IJPSR (2024), Volume 15, Issue 2 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 July 2023; received in revised form, 24 August 2023; accepted, 23 November 2023; published 01 February 2024

PHYTOSOMAL NANOCARRIER LOADED WITH *EMBELIA RIBES* DEVELOPMENT FOR CANCER THERAPY

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Keywords:

Embelia ribes fruit extract, Complexation, Characterization, Phospholipid complex, Anticancer activity

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ABSTRACT: Background: In this study, *Embelia ribes* fruit extract phospholipid complex (ERE-PC) was developed with an attempt to enhance the therapeutic effect by improving its dissolution profile and oral bioavailability. *E. ribes*, an ancient herb possesses anticancer, anti-fertility, antimicrobial and anti-diabetic activities. However, poor aqueous solubility of phytoconstituents of *E. ribes*, lowers the therapeutic effectiveness of the extract. **Objective** To prepare phytosomes of *Embelia ribes* fruit extract (ERE-PC) to improve *in-vitro* release profile and oral bioavailability. **Method:** ERE-PC were formulated by solvent evaporation technique using methanol as reaction mixture which aimed for its improved pharmacological activity. The complex formation was confirmed by FTIR, PXRD, DSC and microscopical studies. The prepared complex was evaluated for functional properties such as solubility, dissolution profile and *in-vitro* cytotoxic activity. **Result:** The data obtained from FTIR, DSC and microscopic studies confirmed the formation of phytosomal complex. Aqueous solubility of the extract significantly increased from 23.04 ± 0.0023µg/ml to 84.02 ± 0.0036µg/ml in ERE-PC. Particle size and zeta potential of optimized phytosome was found to be 219.9 nm and -36.5mV respectively. Cumulative *in-vitro* release of the extract improved significantly due to the phospholipid complexation from 32.34% to 76.56%. In vitro cytotoxicity studies of ERE-PC against MCF-7 cell lines revealed potent cell growth inhibition (GI50<10µg/ml) in comparison to the extract (>80µg/ml). **Conclusion:** Thus, the phytosomal complex of the *E. ribes* fruit extract, could be a potential delivery system for improvement of bioavailability and therapeutic activity of the extract.

INTRODUCTION: Natural products have gained wide popularity in recent years and their usage for the treatment and prevention of various health related issues has gained momentum [1]. Although large number of dosage forms have been explored for the formulation of herbal extracts and phytochemicals, there are few limitations that necessitate the development of novel dosage forms. Bioactive constituents of herbal drugs have lower solubility and higher molecular weight which decrease their bioavailability [2, 3]. Novel drug delivery systems have gained wide interest due to maximum therapeutic effectiveness with minimum toxicity associated with their use [4].

It has been observed that complexation of extracts with certain other clinically useful nutrients substantially improves bioavailability of such extracts and their individual constituents [5]. *Embelia ribes*, (Family: Myrsinaceae) is commonly known as Vavding or Vidang in Ayurveda and Indian traditional system of medicine. Vidhang fruits are mentioned in the classical ayurvedic texts such as

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DOI: 10.13040/IJPSR.0975-8232.15(2).554-62

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(2).554-62

Charak Samhita and are official in Ayurvedic pharmacopoeia of India. The Government of India included *Embelia ribes* as a officinal drug in Indian Pharmacopoeia in 1966 [6]. The fruits of *E. ribes* have been used in 75 Ayurvedic preparations and are formulated into various ayurvedic preparations such as churna, asava, aristha, leha and taila and are widely used for treatment of gastrointestinal, liver, cardiac and nervous disorders. *E. ribes* fruits exhibit antidiabetic, anti-tumour and anthelmintic activities [7, 8].

Various bioactive phytoconstituents such as embelin, vilangin, quercitol and christembine have been identified in the *E. ribes* fruit. Embelin, a major bioactive constituent of *E. ribes*fruits is reported to be present in the concentration of 4.33% and is credited with antioxidant, antidiabetic, antitumour, neuroprotective, cardioprotective and anti-inflammatory activities [9]. Scientific explorations revealed embelin to exhibit potent cytotoxic activity as a result of apoptotic mechanism, inhibition of the X-linked antiapoptotic protein and modulation of NF-κB, p53, PI3K/AKT, and STAT3 signalling pathways [10, 11]. Regardless of the promising pharmacological effect, embelin exhibits poor bioavailability attributed to its large molecular size, low water solubility and unfavourable pharmacokinetics or pharma-codynamic profile [12, 13, 14].

Various lipid-based drug delivery systems are reported to increase the bioavailability of hydrophobic drugs. A phyto-phospholipid complex (Phytosome) is a lipid-based carrier system wherein standardised plant extracts or constituents are incorporated into phospholipids. Phospholipids have amphiphilic in nature and play a crucial role in drug delivery through modification of the solubility and release profile of entrapped drug and improve the drug absorption across various lipophilic biological membranes. Additionally, phospholipids are excellent emulsifiers enhancing bioavailability of co-administered drug. Therefore, the phospholipid complexes of the drug (Phytosome complex) can improve the solubility, bioavailability, stability and release profile of the drug administered through topical and oral routes [15, 16, 17, 18]. The aim of the present study was to formulate ERE-PC to overcome the problems of poor bioavailability and solubility associated with *E. ribes* fruit extract. Further, *in-vitro* cytotoxic efficacy, solubility, and dissolution profile of the formulated phytosomal complex was compared with plain extract.

MATERIALS AND METHODS:

Materials: *E. ribes* berries were purchased from local market of Kalbadevi, Mumbai. The berries were authenticated by Dr. Bindu Gopalkrishnan, Botany Department, Mithibai College, Mumbai. (Voucher Number: MIT0095). Phospholipid, Leciva-s70 was obtained as a gift sample from VAV Life Sciences, Mumbai. All other chemicals were of analytical grade. Cytotoxicity of the samples were tested against Human breast cancer cell line (MCF-7) at Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Mumbai.

Preparation of *Embelia ribes* Fruit Extract (ERE): Dried and powdered fruits of *E. ribes* (100 g) were extracted with 500ml of methanol at 60℃ for 12h. The filtered extract was concentrated on electric water bath to remove the excess solvent and stored at 5℃ for further studies.

Preparation and Optimization of ERE-PC: For the preparation of ERE-PC by solvent evaporation technique, various ratios of ERE and phospholipid (1:1, 1:2, 1:3, 2:1) were placed in 100ml of round bottom flask containing 25ml of methanol and refluxed at 50-60℃ for 3h. The resulting solution was evaporated under vacuum and the precipitate of ERE-PC was separated by filtration and stored in amber coloured glass bottle [19]. Obtained phytosomal complexes were evaluated by microscopic studies and their entrapment efficiency and zeta potential was determined [20].

Microscopy: Physical appearance and surface morphology of prepared ERE-PC was evaluated using motic microscope (System microscope 31 Series).

Entrapment Efficiency [20]: The amount of extract encapsulated in the phytosomal complex was determined by centrifuging complex with distilled water at 5000rpm for 15min at room temperature. The supernatant solution was collected, and absorbance was determined at 277nm using UV-Visible spectrophotometry.

The entrapment efficiency was calculated using the following formula:

% Entrapment Efficiency = (T-S) / T x 100

T: Total embelin contentin extract present in weighed quantity of phytosomal complex.

S: Embelin content in supernatant (unentrapped extract).

T-S: Embelin content in entrapped extract.

Particle Size and Zeta Potential: Particle size and zeta potential of ERE-PC suspension was assayed using Malvern Zetasizer (Malvern Instruments, UK).

Evaluation of ERE-PC: ERE-PC phytosomal complex was characterized using FTIR, DSC and PXRD studies. Additionally, functional properties of the complex such as solubility, dissolution profile and *in-vitro* cytotoxic activity were evaluated [20].

Apparent Solubility Study [20]: An excess of ERE and ERE-PC complex were added to 5 ml water in a sealed glass tube and shaken for 24h. Excess of ERE was removed by centrifugation of the samples at 5,000 rpm for 15 min. The supernatant was filtered through a 0.45 µm membrane filter and the filtrate was diluted to 10ml with distilled water and the absorbance of the sample was measured at 277nm using UV-Vis spectrophotometer (Shimadzu UV-1900).

Fourier Transform Infrared spectroscopy (FTIR) Study: FT-IR spectra of ERE, phospholipid, and optimized ERE-PC complex were obtained by using Perkin Elmer spectrum 1800 spectrophotometer. Pellets were made by pressing dry crystalline KBr and sample in the ratio of 1:100 using hydraulic press and scanning the pellets in the range of 4000–400 cm^{-1}.

Differential Scanning Calorimetric (DSC) Study: DSC analysis was carried out to examine the thermal behaviour of the ERE, phospholipid, and phytosomal ERE-PC complex using an automatic thermal analyser system (DSC, Perkin Elmer, USA). Different samples were placed in an aluminium crimp cell and heated at the speed of 10°C /min from 0 to 300°C for ERE and phospholipid and 0 to 400°C for ERE-PC in the atmosphere of nitrogen. Peak transition onset temperatures recorded by the analysers were compared.

Powder X-ray Diffractometry (PXRD) Study: Crystalline state of ERE in various samples was evaluated by powder X-ray diffractometry (XPERT- PRO). Analysis was done using Cu as tube anode material at 45 kV and 40 mA. The samples were exposed to Cu-Ka radiation (with a α1/ α2 ratio of 0.50000), at temperature of 25°C. XRD spectra obtained for different samples were compared with respect to degree of crystallinity.

Dissolution Studies: *In-vitro* dissolution studies were carried out for ERE and ERE-PC using type I basket type dissolution apparatus, operated at 100 rpm and 37°C. ERE (50 mg) or ERE-PC (equivalent to 50mg of ERE) were accurately weighed and introduced into pH 1.2 buffer and pH 6.8 phosphate buffer. Samples were withdrawn at the intervals of 5, 15, 30, 45, 60, 90 and 120 min, and replaced with fresh media to maintain sink conditions. Withdrawn samples were analysed using UV-Vis spectrophotometer (Shimadzu UV-1900) for the content of embelinat λ_{max} 277nm [21, 22].

Cytotoxicity Study: Cytotoxicity of ERE-PC was evaluated against MCF-7 cell lines using an efficient and inexpensive Sulforhodamine B (SRB) assay. Initially the cell lines were allowed to grow on RPMI 1640 medium containing 10% fetal bovine serum and 2mM L-glutamine. Sample solutions of ERE, ERE-PC, phospholipid and Adriamycin prepared in dimethyl sulfoxide were added in various concentrations such as 10µg/ml, 20µg/ml, 40µg/ml and 80µg/ml.

After the addition of samples, plates were incubated at standard conditions for 48hfollowed by addition of cold trichloroacetic acid, Sulforhodamine B and 0.4% acetic acid. Wells were incubated for 20min to complete staining. After staining residual stain was removed by washing and bound stain was eluted with 10mM trizma base and absorbance was measured. Percent growth inhibition was expressed as the ratio of average absorbance of the test well to the average absorbance of the control wells multiplied by 100 [23].

RESULT AND DISCUSSION:

Formulation of ERE-PC: In the present study ERE-PC was prepared by using simple and reproducible solvent evaporation method. Four batches of ERE-PC comprising of ERE: Phospholipid in different ratios such as 1:1, 1:2, 1:3, 2:1were prepared and designated as F1, F2, F3 and F4 respectively. Formation of the phytosomal complexes were confirmed on the basis of microscopic view, entrapment efficiency and zeta potential. F1 and F2 phytosomal complex batches showed the presence of discrete, spherical shaped uniform, unilamellar vesicles whereas the other two batches (F3 and F4) showed non uniform aggregated vesicles. Microscopic images (40X) of different batches of phytosomal complexes are depicted in **Fig. 1.** Thus, F1 and F2 were chosen for further evaluation. The results of the entrapment efficiency study, particle size analysis and the zeta potential determination are as shown in **Table 1.** As per the results obtained, both F1 and F2 batches exhibited good entrapment efficiency (above 90%). The F2 batch containing ERE: phospholipid in 1:2 ratio exhibited the highest entrapment efficiency of 98.83% compared to the F1 batch. In addition, F2 batch exhibited lower particle size, polydispersity index (PDI) and optimum zeta potential compared to F1 batch. These outcomes indicated that all the constituents of the ERE in F2 formulation batch are physically bonded to polar head of phosphatidylcholine, which reduced negative charge density of phosphatidylcholine and particle size of vesicles along with improved entrapment efficiency in comparison to F1 batch. The formulation batch was found to be stable and the size of vesicles indicated the ease of its absorption by the intestine [24]. Thus, F2 formulation batch containing ERE: Phospholipid in 1:2 ratio was selected as optimized batch for further characterization [25].

TABLE 1: OPTIMIZATION PARAMETERS OF PHYTOSOMAL COMPLEXES

Formulation batch	ERE: Phospholipid	Entrapment efficiency (%)	Particle Size (nm)	Zeta potential (mV)	PDI
F1	1:1	90.10 ± 0.374	257.1	-47.6	0.45
F2	1:2	98.83 ±0.632	219.9	-36.5	0.2

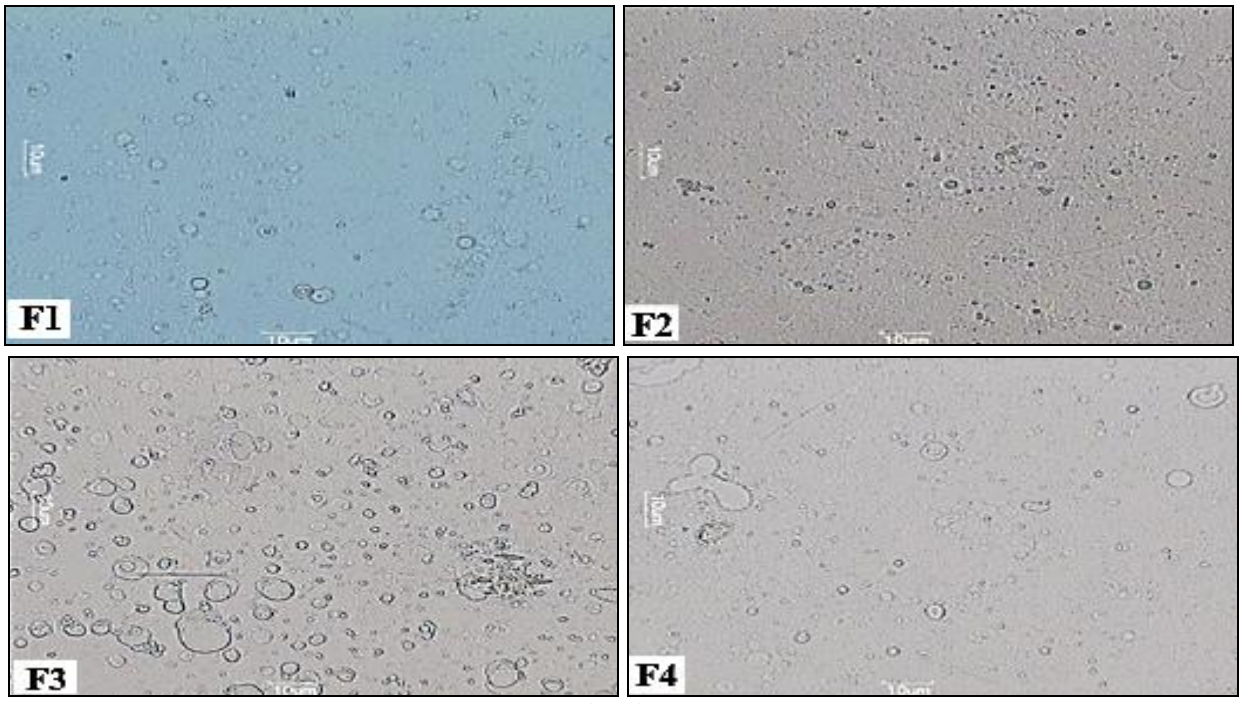

FIG. 1: MICROSCOPIC IMAGES (40X) OF VARIOUS ERE-PC BATCHES

Evaluation of ERE-PC

Solubility Study: Embelin the major active constituent of ERE possesses poor water solubility resulting in poor absorption across intestinal epithelial cells of GI tract, consequently leading to lower therapeutic efficacy. Aqueous solubility of extract estimated in terms of embelin content was observed to improve significantly from

23.04±0.0023µg/ml to 84.02±0.0036µg/ml in the prepared phytosomal complex. This enhancement was attributed to the micellization of the extract by the phospholipid causing increased solubility of hydrophobic constituents in hydrophilic environment [20].

FT-IR Study: FT-IR spectra of ERE, Phospholipid, and ERE-PC are depicted in **Fig. 2**. FT-IR spectroscopy was performed to confirm the interaction between ERE and phospholipid in ERE-PC.FT-IR spectrum of ERE showed the presence of characteristic vibrational bands at 3365.95cm^{-1} (phenolic O-H stretch), 2925.82cm^{-1}(asymmetric -CH_2- stretch of alkanes) and 2852.89cm^{-1} (symmetric -CH_3 and -CH_2- stretching of alkanes), 2359.97cm^{-1} and 2342.40cm^{-1} (CO_2 asymmetrical stretching) and1635.67cm^{-1}(C=O stretch).FTIR spectrum of phospholipid revealed the presence of characteristic bands at2926.45 cm^{-1} and 2854.62 cm^{-1} corresponding to C–H stretching of long chain fatty acid. In addition, band at 1740.07 cm^{-1} (C=O stretch of fatty acid ester), 1230.01 cm^{-1} (P=O stretch), 1069 cm^{-1} (P–O–C stretch, and 972.66 cm^{-1} ($-N^{+}(CH_3)_3$ stretch) were observed in the phospholipid spectrum. IR-spectrum of ERE-PC showed the presence of broad band at 3365 cm^{-1}(O-H stretch). The shift in the wave number of this band to the lower value in the spectra indicated the formation of hydrogen bond between hydroxyl group of extract and phosphate group of phospholipid. Moreover, the frequency region ranging from 1200 $cm^{-1}$to 900 $cm^{-1}$of ERE-PC spectrum corresponding to phosphate group exhibited significant change in the pattern in comparison to phospholipid spectrum, confirming the interaction between phospholipid and phenolic group of phytoconstituents present in the extract. The shift in the band corresponding to choline group in the phospholipid complex spectrum to lower wave number suggested that hydrogen bonding and other weak physical interactions between the extract and phospholipid play an important in the complex formation [26, 27].

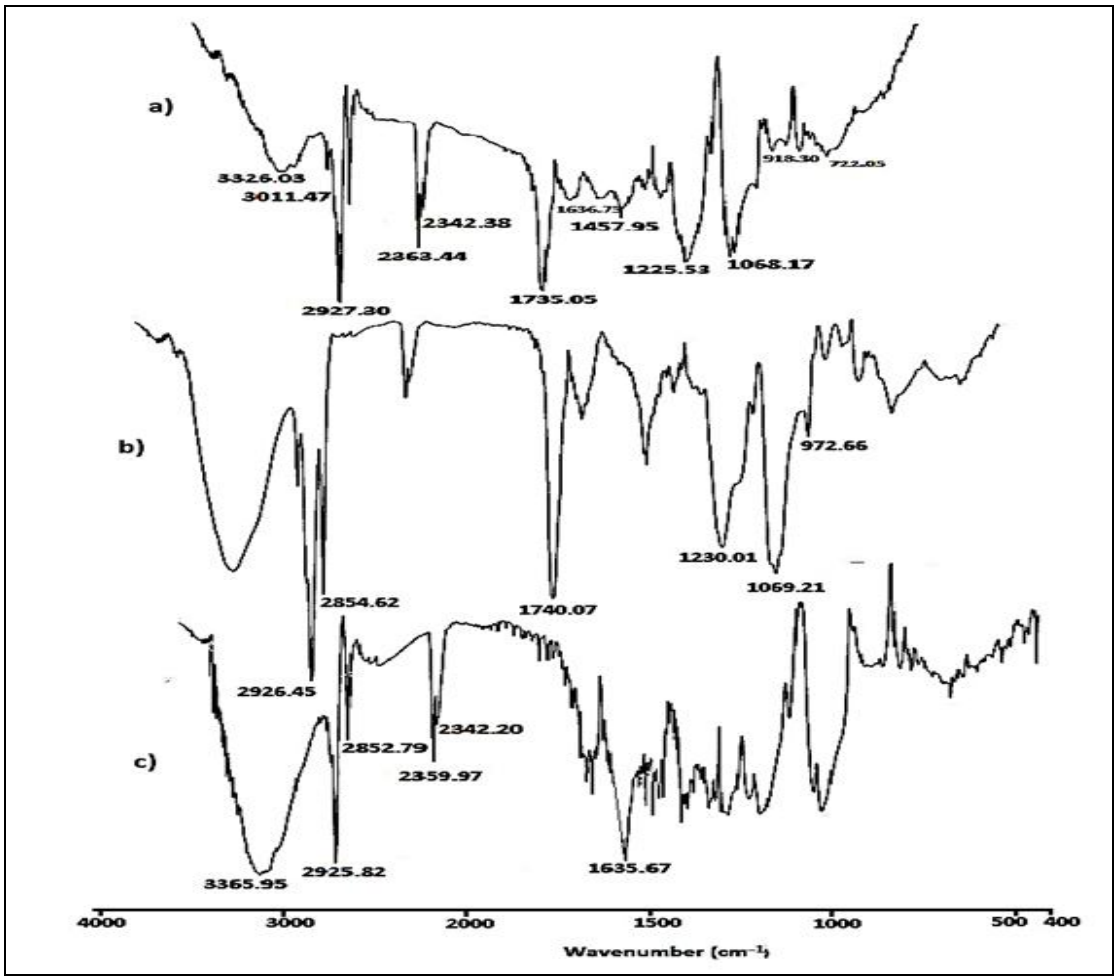

FIG. 2: FT-IR SPECTRA OF (A) ERE, (B) PHOSPHOLIPID (C) ERE-PC

Differential Scanning Calorimetry: DSC thermograms of ERE, Phospholipid, and ERE-PC are depicted in **Fig. 3**. DSC thermogram of ERE showed the presence of an endothermic peak at 127.8°C. On the other hand, DSC thermogram of phospholipid exhibited two endothermal peaks at 140.0°C and 189.4°C. Less intense peak at 140.0°Cwas attributed to heat induced movement of the polar head in phospholipid. More intense sharp peak at 189.4°C could be attributed to phase transition of phospholipid from gel to liquid crystalline state. Thermogram of ERE-PC exhibited the absence of peaksat 127.8°C and 189.4°Ccorresponding to ERE and phospholipid respectively and presence of additional endothermic peaks at 116°C, 263°C and 391°C. Appearance of additional peaks in the thermogram could be attributed to phytosomal complexation process mediated through interactions such as hydrogen bonding or Van der Waals forces [26, 27].

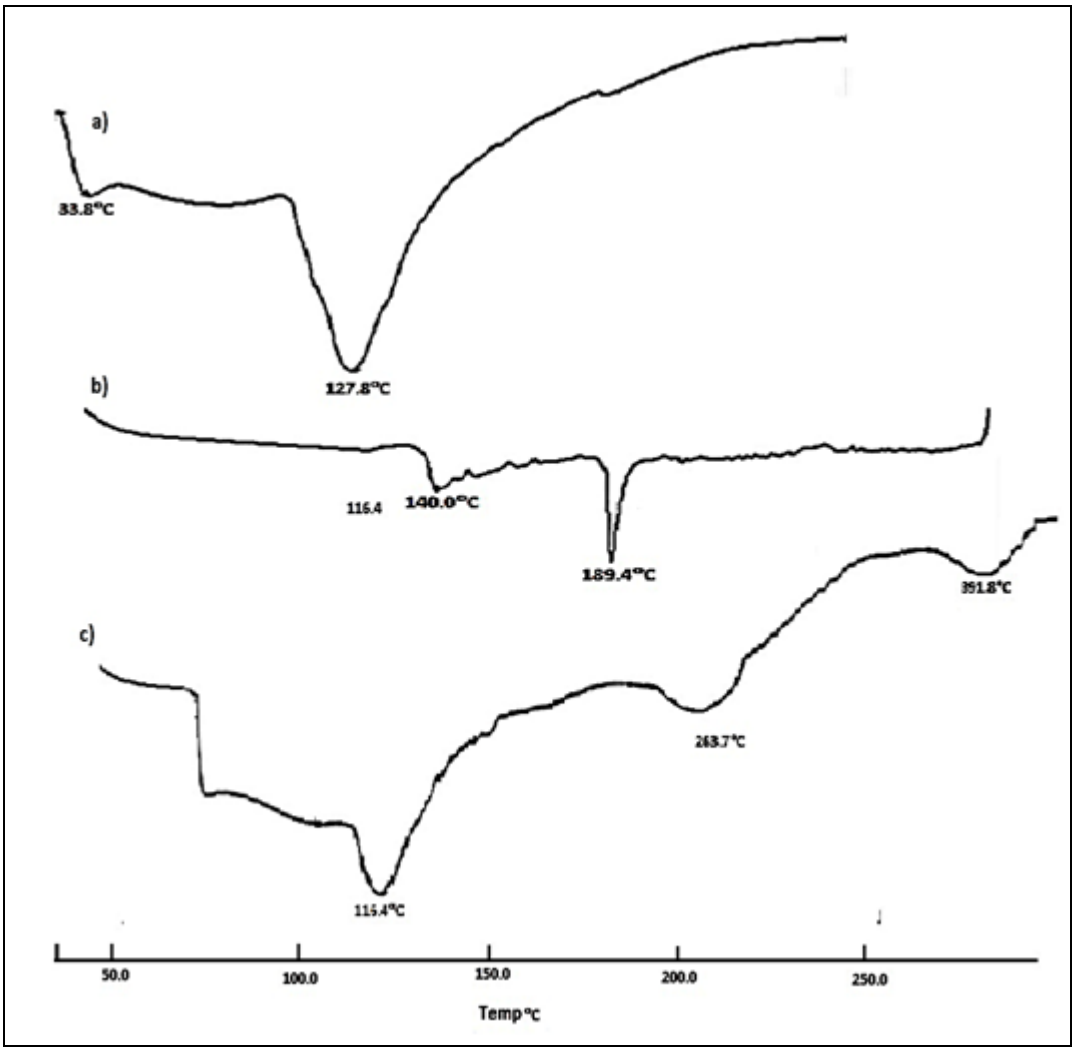

FIG. 3: DSC THERMOGRAMS OF (A) ERE, (B) PHOSPHOLIPID (C) ERE-PC

Powder X-ray Diffraction Study: PXRD analysis is an efficient tool to ascertain the crystallinity of the samples. X-Ray diffraction patterns of ERE, Phospholipid and ERE-PC as shown in **Fig. 4** were studied to understand the change in crystallinity due to complexation. ERE diffractogram showed the presence of two sharp peaks indicating crystalline nature of the extract. On the other hand, diffractogram of phospholipid showed the presence of flat broad peak indicating its amorphous nature. Diffractogram of ERE-PC exhibited the disappearance of ERE peak indicating loss of crystallinity of ERE in the phytosomal complex and the amorphous state of phospholipid attributed to bonding interaction between ERE and phospholipid, reduction in melting point and enthalpy values [28].

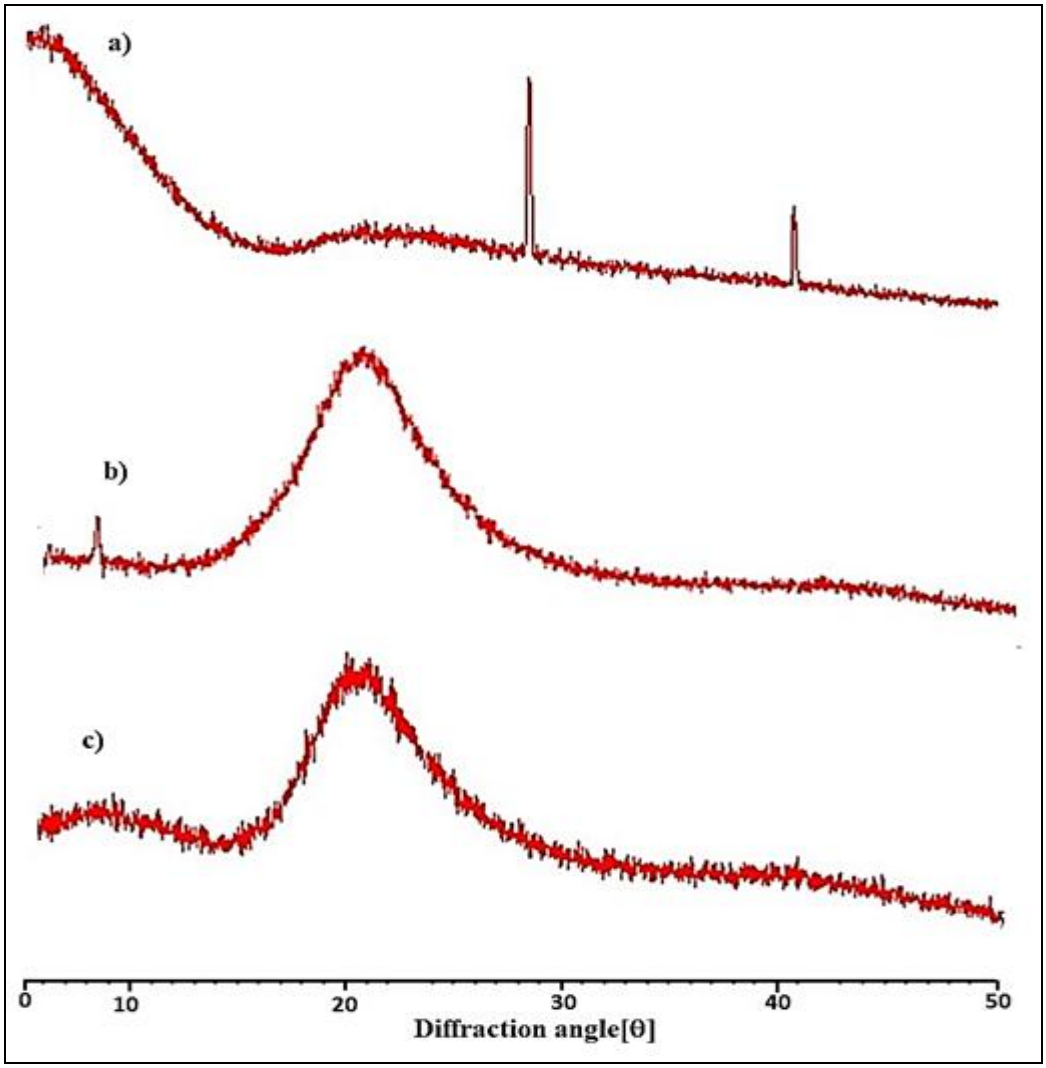

FIG. 4: PXRD SPECTRA OF (A) ERE, (B) PHOSPHOLIPID, (C) ERE-PC

Dissolution Study: *In-vitro* dissolution studies revealed the improvement in dissolution profile of ERE-PC in comparison to ERE in pH 1.2 buffer and pH 6.8buffer.At the end of 120 minutes cumulative percent release in pH 6.8 buffer for ERE and ERE-PC was observed to be 32.34% and 76.56% respectively. However, in pH 1.2 buffer cumulative percent release for ERE and ERE-PC at the end of 120 minutes was obtained as 12.90% and 15.1% respectively. The decrease in cumulative release in acidic pH could be attributed to acidic nature of constituents of extract. Release of ERE from phytosomal formulation followed a slow sustained characteristic release behaviour of phytosomes. Significant enhancement in release of ERE from phytosomes could be attributed to increased solubility and wettability of ERE constituents. Accordingly, phospholipid being amphiphilic in nature improved the solubility of extract by wetting and dispersion phenomenon; thus, enhanced the rate and extent of dissolution of the extract [28]. Dissolution profiles of ERE and ERE-PC are depicted in **Fig. 5**.

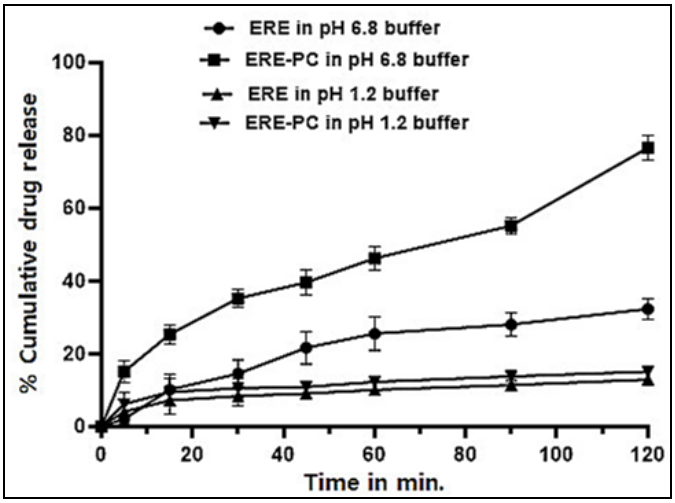

FIG. 5: DISSOLUTION PROFILES OF ERE AND ERE-PC IN PH 1.2 BUFFER AND PH 6.8 PHOSPHATE BUFFER

Cytotoxicity Study: *In-vitro* cytotoxic activity of ERE, ERE-PC and phospholipid was evaluated using MCF-7 human breast cancer cell line. Four different concentrations (10µg/ml, 20µg/ml, 40µg/ml and 80µg/ml) of samples were used for the study. The cytotoxic potential of various samples was expressed in terms of GI_{50} value. ERE and phospholipid revealed GI_{50}>80µg/ml whereas ERE-PC and Adriamycin exhibited GI_{50}<10µg/ml respectively. The percentage growth inhibition was found to increase with increase in concentration of phytosomal complex. Thus, incorporation of ERE into phytosomal complex was shown to improve its cytotoxic activity against MCF-7 cell lines, which can be attributed to enhanced permeability of the phytoconstituents present in ERE into cancer cells [29]. Moreover, phytosome based delivery of ERE could be effective and can be explored in an array of other breast cancer cell lines such as T47D, ZR-75-1, FM3A, ZR-75-30 and MDA-MB-361. However, enhancement in *in-vitro* cytotoxic potential is required to be substantiated by *in-vivo* studies. Thus, ERE-phospholipid complex can serve as a potential therapeutic option for the treatment of various types of cancers mediated through improvement of permeability of *E. ribes* phytoconstituents resulting in enhanced absorption and bioavailability. Growth curves of ERE, Phospholipid and ERE-PC, Adriamycin are displayed in **Fig. 6.**

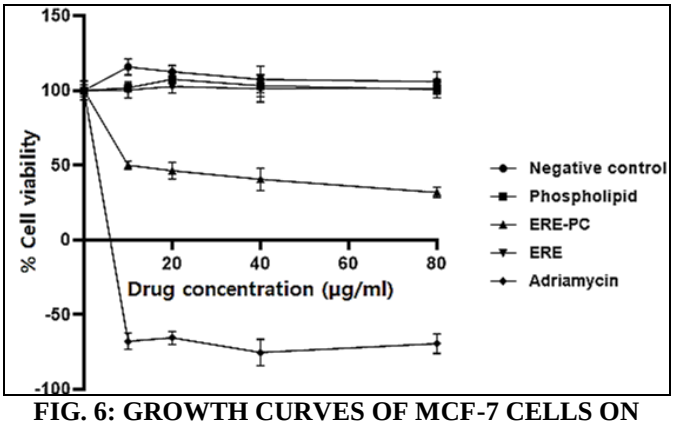

FIG. 6: GROWTH CURVES OF MCF-7 CELLS ON TREATMENT WITH ERE AND ERE-PC

CONCLUSION: Present study primarily focused on extraction of *E. ribes* fruits and assessment of its anticancer property. Using a simple and facile method ERE phytosomes with good entrapment efficiency were prepared. Prepared phytosome showed significant improvement in *in-vitro* cytotoxic potential due to improved penetration of the phytoconstituents present in ERE. Moreover, *in-vivo* research is necessary to be carried out, which will prove its therapeutic effectiveness as a result of improved penetration, better absorption, dissolution and enhanced bioavailability. Findings of the study has proven ERE-PC as an effective tool against various kind of tumours. Hence, it can be concluded that development of phytosome is a viable approach to improve the bioavailability and stability of the extract, which could be an effective drug delivery system for oral administration of ERE.

Ethics Approval and Consent to Participate: Not applicable

Human and Animal Rights: Not applicable

Consent for Publication: Not applicable

Availability of Data and Materials: Not applicable

Funding: None

ACKNOWLEDGEMENTS: Authors are thankful to VAV Life Sciences, Mumbai for providing free gift sample of phospholipid, ATREC for cytotoxicity studies and SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai providing necessary facilities for completion of work.

CONFLICT OF INTERESTS: Declared none

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How to cite this article:
Kadu A, Mallya R and Suvarna V: Phytosomal nanocarrier loaded with *Embelia ribes* development for cancer therapy. Int J Pharm Sci & Res 2024; 15(2): 554-62. doi: 10.13040/IJPSR.0975-8232.15(2).554-62.