Educational Administration: Theory and Practice
2023, 29(4), 1327 - 1336
ISSN: 2148-2403
https://kuey.net/

Research Article

Development, Characterization and Evaluation of Gefitinib-Containing Phospholipid Complex

Priya Chaudhuri[1], Debajyoti Sarkar[2], Mousumi Garai[3], Rahul Pal[4], Prachi Pandey[5], Arindam Kolay[6*]

[1,2] Burdwan Institute of Pharmacy, West Bengal, India.
[3] Seacom Skills University, West Bengal, India.
[4,5,6 *]Department of Pharmaceutics, Nims Institute of Pharmacy, Nims University Rajasthan, Jaipur, 303121, India.

Corresponding Author: *Arindam Kolay
E-Mail Id: kolayarindam2012@gmail.com (Arindam Kolay)

Citation: Arindam Kolay, et al (2023), Development, Characterization and Evaluation of Gefitinib-Containing Phospholipid Complex, *Educational Administration: Theory and Practice, 29(4),* 1327 - 1336
Doi: 10.53555/kuey.v29i4.6362

ARTICLE INFO

ABSTRACT

Objective: To develop, characterize and evaluations of gefitinib loaded phospholipid complex as a nano carrier.

Material and methodology: Gefitinib phospholipid complex was prepared by solvent evaporation method. Gefitinib, phospholipid and complexing solvent (methanol) in different ratios used in the preparation. The batch code from F1 to F7 were prepared in different molar ratio (drug: egg lecithin E80) with 10 ml methanol solvent for each formulation.

Results: The optimized formulation F5 was obtained from F1 to F7 with yellowish thick layer appearance, drug content 95.188±0.532, with uniform regular rigid vesicles. The particle size of F5 was 162.63 nm with PDI 23.9% and zeta potential was -34.5 mV was obtained. The maximum *in-vitro* diffusion study of formulation F5 was calculated up to 24 hr. was 76.191±0.486, the formulation F5 follows Krosmeyer-peppas kinetics with R^2 value 0.9826.

Conclusion: Phospholipid complex formulation of gefitinib was prepared by using the reflux technique method. For optimization of phospholipid complex, different formulations (F1 to F8) were prepared using the various quantities of lipid. Formulation (F5) with maximum n-octanol solubility, drug content and optimum size considered as optimized formulation. The shape and size of the optimized F5 formulation was confirmed through microscope and particle size and found that most of the particles were well identified. Optimized formulation *in vitro* drug release was studied in phosphate buffer saline (PBS) pH 6.8 using dialysis method. The results showed that the drug release of F5 formulation followed Krosmeyer-Peppas which describes that the gefitinib follows a controlled mechanism for release from phospholipid complex.

Keywords: Phospholipid complex, developments, gefitinib, nano-carrier, nano-development, liposomes.

1. INTRODUCTION

Novel drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered.

NDDS such as liposomes, niosomes, phytosomes, etc., which move through the pre-systemic metabolism, reducing adverse effects in pediatric and geriatric patients due to the accumulation of drugs in the non-target areas, and improving the distribution of tissue macrophages. This contributes to physical and chemical degradation safety, such as improved solubility, permeability, stability and sustained delivery [1]. Phospholipids are amphipathic molecules having considerable solubility in aqueous and oily mediums. They have a polar and a non-polar portion in their structures [1-2]. The phospholipids are one of the major components of the mammalian cell membrane. Gefitinib is an orally administered tyrosine kinase inhibitor

primarily used in the treatment of non-small cell lung cancer (NSCLC). It targets the epidermal growth factor receptor (EGFR) by blocking its tyrosine kinase activity, which is crucial for the growth and proliferation of cancer cells. Gefitinib is particularly effective in patients with specific mutations in the EGFR gene, leading to better clinical outcomes in these subsets. As a targeted therapy, it is associated with a different side effect profile compared to traditional chemotherapy, including skin rash and diarrhea, but is generally well-tolerated. Its use represents a significant advancement in the personalized treatment of lung cancer, offering improved quality of life and survival rates for many patients [3].
The current study is to formulate, characterize and evaluate the gefitinib loaded phospholipid complex as a nano carrier.

2. MATERIAL AND METHODS

2.1. Materials

Gefitinib(Chemtech Alloys Pvt Ltd), Hydrochloric Acid (Fisher Scientific India Pvt. Ltd), Methanol (Fisher Scientific India Pvt. Ltd), Potassium Dihydrogen orthophosphate (Thomas Baker), Disodium hydrogen orthophosphate (Thomas Baker), n- octanol (SD Fine-chem. Ltd, Mumbai), Chloroform (Fisher Scientific India Pvt. Ltd) were purchased from their respective suppliers.

2.2. Pre- formulation Studies

Pre-formulation is an integral part of the entire development process. It is the study of the physical and chemical properties of the drug prior compounding process. These studies focus on those physicochemical properties of the drug that could affect its performance and development of an efficacious dosage form.

2.2.1. Organoleptic characteristics: The drug sample was characterized for the physical characterization like color, appearance and odor [4].

2.2.2. Melting point: The melting point of the solid is defined as the temperature at which solid and liquid are at equilibrium at a total pressure. Melting point apparatus (Remi Equipment, Mumbai) is used for the determination of melting point of the drug. A few amount of the drug were placed in a thin walled capillary tube 10-15 mm long, about 1 mm inside diameter, and closed at one end. The capillary, which contains the sample, was suspended to heat the samples slowly and evenly and thermometer placed to check the temperature. The temperature range over where the sample is observed to melt is taken as the melting point of the drug [5-7].

2.2.3. Analytical estimation of Gefitinib via UV- spectrophotometer.
Preparation of Stock Solution: Standard stock solution of Gefitinib was prepared by dissolving 10mg of Gefitinib in 10ml of methanol which gives 1000µg/ml. 10ml of this stock solution was taken and was diluted up to 100ml by using methanol (solvent) to produce a concentration of 100µg/ml solution.
Preparation of Working Solution: The standard stock solution of Gefitinib (100µg/ml) was prepared in methanol. This solution was diluted with methanol, to obtain various dilutions (0.5-3.5µg/ml). Absorbance of these solutions was recorded at 250nm against methanol as blank using UV-visible spectrophotometer and standard curve was plotted against concentration. From the calibration curve intercept, slope, straight line equation and correlation coefficient were obtained.

2.2.4. Solubility studies: For quantitative solubility study, excess amount of drug was taken in thoroughly cleaned test tubes containing 1 ml of different solvents (Methanol, Ethanol, Acetone, Chloroform, 0.1N HCl, water, Phosphate buffer pH 6.8) and test tubes were tightly closed. These test tubes were shaked on water bath shaker for 24 h at room temperature. After 24 h each sample was centrifuged 15,000 rpm and supernatant was withdrawal. After that supernatant was filtered and filtrates was suitably diluted and determined spectrophotometrically.

2.2.5. Determination of partition coefficient: The partition coefficient determination study was performed by using shake flask method. Excess amounts of the drug (Gefitinib) dissolved in 10 ml of two solvents (n-octanol: Water) together (1:1) and placed for 24 h. After 24 h, the two layers were separated and centrifuge for 15 min's at 15,000 rpm. The absorbance was taken in UV spectrophotometer at the respective λ max after appropriate dilution [8-10]

2.2.6. Drug- excipient compatibility study: The compatibility of drug with excipients was as certained by FT-IR (Perkin). FTIR was used as tool to detect any physical and chemical interaction between drug and excipients. Drug and various excipients were mixed thoroughly in ratio of 1:1. Samples were scanned by FTIR under the range of 400-4000 cm-1. The spectra of pure drug and drug with excipients were compared to check any incompatibility and physical changes.

2.3. Preparation of Gefitinib- phospholipid complex

Gefitinib Phospholipid Complex was prepared by solvent evaporation method. Briefly, different molar ratio (0.01:0.01, 0.01:0.02, 0.01:0.03, 0.01:0.04, 0.01:0.05, 0.01:0.06, 0.01:0.07,0.01:0.08) of gefitinib: Phospholipid, and complexing solvent (methanol) were studied for the preparation of gefitinib phospholipid complex as shown in **Table 1**. Briefly, Gefitinib and Lipoid® E80(egg lecithin) were co- dissolved in selected ratio in 10 ml of optimized solvent and refluxed at 40°C for 2 h. The solvent was then evaporated using a rotary evaporator (Perfit, India) to get the gefitinib Phospholipid Complex, then dried under vacuum for overnight to remove traces of solvents. The resultant complex was stored in airtight container at below 20°C [11-14].

Table 1: Composition of Phospholipid complex containing Gefitinib

Phospholipid complex Composition			
Sr.no.	**Formulation Code**	**Drug :Egg lecithin E80 (molar ratio)**	**Methanol (ml)**
1	F1	0.01:0.01	10
2	F2	0.01:0.02	10
3	F3	0.01:0.03	10
4	F4	0.01:0.04	10
5	F5	0.01:0.05	10
6	F6	0.01:0.06	10
7	F7	0.01:0.07	10

2.4. Characterization of Phospholipid complex

2.4.1. Visible appearance: Phospholipid complex can range from translucent to milky, depending on the composition and particle size.

2.4.2. Solubility Study of drug phosopholipid complex: Solubility determination of pure gefitinib and gefitinib- phospholipids complex was carried out by adding equivalent of gefitinib or phospholipids complex to 2 ml of n-octanol in sealed glass containers at 25°C. The liquids were agitated for 24 h, and then centrifuged to remove excessive gefitinib (15 min, 15,000 rpm). The supernatant was collected & the concentration of gefitinib was determined spectrophotometrically [15-18].

2.4.3. Drug content: Drug Content of gefitinib-phospholipids complex loaded can be determined by dissolving accurately weighed 100mg of gefitinib-phospholipids complex in 10ml methanol. After appropriate dilution absorbance may be determined by UV- Spectrophotometer (ʎmax= 250 nm). The drug content was calculated [19,20].

2.4.4. Optical microscopy: A drop of phospholipid complex was placed on a glass slide and covered by a glass cover and observed under microscope

2.4.5. Particle size and zeta potential: Particle size diameter and zeta potential, were determined at room temperature by Zeta Potential/ Particle sizer-analyzer. Phospholipid complex formulations were diluted with water, for Zeta potential and particle size determination, respectively.

2.4.6. *In vitro* drug release study: *In vitro* release kinetics of Phospholipid complex was determined in this work using dialysis method. In brief, Phospholipid complex equivalent of pure drug concentration(250mg) was enclosed in a dialysis bag and then placed in 30 mL of phosphate buffer (PB) pH 6.8 used as release media. The entire system was kept at 37°C ± 0.5°C with continuous magnetic stirring. At selected time intervals (0.25,0.5,1,2,3,4,6,8,12 and 24 hour), 3 mL of solution was withdrawn from the release medium and replenished with the same volume of release medium. The collected samples were suitably diluted and analyzed by UV–visible spectrophotometer at 250nm [21-24].

2.4.7. Drug release Kinetic: Model dependent methods are based on different mathematical functions, which describe the release profile. Once a suitable function has been selected, the release profiles are evaluated depending on the derived model parameters [25,26]. The data obtained from ex vivo permeation studies were plotted in different models of data treatment like as Zero Order model, First Order model, Higuchi's Model and Krosmeyer-Peppas model.

3. RESULTS AND DISCUSSION

3.1. Pre formulation Studies

3.1.1. Organoleptic properties: Organoleptic properties of Gefitinib were found to be as per literature. The Organoleptic properties of Gefitinib were found to the given in table 2.

Table 2: Organoleptic Properties of Gefitinib

Sr. No.	Properties	Inferences
1.	Colour	White
2.	Form	Crystalline

3.1.2. Melting point: The melting point of a substance is the temperature at which the solid phase gets converted to liquid phase under the one atmosphere of pressure. The melting point determination implies the purity of drug. Melting point of Gefitinib was determined by capillary tube method and was found to be quite similar to the reported melting point as shown in **table 3**.

Table 3: Melting Point of Gefitinib.

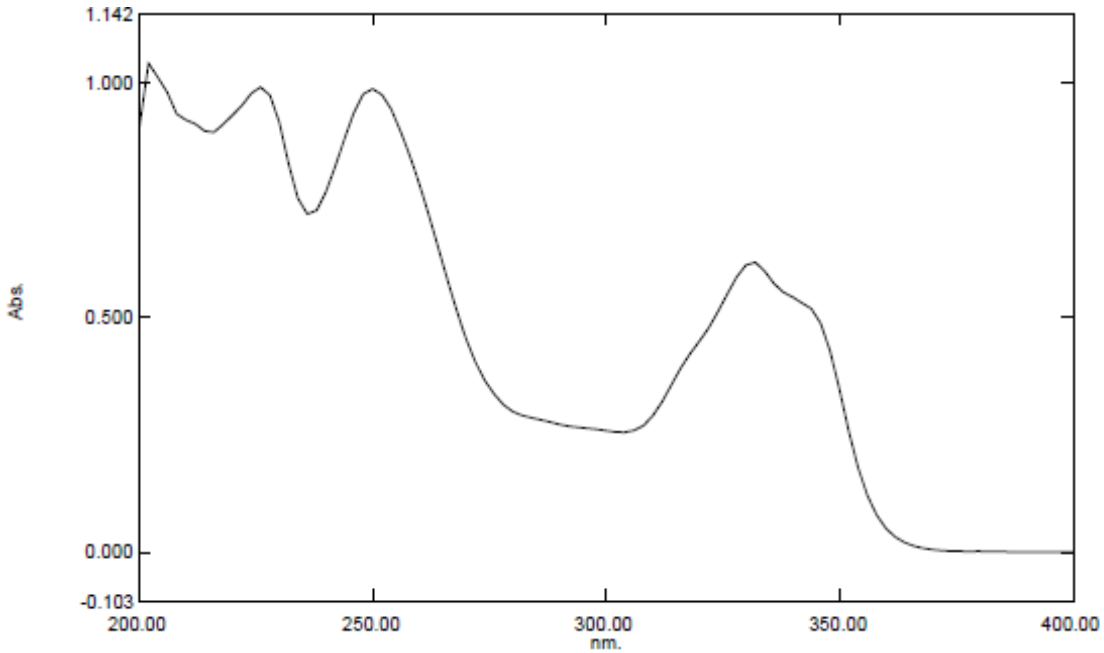
Drug	Reference M.P.	Observed M.P.
Gefitinib	193-195°C	192.33±0.577°C

The melting point of Gefitinib was found to be192.33±0.5770C which is in the range of the pure drug. Hence drug sample was free from any type of impurities.

3.1.3. UV-spectroscopy:

Determination of absorption maxima in Methanol

A double beam UV-visible spectrophotometer (Shimadzu, Japan) was used for quantitative analysis of the drug. A 3.5 µg/ml solution of Gefitinib in methanol was scanned in the range of 200-400 nm. The result of UV spectrum of Gefitinib is shown in **Figure 1**.



[Measurement Properties]
Wavelength Range (nm.): 200.0 to 400.0
Scan Speed: Medium
Sampling Interval: 2.0

[Instrument Properties]
Instrument Type: UV-1800 Series
Measuring Mode: Absorbance
Slit Width: 1.0

No.	P/V	Wavelength	Abs.	Description
1	↑	332.00	0.616	
2	↑	250.00	0.984	
3	↑	226.00	0.988	
4	↑	202.00	1.038	
5	↓	304.00	0.255	
6	↓	236.00	0.718	
7	↓	216.00	0.892	

Figure 1: UV Spectrum of Gefitinib in Methanol

Table 4: Absorption maxima (λ_{max}) of Gefitinib in Methanol

Name of drug	Absorption maxima (λ_{max})	
	Observed	Reference
Gefitinib	250	250

The maximum wavelength of Gefitinib was observed at 250 nm similar to literature (**Table 4**).

Preparation of standard curve of Gefitinib in Methanol

To prepare a standard curve of Gefitinib in methanol for concentrations ranging from 0.5 to 3.5 µg/ml, first accurately weigh and dissolve an appropriate amount of Gefitinib in methanol to prepare a stock solution of a known concentration, for instance, 1 mg/ml. Serially dilute the stock solution with methanol to obtain a series of standard solutions with concentrations of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 3.5 µg/ml. Transfer each standard solution to a separate, clean, and dry volumetric flask, ensuring thorough mixing. Measure the absorbance of each standard solution at the appropriate wavelength using a UV-Vis spectrophotometer. Plot the absorbance values against the corresponding concentrations to construct the standard curve. Ensure all glassware used is clean and dry, and perform all measurements in triplicate to ensure accuracy and precision.

Table 5: Calibration curve of Gefitinib in Methanol (λ_{max}= 250 nm)

Sr. No.	Concentration.(µg/ml)	Mean±SD
1	0.5	0.232±0.001
2	1	0.365±0.001
3	1.5	0.488±0.001
4	2	0.599±0.001
5	2.5	0.717±0.001
6	3	0.847±0.001
7	3.5	0.986±0.001

Value is expressed as mean ± SD; n = 3

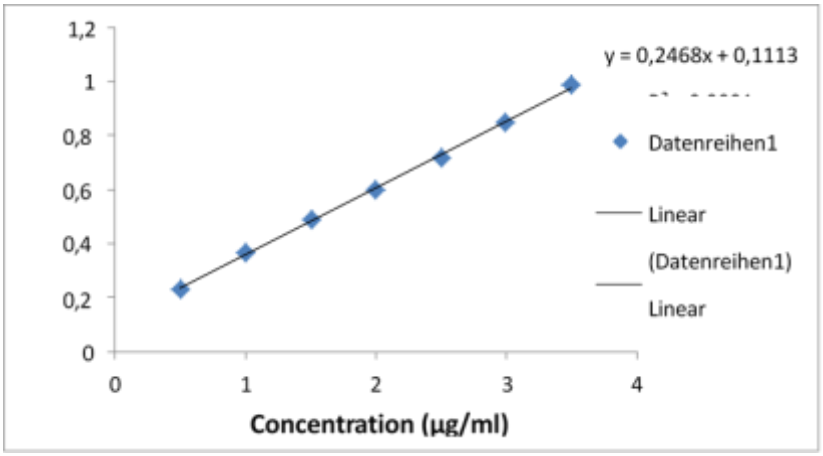


Figure 2: Standard calibration curve of Gefitinib in Methanol

Table 6: Result of regression analysis of UV method

Statistical parameters	Results
λmax	250 nm
Regression equation (y =mx+ c)	y=0.2468x + 0.1113
Slope (m)	0.2468
Intercept (C)	0.1113
Correlation coefficient (R^2)	0.9991

The calibration curve for Gefitinib was obtained by using the 0.5 to 3.5 µg/ml concentration of Gefitinib in methanol. The absorbance was measured at 250 nm. The calibration curve of Gefitinib as shows in graph indicated the regression equationy=0.2468x + 0.1113and R^2 value0.9991, which shows good linearity as shown in **Table 5, Table 6 and Figure 2**.

3.1.4. Solubility studies: Solubility of drug in various solvents, were carried out in order to screen for the components to be used for formulation development. Analysis of the drug was carried out on UV Spectrophotometer at 250 nm.

Table 7: Solubility studies of Gefitinib for different solvents

Sr.No.	Name of Solvents	Solubility in mg/ml	Solubility
1	Ethanol	1.176±0.030	Slightly soluble
2	Methanol	1.054±0.030	Slightly soluble
3	Chloroform	1.044±0.046	Slightly soluble
4	Acetone	1.014±0.018	Slightly soluble
5	0.1 N HCL	0.012±0.001	Insoluble
6	Phosphate buffer pH 6.8	0.003±0.001	Insoluble

7	Water	0.001±0.046	Insoluble

From the above data, it is clearly seen that Gefitinib is slightly soluble in Ethanol, methanol and chloroform (**Table 7**).

3.1.5. Partition coefficient determination: Partition coefficient of the Gefitinib was determined using n-octanol and water. Log P greater than one indicates that the drug is lipophilic in nature, whereas those with partition coefficients less than one are indicative of a hydrophilic drug. This indicated the lipophilicity and purity of drug.

Table 8: Partition coefficient determination of Gefitinib

Partition coefficient of drug	Solvent system	Log P Values	Reference
Gefitinib	n-octanol: water	3.220±0.039	3.2

Value is expressed as mean ± SD; n = 3

The partition coefficient of Gefitinib in n-octanol: water was found to be3.220±0.039, this indicates that the drug is lipophilic in nature (**Table 8**) which is similar to the literature.

3.2. Characterization of Phospholipid complex

3.2.1. Visible appearance of phospholipid complex: The appearance of phospholipid complex formulations are shown in **Table 9** as given below.

Table 9: Visual Appearance of Phospholipid complex

Sr. No.	Formulation Code	Appearance
1	F1	Yellowish thin layer
2	F2	Yellowish thin layer
3	F3	Yellowish thick layer
4	F4	Yellowish thick layer
5	F5	Yellowish thick layer
6	F6	Yellowish thick layer
7	F7	Yellowish thick layer

Freshly prepared drug loaded phospholipid complex formulations F1-F2 was found to be yellowish thin layer and F3-F7 was found to be yellowish thick layer.

3.2.2. Solubility study of drug phospholipid complex: The solubility for the formulations with the ratio of drug to phospholipid ratio is discussed in **Table 10.**

Table 10: n-Octanol Solubility of Pure drug & gefitinib-phospholipid Complex

Sr.No.	mulation Code	Phospholipid ratio(M)	Solubility in n- octanol (mg/ml)± SD
1	F0	Pure drug	0.436±0.004
2	F1	0.01:0.01 Complex	0.54±0.015
3	F2	0.01:0.02 Complex	0.635±0.004
4	F3	0.01:0.03 Complex	0.715±0.006
5	F4	0.01:0.04 Complex	0.809±0.004
6	F5	0.01:0.05 Complex	1.152±0.005
7	F6	0.01:0.06 Complex	0.85±0.004
8	F7	0.01:0.07 Complex	0.727±0.005

The **Table 10** represents the solubility of gefitinib and gefitinib-phospholipid Complex in organic phase (n-octanol). The data showed the solubility of Gefitinib-phospholipid Complex in n-octanol was more than that of gefitinib and 0.01:0.05 ratio (Pure drug: Phospholipid) showed higher solubility (1.152mg/ml).

3.2.3. Drug content: The percentage drug content of different phospholipid complex formulation containing gefitinib is shown in **Table 11** as shown below. The analysis was under taken by UV-visible spectroscopy (Shimadzu, Japan).

Table 11: Percentage drug content of different Phospholipid complex formulation containing Gefitinib

Sr. No.	Formulation Code	% Drug content
1	F1	78.800±0.092
2	F2	84.445±0.921
3	F3	88.435±0.532
4	F4	89.049±0.921
5	F5	95.188±0.532
6	F6	93.653±0.921

7	F7	91.812±0.921

The drug content of Phospholipid complex content was found to be 78.800±0.092 and 95.188±0.532 respectively. The percentage drug content of all formulations was found to be satisfactory. Hence, the method adopted for phospholipid complex formulations was found to be suitable.

Optical microscopy: Optical Microscopy of drug loaded Phospholipid complex formulation was determined by optical microscopy at 100 magnification and result was shown in **Fig. 3**.

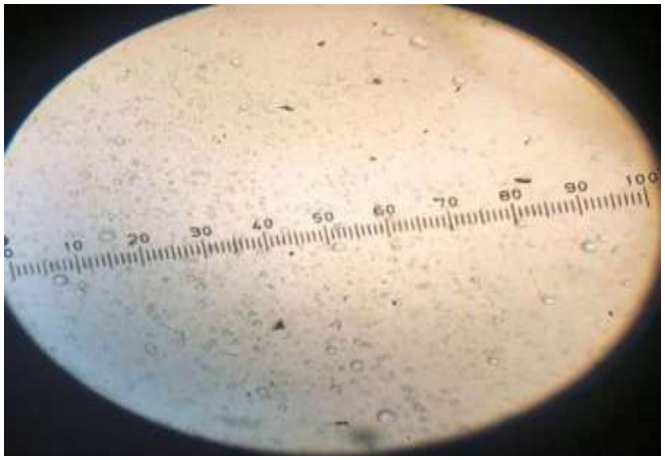
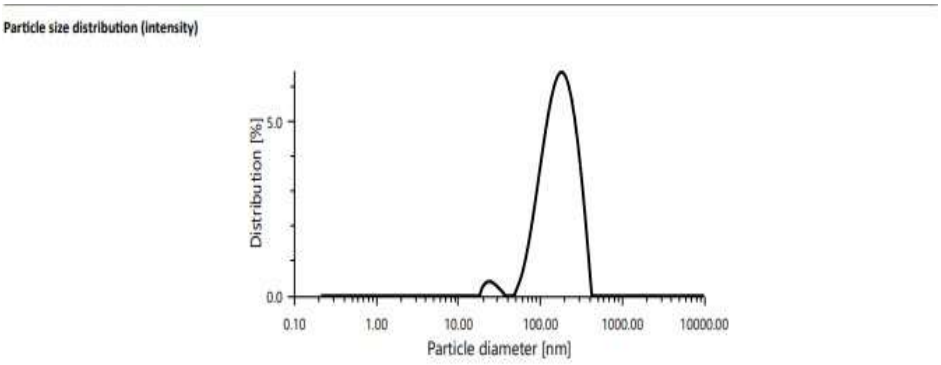


Figure 3: Optical Microscopy of Phospholipid complex formulation

Uniform, regular and rigid vesicles were observed in optical microscopic view

3.2.4. Particle size and zeta potential determination:

Particle Size analyzer (Anton Paar) was used to analyze the size of the particle, zeta potential and PDI.

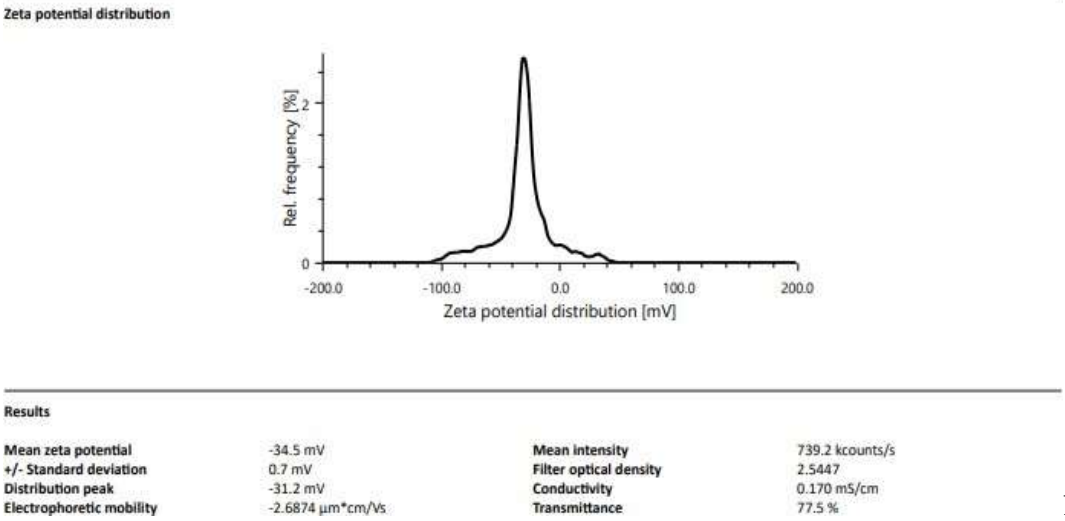


Results			
Hydrodynamic diameter	162.63 nm	Mean intensity	308.4 kcounts/s
Polydispersity index	23.9 %	Absolute intensity	59691.8 kcounts/s
Diffusion Coefficient	3.0 µm²/s	Intercept g1²	0.9155
Transmittance	71.1 %	Baseline	1.006

Figure 4: Particle size peak of phospholipid complex formulation (F5)

The Fig. 4 demonstrates particle size of phospholipid complex formulation was 162.63nm with PDI 23.9%. A zeta potential of -34.5 mV suggests a highly stable colloidal suspension, as values more negative than -30 mV typically indicate strong electrostatic repulsion forces preventing particle aggregation.

Figure 5: Zeta potential graph of P



hospholipid complex formulation (F5)

The **Fig. 5** demonstrates zeta potential of phospholipid complex formulation (F5) was -34.5mV represents stability of formulation.

3.2.5. FT-IR of optimized formulation: The FT-IR (Perkin) for the optimized formulation (F5) was shown in the **Figure 6**.

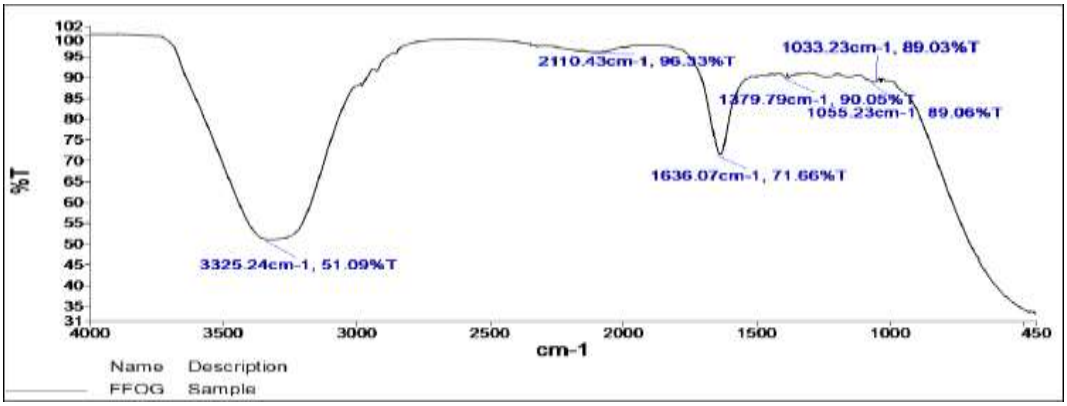


Figure 6: The FTIR of F5 formulation batch

FTIR spectrum of final formulation demonstrated that the characteristic peak of drug was either disappeared or slightly shifted with reduced intensity, thus indicated the encapsulation of drug in drug phospholipid complex formulation.

3.2.6. *In vitro* drug release study: The *in vitro* of the formulations were carried out by Franz diffusion cell (Orchid scientific) for 24 hours at a decided interval of time.

Table 12: Percentage drug release of Formulation F5 and Pure drug

Time interval (Hour)	% Drug release of Pure Drug	% Drug release of Formulation(F5)
0	0	0
0.25	2.447±0.281	4.230±0.486
0.5	5.851±0.743	8.282±0.281
1	6.661±0.486	12.010±0.486
2	8.444±0.281	17.034±0.281
3	10.551±0.486	25.138±0.486
4	13.306±0.743	32.431±0.486
6	18.493±0.743	44.100±0.486
8	23.193±0.486	55.122±0.743
12	29.028±0.486	63.712±0.743

24	37.455±0.281	76.191±0.486

Drug release graphs for pure drug & drug phospholipid Complex were significantly different from the profile of drug alone. In the pure drug solution, 37.455% gefitinib was released within 24hr. On the other hand, the release of drug phospholipid Complex was release upto 76.191% within 24 hr followed by controlled manner. The in-vitro drug release of formulation F5 and Pure drug was given in a **Table 12**.

3.2.7. *In vitro* drug release kinetic: The *in vitro* drug release kinetic was performed by *in vitro* drug release data by plotting the graph as per the models on Microsoft excel 2014. Mathematical models are commonly used to predict the release mechanism and compare release profile. For all the optimized formulations, the % drug release vs time (zero order), log percent drug remaining vs time (first order), log per cent drug release vs square root of time (Higuchi plot), and log of log % drug release vs. log time (Korsmeyer-Peppas Exponential Equation) were plotted.

Table 13: Kinetic equation parameter of formulation F5

Formulation	Zero order		First order		Higuchi		Krosmeyer- Peppas	
	R^2	K_o	R^2	K_o	R^2	K_o	R^2	K_o
F5	0.8313	3.2771	0.9403	-0.0265	0.9635	18.006	0.9826	0.659

In each case, R^2 value was calculated from the graph and reported in **Table 13.** Considering the determination coefficients, Krosmeyer-Peppas model was found (R^2=0.9826) to fit the release data best. It could be concluded from the results that the drug was released from phospholipid complex by a controlled release mechanism.

CONCLUSION

Gefitinib is an oral medication &used for the treatment of certain cancers such as colon, lung, ovarian, and breast cancer. It acts by inhibiting epidermal growth factor receptor tyrosine kinase and belongs to Biopharmaceutical Classification System class II. Drug-phospholipid complexes improve the bioavailability of drugs which have either very low lipid solubility or very poor water solubility. Therefore, drug can be complexed for improving biopharmaceutical properties. Phospholipid complex formulation of gefitinib was prepared by using the reflux technique method. For optimization of phospholipid complex, different formulations (F1 to F8) were prepared using the various quantities of lipid. Formulation (F5) with maximum n-octanol solubility, drug content and optimum size considered as optimized formulation. The shape and size of the optimized F5 formulation was confirmed through microscope and particle size and found that most of the particles were well identified. Optimized formulation in vitro drug release was studied in phosphate buffer saline (PBS) pH 6.8 using dialysis method. To know precisely, the rate and mechanism of drug release, the in vitro data was fitted to zero order, first order, Higuchi and Krosmeyer-Peppas model. The results showed that the drug release of F5 formulation followed Krosmeyer-Peppas which describes that the gefitinib follows a controlled mechanism for release from phospholipid complex.

Abbreviation

Drug Delivery System **DDS**, Novel Drug Delivery System **NDDS**, Human ovarian cancer **HOC**, Vascular Endothelial Growth Factor **VEGF**, Cholesterol **CH**, Fourier Transform Infrared **FTIR**.

Author contribution: All author has equally contributed in the research work.

Ethical Consideration: Not applicable

Funding: NIL

Conflict of interest: All authors have none to declare.

REFERENCES

1. Patel RR, Patel JK. Novel Technologies of Oral Controlled Release Drug Delivery System, Dep. Pharm. Tech. Systematic Reviews in Pharmacy. 2010; 1(2);128-132
2. Gold J, Laxer D, Rochon P. Herbal remedies; a critical perspective. Ann R Coll Physician Surg Can 2000; 33: 497-498.
3. Pal R, Pandey P, Maurya VK, Saxena A, Rizwan M, Koli M, Shakya S, Pinki K. Optimization And Formulation of Doxorubicin (DOX) Loaded Liposome Well-Used in Chemotherapy Involving Quality by Design (QBD): A Transitory Research. European Chemical Bulletin. 2023;12:4491-510.
4. Gupta A, Ashawal MS, SarafS.Phytosome: a novel approach towards functional cosmetics. J Plant Science.

2007:644-649.
5. Kumari P, Singh N, Cheriyan P, Neelam.Phytosome: a noval approach for phytomedicine. Int J of Institutional Pharmacy and Life Sciences.2011; 1: 89-100.
6. More MS, Shende MA, Kolhe DB, J. N. M. Herbosomes: herbo-phospholipid complex an approach for absorption enhancement, Int. J. Biol. Pharm. Res., 2013;4(9):634–639.
7. Kuamwat RS, Mruthunjaya K, G. M. K. Preparation, characterisation and antioxidant activities of gallic-acid phospholipid complex, Int. J. Res. Pharm. Sci., 2012;2:138–148.
8. Pathak K, Das RJ. Herbal Medicine-A Rational Approach in Health Care System, Int. J. Herb. Med. IJHM1, 2013;1(13);86–89.
9. Pal, R., Pandey, P., Rizwan, M., Koli, M., Thakur, S.K., Malakar, R.K., Gupta, H., Khadam, V.K.R. and Chawra, H.S., 2023. The Utilization of Response Surface Methodology (RSM) In the Optimization of Diclofenac Sodium (DS) Liposomes Formulate through the Thin Film Hydration (TFH) Technique with Involving Computational Method. *Journal of Advances in Medicine and Medical Research*, *35*(22), pp.287-300.
10. Tripathy S, Patel DK, Barob L, Naira SK. A review on phytosomes, their characterization, advancement & potential for transdermal application, J. Drug Del. and Ther., 2013;3(3):147-152
11. Jing Li, Xulin W, Ting Z, Chunling W, Zhenjun H, Xiang L, Yihui D. A review on phospholipids and their main applications in drug delivery systems, Asian J. Pharm. Sci., 2104;10(2):81–98.
12. Dhiman A, Nanda A, S. A. Novel Herbal Drug Delivery System (NHDDS) : the need of hour, Int. Conf. Environ. Energy Biotechnol, 2013;51(26):139–142.
13. Jadhav S. M, Morey P, Karpe MM, Kadam V. Novel vesicular system: An overview, J. Appl. Pharm. Sci., 2012;2(1):193–202.
14. Saraf S, Khan J, Alexander A, Ajazuddin&Saraf S. Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives, J. Control. Release, 2013;168(1):50–60.
15. Amit P, Tanwar YS, Rakesh S, Poojan P. Phytosome :Phytolipid Drug Delivery System for Improving Bioavailability of Herbal Drug, J. Pharm. Sci. Biosci. Res., 2013;3(2):51– 57.
16. Bombardelli E. Phytosome: new cosmetic delivery system. Boll Chim Farm. 1991; 130 (11): 431-438.
17. Pal R, Pandey P, Khadam VK, Chawra HS, Singh RP. The diverse marketed formulations of advanced nano drug carrier vehicles (and CVS) in different biomedical treatments: a complete descriptive review. International Journal of Pharma Professional's Research (IJPPR). 2024 Jun 4;15(2):1-6.
18. Manthena S., Srinivas P. Sadanandam. Phytosome in herbal drug delivery. J of natural Pharmaceutils. 2010; 1(1):16.
19. Qunyou Tan, Shan Liu, Xueliang Chen, Mingjun Wu, Hong Wang, Huafeng Yin, Dan He, HuarongXiong, and Jingqing Zhang. Design and evaluation of a novel evodiamine- phospholipid complex for improved oral bioavailability. AAPS PharmSciTech. 2012; 13(2): 534–547.
20. Bruce A, Alexander J, Julian L, Martin R, Keith R, Peter W. Molecular Biology of the Cell. 4th ed. New York; Garland Sciences: 2002.
21. Constantinides PP, Chaubal MV, Shorr R. Advances in lipid nanodispersions for parenteral drug delivery and targeting. Adv Drug Deliv Rev 2008;60(6):757-67.
22. Singh A, Saharan VA, Singh M, Bhandari A. Phytosome: Drug delivery system for polyphenolicphytoconstituents. Iranian J of Pharm Sci. 2011; 7: 209-219.
23. Zierenberg O, Grundy SM. Intestinal absorption of polyenephosphatidylcholine in man, J Lipid Res. 1982; 23: 1136-1142.
24. Chaurio RA, Janko C, Munoz LE, Frey B, Herrmann M, Gaipl US. Phospholipids: Key Players in Apoptosis and Immune Regulation. Molecules 2009;14(12):4892-914.
25. Sarika D, Khar RK, Chakraborthy GS, Saurabh M. Phytosomes:A Brief overview. J Pharm Res 2016;15(2):56-62.
26. Suslick KS. Kirk-Othmerencyclopedia of chemical technology. New York: Wiley&Sons; 1998.