use. A drug formulation is said to be stable if it fulfills the following requirements.

- It should contain at least 90 % of the stated active ingredient.
- It should contain an effective concentration of added preservatives, if any
- It should exhibit neither discoloration nor precipitation, nor foul odor.
- It should not develop irritation or toxicity.

From ten batches of prepared phytosomes, the ideal formulations were selected for stability studies. They were subjected for short-term stability studies and accelerated stability studies. Short-term stability studies were carried out at 5°C ± 3°C and 30°C ± 2°C, 40% ± 5% RH. The samples were stored at the above said condition for minimum3 months and their % drug content and *in vitro* release was determined for every 1 months. Similarly an accelerated stability study was carried out by storing the selected preparation at 40°C±2°C, 75%±5% RH for about 3 months. The %drug content and *in vitro* release were determined for every 1 month.

## RESULTS

### PREFORMULATION STUDIES

### Determination of Curcumin solubility and melting point

The solubility was found to be 0.0057mg/ml in water and melting wasfound to be in the range 179-183ºC.

### PREPARATION OF CURCUMIN PHYTOSOMES

Curcumin phytosomes complex prepared by Reflux method and rotary evaporator method in the ratios of (1:1, 1:2, 1:3, 1:4, and 1:5) by varying the polymer concentration.

**Table 2: Composition of Phytosomes formulations prepared by Reflux methodand Rotary evaporation method**

| SL.No | FormulationCode: (Reflux method) | Formulation Code: (Rotaryevaporator method) | Ratio ofDrug : Soy lecithin | Dichloro methane(ml) | Hexane(ml) | PBS (ml) |
|---|---|---|---|---|---|---|
| 01 | FA1 | FB1 | 1:1 | 20ml | 15ml | 5ml |
| 02 | FA2 | FB2 | 1:2 | 20ml | 15ml | 5ml |
| 03 | FA3 | FB3 | 1:3 | 20ml | 15ml | 5ml |
| 04 | FA4 | FB4 | 1:4 | 20ml | 15ml | 5ml |
| 05 | FA5 | FB5 | 1:5 | 20ml | 15ml | 5ml |

**Fig 1: FA1-FA5 Curcumin phytosomes**

**Fig 2: FB1-FB5 Curcumin phytosomes**

**Characterization of Curcumin PhytosomesDifferential scanning calorimetry**

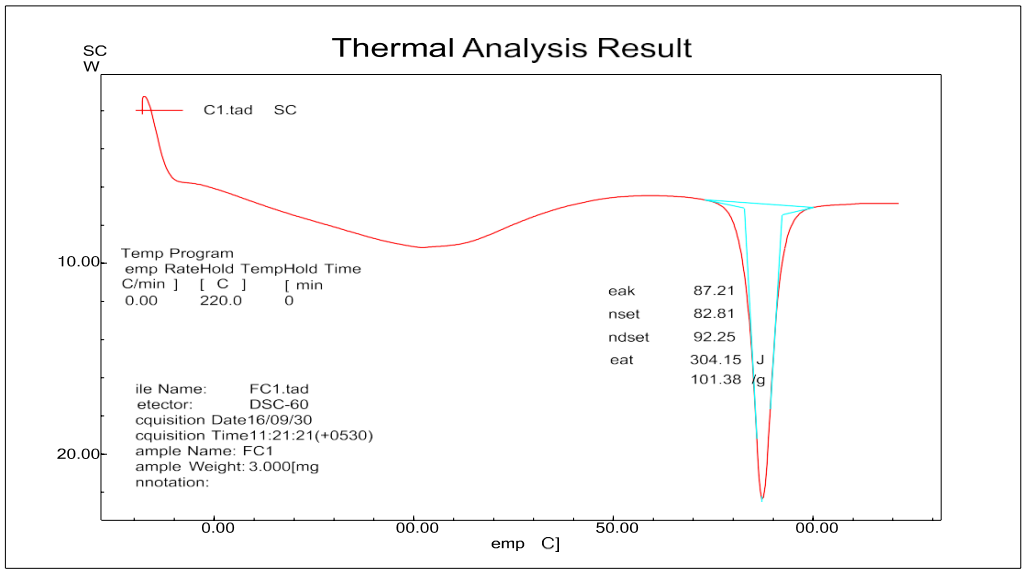


**Fig 3: DSC Thermograph of Curcumin**

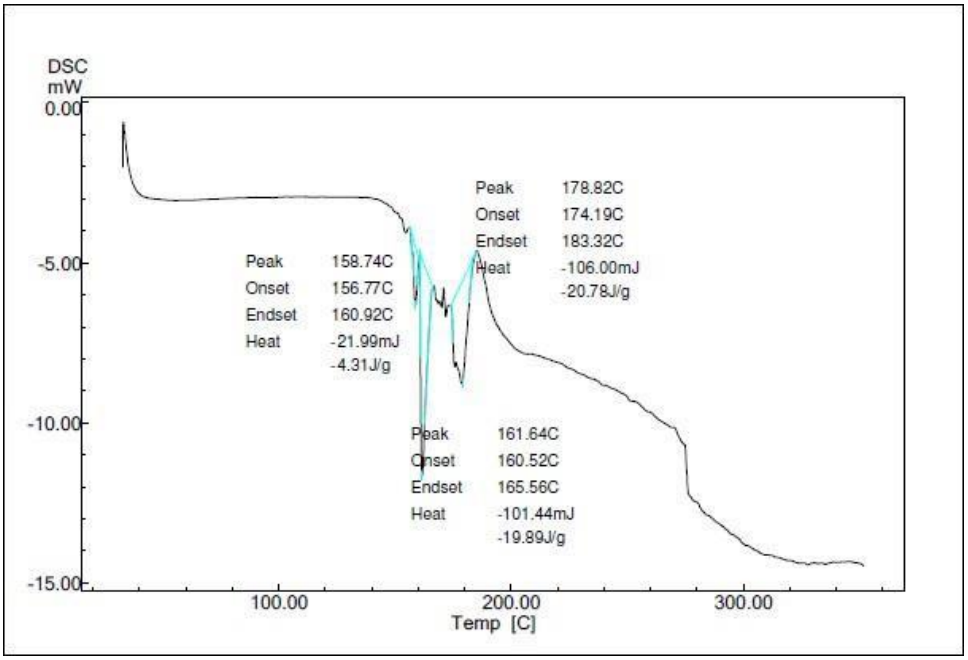


**Fig 4: DSC Thermograph of Curcumin + Soya lecithin mixture**

## Percentage yield, drug content and entrapment efficiency

**Table 3: Percentage yield, drug content and entrapment efficiency ofFormulations FA1-FA5**

| Formulationcode | Percentageyield | % DrugContent | % Entrapment Efficiency |
|---|---|---|---|
| **FA1** | 68.26 | 78.63 | 76.83 |
| **FA2** | 72.41 | 82.34 | 80.59 |
| **FA3** | 76.57 | 85.87 | 83.37 |
| **FA4** | 83.42 | 87.51 | 86.25 |
| **FA5** | 85.35 | 88.82 | 87.26 |

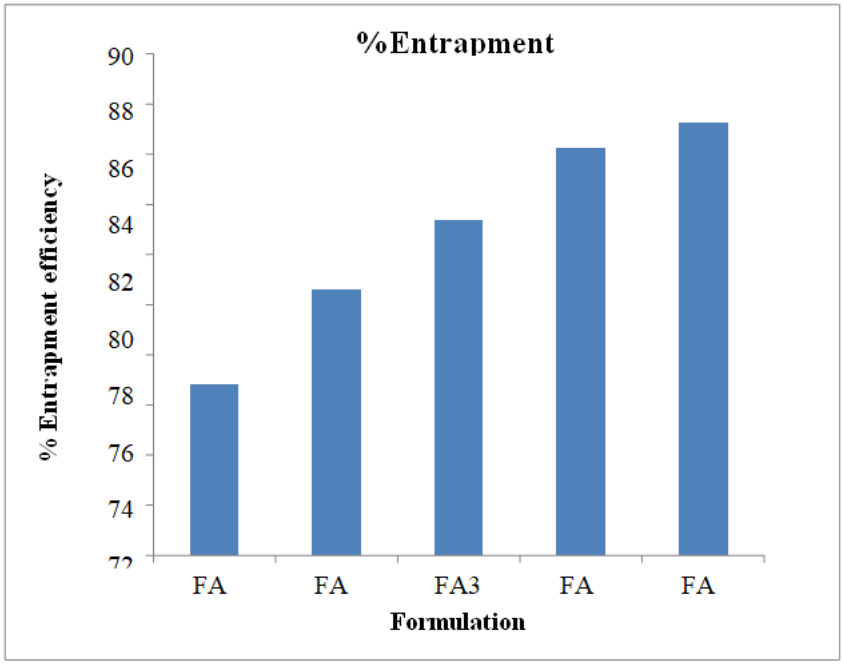


**Fig 5: Entrapment efficiency of Formulations FA1-FA5**

**Table 4: Percentage yield, drug content and entrapment efficiency ofFormulations FB1-FB5**

| Formulationcode | Percentage yield | % Drug Content | % Entrapment Efficiency |
|---|---|---|---|
| FB1 | 70.28 | 78.98 | 76.95 |
| FB2 | 75.65 | 83.43 | 81.21 |
| FB3 | 80.92 | 86.89 | 83.56 |
| FB4 | 86.84 | 87.64 | 86.42 |
| FB5 | 89.57 | 88.91 | 87.61 |

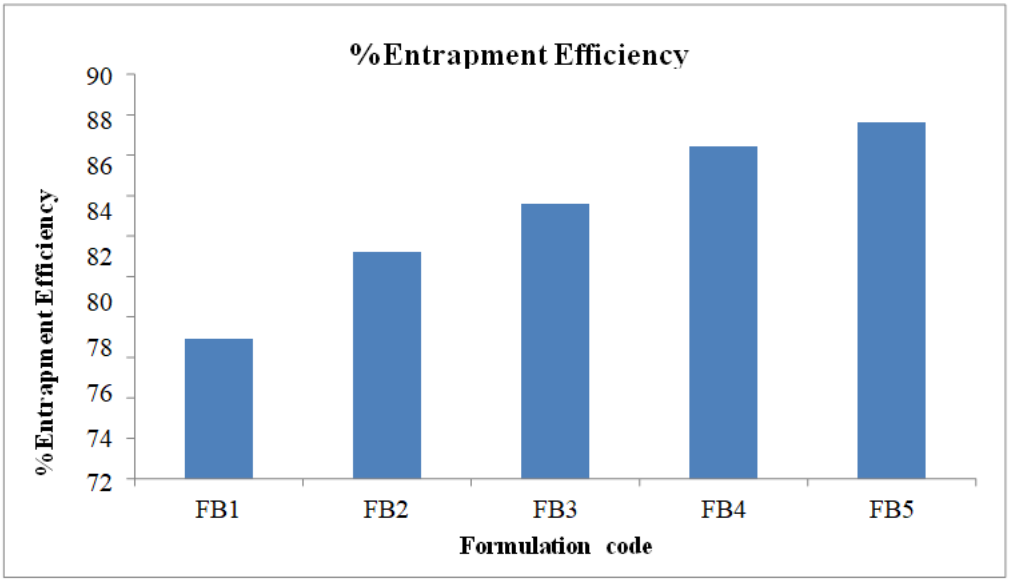


**Fig 6: Entrapment efficiency of Formulations FB1-FB5**

## Surface morphology

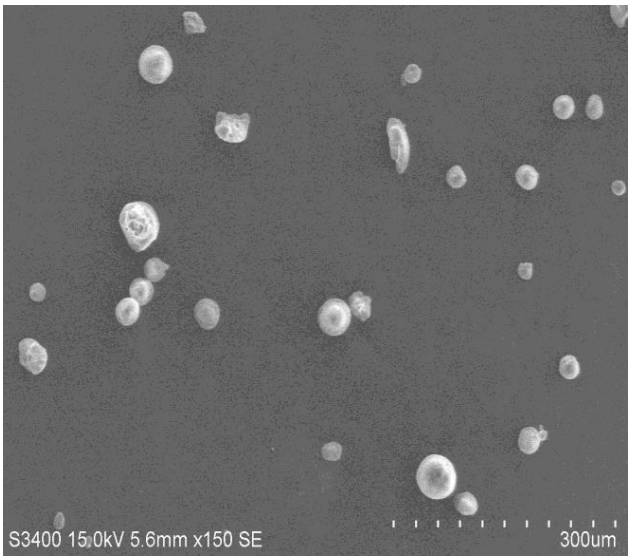


**Fig 7: SEM image of Formulation FA5**

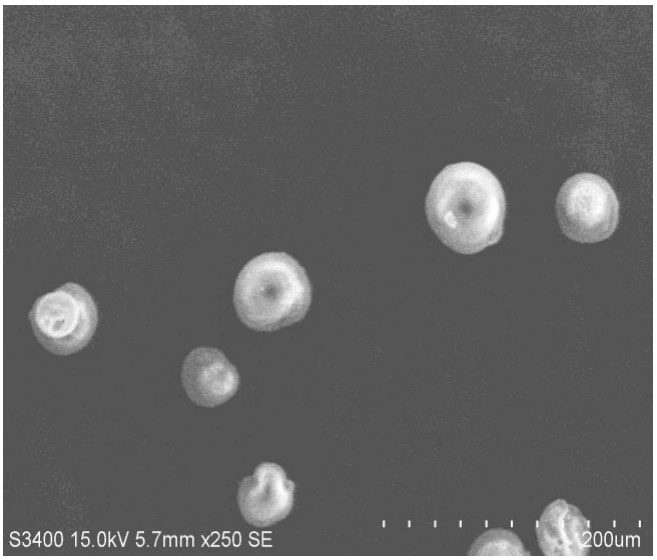


**Fig 8: SEM image of Formulation FB5**

## *In vitro* release studies

**Table 5: *In vitro* release profile of Formulations FA1-FA5**

| Time(hrs) | % Cumulative drug release | | | | |
|---|---|---|---|---|---|
| | **FA1** | **FA2** | **FA3** | **FA4** | **FA5** |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 19.28 | 17.38 | 14.99 | 10.71 | 6.42 |
| 2 | 36.42 | 32.39 | 29.36 | 27.32 | 23.57 |
| 3 | 49.28 | 47.52 | 45.21 | 42.75 | 38.32 |
| 4 | 62.14 | 60.63 | 57.02 | 55.62 | 53.84 |
| 8 | 74.98 | 72.15 | 70.76 | 66.82 | 64.28 |
| 12 | 88.68 | 86.08 | 83.57 | 81.42 | 79.36 |

**Table 6: *In vitro* release profile of Formulations FB1-FB5**

| Time(hrs) | % Cumulative drug release | | | | |
|---|---|---|---|---|---|
| | **FB1** | **FB2** | **FB3** | **FB4** | **FB5** |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 17.14 | 14.99 | 12.85 | 10.71 | 8.57 |
| 2 | 34.28 | 29.36 | 27.32 | 25.75 | 21.42 |
| 3 | 47.52 | 45.21 | 42.82 | 38.32 | 34.28 |
| 4 | 60.63 | 57.02 | 55.62 | 53.84 | 51.46 |
| 8 | 72.15 | 70.76 | 68.57 | 64.28 | 62.14 |
| 12 | 87.85 | 85.08 | 81.42 | 79.36 | 77.12 |

**Stability studies**

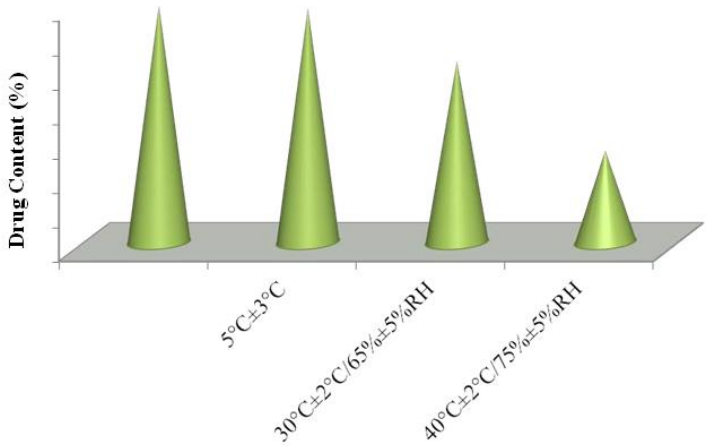


**Fig 9: Stability study - % drug content of formulation FB5 after three month of storage at 5º± 3ºC, room temperature 30º± 2ºC/65%RH and 40º±2ºC/75% RH.**

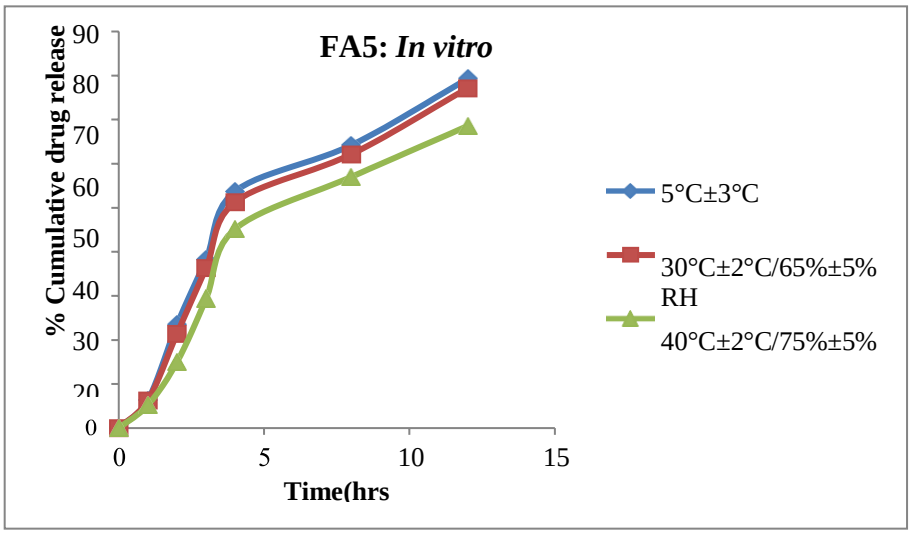


**Fig 10: Stability study - *In vitro* drug release of formulation FA5 after three month of storage at 5º± 3ºC, room temperature 30º ± 2ºC/75% ± 5% RH and 40±2ºC/75% ± 5%RH.**

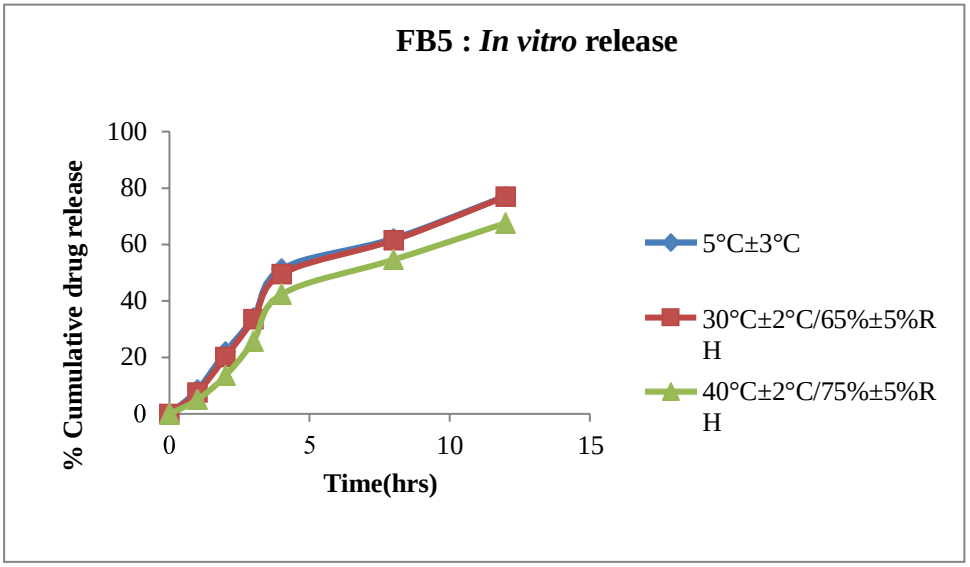


**Fig 11: Stability study - *In vitro* drug release of formulation FB5 after threemonth of storage at 5º± 3ºC, room temperature 30º± 2ºC/65% ± 5% RH and 40± 2ºC/75% ± 5% RH.**

## DISCUSSION

### Preparation of Curcumin Phytosomes

The Curcumin Phytosomes were prepared as per the technique described. The preparation of Curcumin Phytosomes, based on an Reflux and Rotary evaporation method and number of experiments was performed to determine theappropriate conditions for the incorporation of the drug Curcumin and Polymer Soya lecithin. A successful entrapment was achieved by using the drug Curcumin and Polymer Soya lecithin in the Dichloromethane and Phosphate buffer solution solution.

### Characterization of Curcumin Phytosomes
### Differential scanning calorimetry

Thermal properties of pure Curcumin powder, and formulation were evaluated by the method described to evaluate any possible drug- polymer interaction and the thermo grams of pure Curcumin were shown in fig 3, 4. The DSC results presented in Fig 5.8 demonstrated a sharp endothermic peak for Curcumin at 182.81ºC, which corresponds to its melting point. The meltingpoint range for Curcumin was 179-183ºC indicating the crystalline nature of the drug. The thermogram of formulation Fig 5 also showed the same endothermic peak at the similar temperature, confirming that there is no drug to polymer interactionin the formulation. Similar endothermic peaks were observed for the Curcumin and Soya lecithin mixture at 174.17°C the corresponding melting point. This study confirmed that there was no chemical interaction and the drug may be entrapped in Soya lecithin.

### Drug content and Percentage drug entrapment efficiency

The drug content of the prepared Curcumin and percentage drug entrapmentefficiency of the drug loaded Phytosomes were determined by the general procedure described. The sample was analyzed after making appropriate dilutions using the developed analytical method. The drug content of Curcumin Phytosomes was found to be 78.63%, 82.34%, 85.87%, 87.51%, 88.82% for FA1, FA2, FA3, FA4, FA5 and 78.98%, 83.43%, 86.89%, 87.64%, 88.91% for FB1, FB2, FB3, FB4, FB5 respectively was given in table 5.5 and 5.6 The Entrapment efficiency of formulation FA1, FA2, FA3, FA4, FA5 and FB1, FB2, FB3, FB4, FB5 containing Drug: Polymer in various ratiosof 1:1, 1:2, 1:3, 1:4, and 1:5 respectively was determined and tabulated in table 5.5 and Fig 5.10. The formulation FA1 and FB1 with drug: polymer ratio of 1:1 showedentrapment efficiency of 76.83% and 76.95%, Formulation FA2 and FB2 with ratio 1:2 showed 80.59%, 81.21% and formulation FA3 and FB3 with 1:3 ratios showed 83.37%, 83.56%. Formulation FA4 and FB4 with ratio 1:4 showed 86.25%, 86.42%and formulation FA5 and FB5 with 1:5 ratios showed 87.26%, 87.61%. Thus, there was a steady increase in the entrapment efficiency on increasing the polymer concentrationin the formulation. The formulation FB5 registered highest entrapment of 87.61% thancompare to other formulation and found to be the best formulation. However, theencapsulation efficiency was dependent on the polymer ratio, stirrer rpm and batch size (Table 3).

## Surface morphology

SEM of the prepared Curcumin Phytosomes was determined by the methoddescribed. SEM photographs of formulation FA5 and FB5 the surface morphology of the Curcumin Phytosomes. Magnification of 150-250X was used while taking these photographs. Surface smoothness of the Curcumin Phytosomes was increased by increasing the polymer concentration, which was confirmed by SEM. Morphology of the drug loaded Soya lecithin Phytosomes were found to be discrete and spherical in shape.

## *In vitro* release studies

*In vitro* release study of Curcumin from various formulations was conducted for12 hrs by using dialysis membrane. Cumulative % drug release was plotted against time. All the formulation showed more than 5% in the first 1 hr due to the presence of un-entrapped drug and the drug entrapped on the surface of polymer core which released faster showing dose dumping which is suitable to produce the initial effect of drug. It has been found that from the phytosomes formulation, FA1-FA5 prepared by Reflux method shows FA1-88.68%, FA2-86.08%, FA3-83.57%, FA4-81.42% and FA5-79.36 was shown in Fig 5.13 & Table 5.17. The increase in Soya lecithin ratio from FA1 to FA5 causes decrease in the drug release and the release was more controlled by increasing the Soya lecithin ratio. The phytosomes of formulation FA1- FA5 prepared by Rotary evaporation method shows FB1-87.85 %, FB2-85.08 %, FB3-81.42 %, FB4-79.36% and FB5-77.12 % were shown in Fig 5.14 & Table 5.8. The increase in Soya lecithin ratio from FB1 to FB5 causes decrease in the drug release. But, when comparing the two different methods, the formulation with Soya lecithin polymer shows controlled release rate than with formulation with Soya lecithin polymer, because Soya lecithin contains higher amount of quaternaryammonium groups, which renders it more permeable and accelerates the drug release.

## Release Kinetics

The release data obtained for formulation FA1-FA5 and FB1-FB5 plot of cumulative drug release as a function of time for all 10 formulations. In order to describe the release kinetics of all 10 formulations the corresponding dissolution data were fitted in various kinetic dissolution models like zero order, first order, Higuchi and Peppas respectively. Calculated regression co- efficient values for all formulations compared with each other for model and drug equation. As indicated by$r^2$ values, the drug release from all formulation follows First order and Higuchi followed by Peppas model. Since it was confirmed as Higuchi release mechanism wasdiffusion controlled. The peppas model is widely used to confirm whether the release mechanism is Fickian diffusion, non Fickian diffusion or zero order. 'n'value could be used to characterise different release mechanisms. Peppas-Korsmeyer equation is as follows:

$$\%R = K t^n \quad \text{Or} \quad \text{Log}\% R = \log K + n \log t$$

Where,

R=drug releasen=slope K=constant t=time

The 'n'values of all formulations were found to be more than 0.5 This indicatesthat the release approximates Non-fickian diffusion mechanism.

## Stability Studies

The results of drug content after 90 days of stability testing at different storageconditions. *In vitro* release profiles for the same formulation stored at different storage conditions. Based on % Drug content and *in vitro* release Formulation FA5 and FB5 were selected as an optimized formulations for stability studies. It was observed that there was a slight decrease in drug content when the formulation was stored at 5°C ± 3°C and room temperature, but there was significant decrease in drug content when the formulation was stored at 40°C ± 2°C.*In vitro* release studies revealed that the formulation stored at 5ºC ± 3ºC showed 87.79% & 88.83% for FA5 & FB5 respectively which was stored at room temperature showed 87.34% & 87.24% for FA5 & FB5 respectively and the formulation stored at 40°C ± 2°C showed & 83.37% 84.64% for FA5 & FB5 respectively. At higher temperature, there might be chances fordrug degradation that decreased the drug release.

## SUMMARY

This study deals with the studies carried out on the topic "Preparation and evaluation of Curcumin phytosomes." The first chapter starts with the introduction of Cancer, Novel Herbal Drug Delivery System, Controlled release, Phytosomes, Phospholipids, Commercial products and patents on Phytosomes. The second chapter contains the objective of the study. The third chapter contains literature survey; describe the brief information about the past work carried out on Phytosomes. It also contains the drug profile of Curcumin and polymer profile of Soya lecithin. The fourth chapter deals with the materials and methods. It describes the detailed procedure for the preformulation studies, preparation of Phytosomes,characterization of Phytosomes and stability studies as per ICH guidelines.

In the present study, an attempt was made to develop Phytosomes delivery system for low water-soluble anticancer

drug. Curcumin by using Soya lecithin polymer. Curcumin an anticancer agent used in the treatment of cancer having moderate half-life of 6-7 hours thus it is a good candidate for the formulation of Controlled release dosage forms. The Curcumin loaded Phytosomes were prepared by Reflux method of soyalecithin with Dichloromethane and hexane and Phosphate buffer solution. Phytosomes of different core: coat ratio were prepared and evaluated for process yield, loading efficiency, particle size, zeta potential, *in vitro* drug release, kinetic studies and stability studies. The infrared spectra and differential scanning calorimetry thermographs showed stable character of Curcumin in the drug-loaded Phytosomes and revealed the absence of drug polymer interactions. The drug content of Curcumin Phytosomes was found to be 78.63%, 82.34%, 85.87%, 87.51%, 88.82%.for FA1, FA2, FA3, FA4, and FA5 respectively. The formulationFA5 registered highest entrapment of 88.82%. The Curcumin phytosomes have a particle diameter ranging approximately 152.3nm and a zeta potential 30.4mV. The*in vitro* release behavior from all the drug-loaded batches were found to follow first order and provided Controlled release over a period of 12 hours and the release mechanism was swelling, and diffusion controlled. The study indicatedthat the amount of drug release decreases with an increase in the polymer concentration. Among the different Curcumin Phytosomes formulations, the formulation FA5 (drug polymer ratio 1:5) was selected as the ideal formulation, after considering itsoptimum mean particle size, better drug loading capacity and also drug release at Controlled manner up to 12 hours, for further stability studies. No appreciable difference was observed in the extent of degradation of product during long-term stability studies. According to the data obtained, this Soya lecithin- based phytotechnology opens new and interesting perspectives as drug carriers.

The Curcumin loaded Phytosomes were prepared by Rotary evaporation method of Soya lecithin with Dichloromethane and Ethanol Phosphate buffer solution. Phytosomes of different core: coat ratio were Prepared and evaluated for process yield, loading efficiency, particle size, zeta potential, in vitro drug release, kinetic studies, and stability studies. The prepared Phytosomes were white, free flowing and spherical in shape. The infrared spectra and differential scanning calorimetry thermographs showed stable character of Curcumin in the drug-loadedPhytosomes and revealed the absence of drug polymer interactions. The drug content of Curcumin phytosomes was found to be 78.98%, 83.43%, 86.89%,87.64% and 88.91% for FB1, FB2, FB3, FB4, and FB5 respectively. The Soya lecithin phytosomes have a particle diameter ranging approximately 181.6nm anda zeta potential 33.2mV. The formulation with the initial Curcumin concentration of 0.5 mg/ml provided the highest loading capacity. The *in vitro* release behavior from all the drug loaded batches were found to follow first order and provided Controlled release over a period of 12 hours. The release of Curcumin was influenced by the drug to polymer ratio and particle size & was found to be diffusioncontrolled. The study indicated that the amount of drug release decreaseswith an increase in the polymer concentration. Among the different Curcumin phytosomes formulations, the formulation FA5 (drug polymer ratio 1:5) was selected as the idealformulation, after considering its optimum mean particle size,better drug loading capacity and also drug release at Controlled manner up to 12 hours, for further stability studies. No appreciable difference was observed in the extent of degradation of product during long-term stability studies.

**Table 7: The characteristics of the ideal formulations**

| Characteristics | Curcumin phytosomes byReflux method | Curcumin phytosomes byRotary evaporation method |
|---|---|---|
| Ideal batch | FA5 | FB5 |
| % Drug content | 88.82% | 88.91% |
| Particle size | 152nm | 181.6nm |
| Zeta potential | 30.4mV | 33.2mV |
| In vitro release | 79.36 % | 77.12% |
| Mechanism | Non Fickian diffusion | Non Fickian diffusion |
| Stability | 5º±3ºC, 30º±2ºC/ 65%±5%RH | 5º±3ºC, 30º±2ºC/ 65%±5%RH |

This work confirms that Reflux and Rotary evaporation method is useful for the development of Soya lecithin Phytosomes. The concentrations of polymer and cross linking agent are important factors in the development of Soya lecithin Phytosomes. In the present study, Phytosomes containing anticancer drugs were prepared and the prepared Phytosomes are spherical, discrete, and free flowing. They show goodencapsulation efficiency and particle size is in micro range. Zeta potential determination shows that they are moderately stable. *In vitro* release studies show first order release kinetics, the release mechanism is swelling, and diffusion controlled. Stability studies shows that 5º ± 3ºC, 30º ± 2ºC/65% ± 5%RH conditions are suitablefor storing the prepared phytosomes. Based on the observations, it can be concluded that the formulated Phytosomes delivery system of selected anticancer drugs using widely accepted and physiologically safe polymer Soya lecithin was capable of exhibiting Controlled release properties for a period of 12 hours. Hence, it may be used as an alternative and cheaper carrier in site-specific delivery of anticancer drug. In turn, it may be useful in reducing the total cost of the therapy. They are thus may reduce frequency of dosing, thereby minimizing the occurrence of side effects, improve bioavailability and increase the effectiveness of the drug.

## CONCLUSION

From the experimental results it can be concluded that Rotary evaporation method is suitable for preparing the phytosomes of Curcumin than Reflux method. Among different drug polymer ratios FB5 prepared by Rotary evaporation method showed maximum drug content than FA5 prepared by Reflux method. The percentage drug entrapment efficiency is maximum for FB5 which was found to be 87.61% when compared to the formulation FA5 shows 87.26. After carrying out the particle size analysis, the phytosomes were found to be in thenanometer range and showed ideal surface morphology. The average particle size for formulation FA5 prepared by Reflux method was in the range of 152.3 nm and formulation FB5 shows more average particle size of 181.6nm. The zeta potential for FA5 was found to be moderately stable, where the formulation FB5 shows moderately stable. Formulation FB5 prepared by Rotary evaporation method showed proper controlleddrug release after 12 hrs of *in vitro* studies when compared to FA5 formulation prepared by Reflux method. Based on drug content, drug entrapment efficiency, particle size, surface morphology, zeta potential and *in vitro* release FB5 prepared by Rotary evaporation method was selected as a best formulation. It was apparent that *in vitro* release of Curcumin showed a very rapid initial burst, and then followed by a very slow drug release. An initial fast release suggests that some drug was localized on the surface of the phytosomes. Overall the curve fittingin to various mathematical models confirmed that the *in vitro* release of the all formulation were best fitted into First order followed by Higuchi and Peppas model.The 'n'values are more than 0.5 which indicates that the mechanism in which the drug release from phytosomes follows Non-fickian diffusion controlled system. Stability studies were carried out for the selected formulation FA5 and FB5 prepared by Reflux method and Rotary evaporation method respectively. Stability studies shows that 5 ºC ± 3 ºC, 30 ºC ± 2 ºC/40% ± 2%RH conditions are suitablefor storing the prepared phytosomes.

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