RESEARCH PAPER

Development of Docetaxel Loaded Phospholipid Complex Encapsulated in Pluronic Micelles for Improved Solubility and Efficacy

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ABSTRACT
Water solubility, drug permeability, and metabolism are some of the elements that affect a medication's oral bioavailability. In medication development, poor solubility is a problem that frequently calls for particle size reduction methods like nanosization, which improves bioavailability. Important model terms and the significance of model reduction are revealed by statistical analysis. Additionally, thermal examination revealed a melting peak at 187.11°C and confirmed the successful synthesis of DXLPhP complex PF127 micelles with an average particle size of 154.2 nm, demonstrating Docetaxel's excipient compatibility. In comparison to traditional solutions, the improved formulation showed delayed drug release and a drug encapsulation effectiveness of 94.48%. Higher concentrations of the formulations reduced cell survival, according to studies on cell viability.
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Introduction

The amount and speed at which a drug's active component is absorbed from an oral dosage form and becomes accessible at its site of action is known as oral bioavailability.

This parameter is essential to demonstrate the effectiveness of drug because the amount of drug reaches the target site can only shows therapeutic effect. Factors like drug solubility, absorption rate, and individual patient differences can significantly influence oral bioavailability. Low oral bioavailability is often associated with drugs that are poorly soluble in water, absorbed slowly, or have insufficient time for absorption in the gastrointestinal tract [1, 2]. According to the U.S. Pharmacophobia, a drug is considered water-soluble if its maximum dosage dissolves in 250 milliliters of aqueous solutions with a pH range of 1 to 7.5. [3]. Many strategies have been tried to increase the drug's solubility and bioavailability in order to go over the solubility barrier. These include, among other things, complexation, particle size reduction, crystal engineering, solid dispersion, and salt creation. [4]. As a result, poor water solubility of the lipophilic compounds has become a persistent issue in both the early and late phases of pharmaceutical development as well as drug discovery. Additionally, it was said that 40% of already marketed medications and up to 70% of DXL recently developed substances may have low water solubility [5-7].

BCS class II drugs, as defined by the Biopharmaceutics Classification System, are characterized by lower solubility and higher permeability. For these drugs, the dissolution rate is the primary limiting factor affecting absorption, while permeability generally does not pose significant constraints. To enhance its oral bioavailability, several strategies are employed, including the reduction of particle size through methods such as nanocrystal formulation, the creation of solid dispersions, salt formation, and enhancement of solubility dependent on pH. Notable examples of BCS II drugs include itraconazole, glibenclamide, chloramphenicol, griseofulvin, danazol, and ketoconazole. It is important to recognize that the classification of these drugs may vary slightly depending on pH levels and specific formulations [8].

Particle size and surface engineering techniques enhance drug solubility and dissolution. Nanocrystals boost surface area; amorphous solid dispersions increase solubility. Spherical agglomeration creates submicron particles, while surfactant coatings improve wetting. Carriers stabilize supersaturated solutions,

with methods like hot-melt extrusion generating solid dispersions. Amorphous forms and co-crystals elevate solubility without altering pharmacology [9]. Salt forms enhance stability and solubility, supported by pH-dependent strategies. Surfactants reduce surface tension and create self-emulsifying systems. Lipid delivery systems and cyclodextrin complexes further improve solubility. Prodrugs enhance drug permeability, and advanced platforms like in situ gelling sustain release. Key factors for strategy selection include drug properties, target site, stability, manufacturability, and therapeutic window [10, **11**].

Phospholipid complexes enhance the solubility and permeability of poorly soluble drugs by complexing them with a natural phospholipid, typically phosphatidylcholine. This interaction alters the drug's hydrophobicity/hydrophilicity balance, improving its solubility in lipid environments and membrane permeability, particularly for lipophilic drugs. DPCs serve as an alternative to solid dispersions and liposomes, offering simple manufacturing and potential stability. Methods to prepare these complexes include solvent evaporation, co-precipitation, and ultrasonic mixing. While they can enhance solubility and bioavailability, stability issues, especially oxidation, and drug-specific effectiveness must be addressed, necessitating thorough characterization and understanding of regulatory considerations [12, 13, 14]. Phytosomal micelles represent a formulation strategy that merges plant-derived phospholipids (phytosomes) with micellar systems to enhance the solubility and bioavailability of poorly soluble drugs or phytochemicals. Phytosomes facilitate improved membrane permeability and solubility by forming complexes with lipophilic drugs, while micelles solubilize these compounds using their amphiphilic nature. This hybrid approach offers improved solubility, enhanced bioavailability, and potential applications for both oral and topical formulations [15]. Key formulation methods include phytosome-micelle hybrids, co-assembly, and solvent exchange. Important considerations revolve around drug properties, phospholipid and surfactant choice, stability, and characterization metrics such as particle size distribution and drug loading. Notably, phytosomal micelles may provide synergistic benefits in solubility enhancement and stability over traditional formulation approaches [**16, 17**].

Docetaxel (DTX) is a hydrophobic anti-cancer agent requiring formulation strategies for effective delivery due to its poor water solubility. Micellar formulations enhance solubility, stability, and pharmacokinetics, assisting in intravenous or oral administration. Key advantages of micellar systems include solubilization of DTX via a hydrophobic core, protection against degradation, improved pharmacokinetics through enhanced permeability and retention (EPR) for tumor targeting, and reduced exposure to toxic solvents like Cremophor EL [18].

Common micellar strategies employ polymeric micelles made of block copolymers, mixed or biomimetic micelles with PEGylated lipids, surfactant-based micelles using nonionic surfactants, and targeted micelles modified with ligands for active targeting. Formulation design considerations encompass drug loading capacity, particle size (ideally 10–100 nm for IV delivery), zeta potential for aggregation prevention, stability both physically and chemically, and polymer/drug compatibility. Release kinetics are critical for controlling drug availability at the tumor site. Typical micellar components include polymers like PLGA and PCL for the hydrophobic core, hydrophilic PEG segments for stealth properties, stabilizers such as phospholipids, and optional targeting ligands. Preparation methods like self-assembly, solvent displacement, and ultrasonication are utilized, while characterization tests involve measuring particle size, morphology, drug loading efficiency, and in vitro release kinetics. [19, 20]. Safety and regulatory considerations highlight the need to avoid toxic solvents and ensure that excipients are pharmaceutically acceptable. A practical development plan could involve achieving a targeted DTX-loaded micelle size of 40–80 nm, with a drug loading capacity greater than 5–10% and over 80% release within 24–48 hours in simulated tumor conditions. The design of experiments (DoE) could screen factors such as polymer type and drug-to-polymer ratio, with a focus on critical quality attributes like size, drug loading, and leakage rate [21, 22]. In this study we have developed phospholipid-based micelles to enhance the solubility and efficacy of docetaxel. Design of experiment was used to optimized the formula and optimized formulation was demonstrated for various parameters.

Material and methods

Material

Pluronic F127 was supplied by Himedia Laboratories in Thane, Maharashtra, India, whereas Docetaxel was supplied by SRL Pharma. In Mumbai, India, Merk Specialties Pvt. Ltd. sold us DMSO and other solvents. The investigation also made use of analytical-grade solvents. Milli-Q water served as the solvent.

Cell line and culture condition

The human breast cancer cell line MCF-7 (RRID: CVCL_0031) was grown in DMEM with 10% fetal bovine serum and incubated at 37°C with 5% $CO2$. Cells were planted at a density of 1x10^4 cells/ml for a whole day. For the MTT Assay, 10^4 cells were placed in 96-well microplates with 70 µL of growth media per well, and sample volumes varied from 10 to 100 µL. Control wells contained cell lines and 0.2% DMSO in PBS. Each sample was incubated in three duplicates at 37°C with 5% CO2 for twenty-four hours. This method was used to assess the in vitro efficacy of Pluronic F127 micelles encapsulated with Docetaxel phospholipid (DXL-PhP) complex.

Compatibility Study by DSC and FTIR

The combination of FTIR spectroscopy with DSC is a reliable technique for material compatibility tests, particularly in the creation of pharmaceutical formulations. While FTIR offers details on molecular interactions and chemical structure, DSC sheds light on a material's thermal characteristics.

DSC analysis

DSC calculates a sample's heat absorption or release as a function of temperature. Deviations in a mixture's thermogram compared to the individual components can indicate an interaction.

FTIR analysis

FTIR spectroscopy measures the vibrational and rotational movements of a material's functional groups by exposing it to infrared light. The resulting spectrum is essentially a molecular fingerprint.

Preparation of DXL-PhP complex-encapsulated Pluronic F127 micelles

A modified method from the previously described thin film hydration technique (TFH) was used to create PF127-micelles encapsulated with the DXL-PhP-complex [23]. In summary, 150 mg of PF127 copolymer were dissolved using around 100 mg of DXL-PhP complex and 10 mL of water and methanol. In an ice bath, ten three-minute cycles (30 minutes) of ultrasonication were carried out. A rotary evaporator that was set to 45°C for 30 minutes was used to extract the solvent. The formation of the thin film was observed. Five milliliters of miliQ water were used to disperse the film after it had been continuously stirred for an hour at 40°C on a magnetic stirrer. This results into the formation of micelles. A membrane filter with 0.22 µm pores was then used to filter it.

Experimental design

Micellar drug delivery systems are frequently optimized using the Box-Behnken design (BBD), an efficient response surface methodology (RSM) approach. Three-level design for independent factors, quadratic modeling to account for non-linear effects, and efficiency by requiring fewer experimental runs than other designs are some of BBD's key characteristics. In particular, BBD helps create micelles by enhancing factors like drug-to-polymer ratio and surfactant concentration. Examples from the literature show how BBD can optimize formulations for improved medication solubility and bioavailability. In the optimization process, independent factors are chosen, response variables are defined, and software is used for experimental runs. Polynomial modeling and real-world experimentation are then used to validate the projected results.

Table 2: Independent and dependent variables considered in Box-Behnken Design

Factor	**Level**		
	-1	**0**	**+1**
Independent variables			
Conc. of DXL-PhP complex	20	40	60
(X_1, mg)	50	100	150
Conc. of PF127 (X_2, mg)	40	45	50
Temperature (X_3, °C)			
Dependent variables			
Particle Size (Y_1, nm)			
Entrapment Efficiency (Y_2, %)			

Physicochemical characterization of drug loaded nanocarriers

Particle size and zeta potential

These two are the most important characteristics to assess in order to define nanocarriers and guarantee their efficacy. Zeta potential predicts the stability of the nanocarrier dispersion, whereas particle size influences how the nanocarrier is dispersed and absorbed by cells [24, 25]. A nanocarrier's biodistribution, circulation time, and capacity to pass through biological barriers are all significantly impacted by its particle size [26]. The uniformity of the nanocarrier size within a sample is indicated by the polydispersity index (PDI), a number that usually ranges from 0 to 1. A smaller, more homogeneous size distribution is indicated by a low PDI value.

The effective surface charge of particles in a colloidal suspension is measured by the zeta potential (ζ). The "slipping plane," or the line separating the moving particle from the surrounding fluid, is where it measures the electric potential. Strong electrostatic repulsion between particles, which keeps them from

settling and aggregating, is indicated by a high zeta potential, either positive or negative. A stable nanosuspension is typically thought to require a minimum absolute value of 30 mV.

Determination of drug content

The amount of a medication loaded into the formulation is indicated by drug content, sometimes referred to as drug loading content (DLC), a crucial quality feature for nanocarriers. Usually, it is stated as the mass of the medicine per unit mass of the nanocarrier or as a percentage of the overall weight of the nanocarrier system.

Entrapment efficiency

One of the most important steps in assessing nanocarrier formulations is determining entrapment efficiency (EE). It provides information about the effectiveness of the formulation process by calculating the proportion of the original medication that is successfully encapsulated within the nanocarrier. The fraction of free drug was measured and compared to the total amount of drug added during formulation to determine entrapment efficiency.

***In vitro* drug release from nanocarriers**

To assess nanocarriers and comprehend how the medication is released over time under regulated, physiologically realistic settings, an in vitro drug release study is essential. It offers important details about the stability, performance, and possible therapeutic efficacy of the nanocarrier.

The drug release from the nanocarriers will be evaluated by employing a Franz diffusion cell, This helps to track the drug's diffusion across a cellophane membrane.

The donor compartment and the receptor compartment were separated by activated cellophen membrane. The formulation was introduced from donor compartment and allowed to release drug into receptor compartment which contains 18 mL of phosphate buffer saline solution (PBS, pH 7.4) kept at 37 0.5°C. This PBS was served as the release medium in the receptor compartment.

Aliquots of the release medium will be taken out and replaced with an equal amount of new release medium at predetermined intervals.

To measure the amount of medication released, samples of the receptor media was taken out at predetermined intervals and examined using UV-Vis spectrophotometry.

Scanning electron microscopy (SEM)

A fundamental method for describing nanocarriers is scanning electron microscopy (SEM), which produces high-resolution, three-dimensional pictures of their exterior shape. Important characteristics of nanocarriers, including size, shape, surface roughness, and aggregation, are directly and thoroughly revealed by this visual study.

***In vitro* cytotoxicity study by MTT assay**

A popular colorimetric method for determining a substance's cytotoxicity on a population of cells is the MTT (3-[4, 5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay. Based on the capacity of metabolically active cells to convert the yellow, water-soluble MTT dye into insoluble purple formazan crystals, this technique is sensitive, quick, and economical. The MTT assay is used in many disciplines, such as pharmacology, toxicology, and cancer research, to find the concentration of a test item (such as a drug or nanocarrier) that either stops cell growth or kills cells.

The MCF-7 cell line was kept in an appropriate culture medium supplemented with fetal bovine serum (FBS) and antibiotics in order to conduct an in vitro cytotoxicity research. The cells should be incubated at 37°C with 5% CO2 in a humidified environment. Trypan blue exclusion staining and a hemocytometer were used to count the viable cells. The cells are then seeded into a 96-well microplate at a density suitable for the cell type, guaranteeing a consistent quantity of cells per well. For a full day, the cells were allowed to adhere and multiply.

Using the proper cell culture medium, the medication solution and nanocarrier dispersion were diluted to various quantities. The various concentrations of the test material were then added to the microplate's medium. To enable the cells to engage with the material, the plates are incubated for 72 hours.

The medium was carefully taken out of each well at the conclusion of the treatment time. To get rid of any leftover medication or serum, adherent cells were gently washed with phosphate-buffered saline (PBS). A solution of MTT (usually 0.5 mg/mL in PBS or serum-free media) was applied to each well. After that, the plates were incubated for two to four hours, or until purple formazan crystals could be seen under a microscope [27, 28].

The purple formazan crystals were dissolved by carefully removing the MTT solution and adding DMSO to each well. To guarantee full dissolution, the plate was then gently shaken for fifteen minutes on an orbital shaker. Lastly, a microplate reader was used to measure the absorbance at a wavelength of 570 nm.

Result and discussion

Experimental design and optimization of formula

By examining the impact of three independent variables—temperature, surfactant concentration, and complex concentration—a Box-Behnken design can be used to optimize micelle formulation. The evaluation of these elements' effects on micelle entrapment efficiency and particle size is made possible by this experimental design. A thorough grasp of the behavior of the formulation is made possible by the design's structure, which makes it easier to assess quadratic effects and interactions between the variables. Finding the ideal circumstances to produce desirable micelle properties, including a certain particle size and high entrapment, is the aim.

Table 3: Seventeen batches of DXL-PhP complex encapsulated PF127 micelles by employing Box-Behnken Design

Batch	Factor 1 A: Concentration of DXL-PhP Complex	Factor 2 B: Concentration of Pluronic F127	Factor 3 C: Temperature	Response 1 Particle Size (nm)	Response 2 Entrapment Efficiency (%)
	mg	mg	°C	nm	%
1	40	100	45	152	94.4
2	60	100	40	168	86
3	40	50	40	160	77.5
4	20	150	45	182	96.2
5	20	100	40	162	92.4
6	40	100	45	150	94.3
7	60	100	50	170	89.8
8	40	150	40	185	93.5
9	40	100	45	155	94.1
10	20	100	50	167	92.9
11	20	50	45	158	79.5
12	60	50	45	161	69.8
13	40	100	45	152	95
14	60	150	45	188	93.7
15	40	150	50	186	95.3
16	40	100	45	153	94.8
17	40	50	50	164	71.6

ANOVA for Quadratic model

The Model F-value exceeded 0.05 leads to the significant model terms. Here in this case the Model F value was found to be 128.04 which indicate the model was significant. Hence there was only a 0.01% chance of increases value because of noise.

In contrast whenever the P-value is lower than 0.0500 indicate the significant model term. Overall results shows that the A, B, C, and A^2 B^2 C^2 are important model terms which were non-significant if the value is ≥0.1000.

A non-significant lack of fit always good and free of error.

The difference between the Adjusted R^2 value which was 0.9862 and the Predicted R^2 value i.e. 0.9767 was less than 0.2 indicate the significant model.

The signal to noise ratio larger than 4 with sufficient signal was about 30.558.

$$\text{Particle size} = 152.4 + 2.25\,A + 12.25\,B + 1.5\,C + 0.75\,AB + -0.75\,AC +$$

Entrapment efficiency %

Higher the F-value lower the chance of risk. Hence in this case the risk factor was about only 0.01% for 9.39 F-value.

The F-value of 23.92 which is greater than 0.05 indicated the significant Lack of Fit. However about 0.51% probability of non-significant Lack of Fit F-value.

$$\text{.Entrapment efficiency} = 94.52 + -2.7125\,A + 10.0375\,B + 0.025\,C + 1.8\,AB + 0.825\,AC + 1.925BC + -1.96\,A^2 + -7.76\,B^2 + -2.285\,C^2$$

The difference between the Adjusted R^2 value i.e. 0.9805 and the Predicted R^2 value i.e. 0.8700 was ≤0.2.

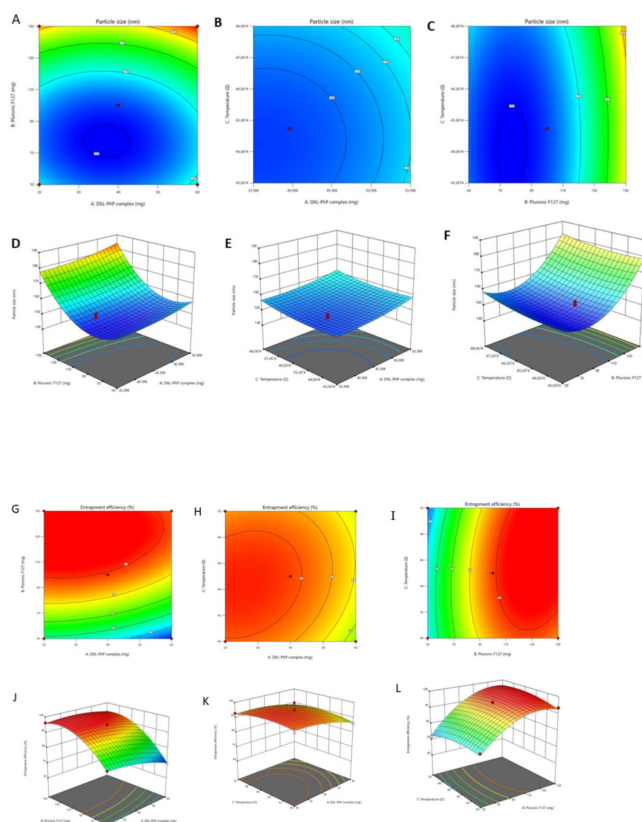


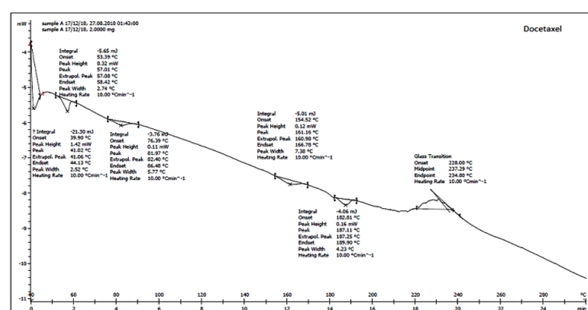
Figure 1: Contor plot of particle size (nm) against A) concentration of drug and polymer, B) concentration of drug and temperature, C) concentration of polymer and temperature; 3D surface plots of particle size (nm) against D) concentration of drug and polymer, E) concentration of drug and temperature and F) concentration of polymer and temperature. Contor plot of entrapment efficiency (%) against G) concentration of drug and polymer H) concentration of drug and temperature and I) concentration of polymer and temperature; 3D surface plots of entrapment efficiency (%) against J) concentration of drug and polymer, K) concentration of drug and temperature and L) concentration of polymer and temperature

Drug's excipient compatibility

The physical mixing of Docetaxel with excipients and the outcomes of the thermal analysis proved the drug's excipient compatibility.

DSC analysis

A novel molecule or chemical change is indicated by peak features such as broadening and tapering with variations in initiation time. When pure docetaxel was subjected to DSC analysis, thermograms showed a notable melting peak at about 187.11°C. Figure 2B shows the correlation between the melting point and peak value of docetaxel. Another thermogram of the PF 127 shows a glass transition at 40.39 °C (see Figure 2A).



(A)

(B)

Figure 2: DSC of Docetaxel and their mixture with other excipients

FTIR Study

In the FTIR spectroscopic analysis of pure Docetaxel, the hydroxyl group (-OH), carboxyl group (C=O), alkyl group (C=C), and ester group (-COO-) are represented by separate peaks at wave numbers 3457, 2928, 2342, 1700, and 1247 (cm−1), respectively (see Figure 3A). C–H stretching vibrations in aliphatic groups are typically attributed to a peak about 2928 cm^{-1}. Carbonyl (C=O) stretching vibrations are usually linked to an absorption at around 1700 cm^{-1} (see Figure 3B). The bands at 3420, 2881, 1728, and 1277 cm^{-1} are typical for hydrogen-bonded O–H stretching in alcohols or carboxylic acids, a symmetric or asymmetric C–H stretching from $-CH_2-$ and $-CH_3$ groups, strong carbonyl (C=O) stretching, and frequently C–O stretching for ethers and esters, respectively (see Figure 3C).

(A)

(B)

(C)

Figure 3: FTIR spectra of Docetaxel A), PF127 B) and their mixture C)

Particle Size

Measuring the hydrodynamic diameter of nanomaterials using a DLS-based method is a crucial initial step since particle size influences material transport over the membrane. The bioavailability of particles in the 200–400 nm size range is greater than that of their original substance or material with micro-sized particles, according to earlier research [29, 30]. The PF127-Ccm micelles had an average particle size of 154.2 nm (Figure 4A). The DXL-PhP complex PF127 micelles were discovered to have zeta potentials of -16.1 mV (see Figure 4B).

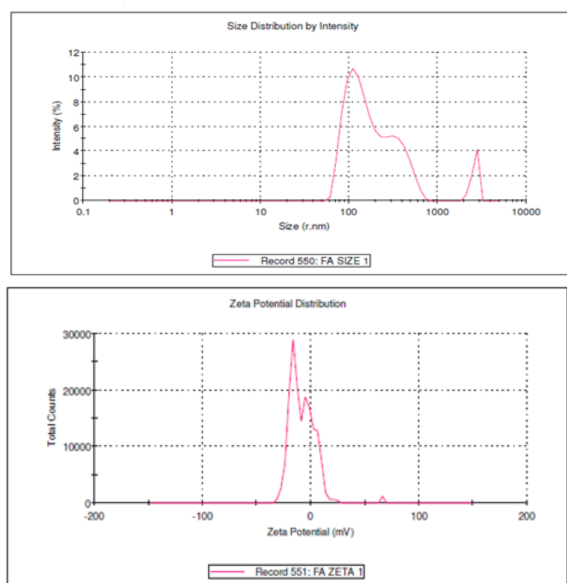
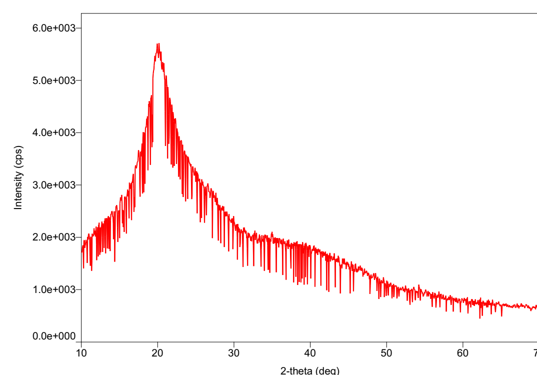


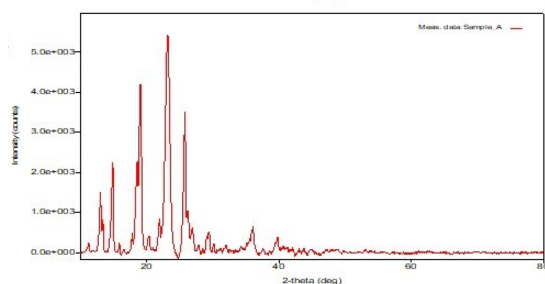
Figure 4: Particle size and zeta potential of DXL-PhP complex PF127 micelles

Powder X-ray diffraction (P-XRD)

The docetaxel diffractogram shows the distinctive peaks at the Bragg angle, 2_ h = 14.00, 20.10, 21.15, and 23.28, with intensities of 238, 937, 416, and 193, respectively. At the Bragg angle, 2_ h = 16.134, 18.079, 20.778, 23.055, 29.384, 30.953, and 36.294, other figures 5B and 5C showed distinctive peaks. These results showed that the formation of the DXL phospholipid complex was successful. DXL was successfully contained inside the phospholipid complex, as shown by the XRD pattern of the DXL-phospholipid complex, where the distinctive peaks of phospholipid appeared and the characteristic peaks of DXL disappeared (see Figures 5A, 5B, and 5C).



(A)



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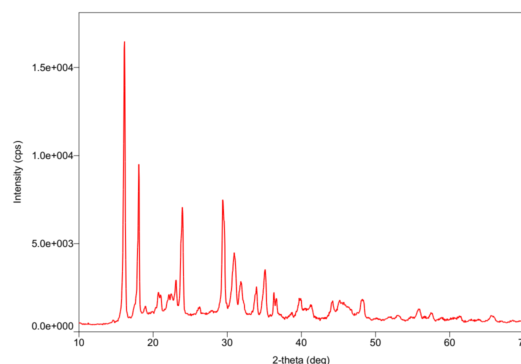


(C)

Figure 5: XRD diffractogram of Docetaxel, Phospholipon 90H and PF127 their physical mixture

Entrapment efficiency

The %EE of optimized formulation of nanocarriers was found to be 94.4± 1%.

***In vitro* drug release study**

Using the dialysis approach, the drug release pattern of DXL from the optimized batch of DXLPhP-PF127 micelles and the conventional Docetaxel solution was assessed during a 24-hour period (see Figure). The improved batch of DXLPhP-PF127 micelles is compared to the standard Docetaxel solution (see Figure 6A). The optimized batch displayed a 97.78±0.22% release after a full day. As a result, as compared to traditional Docetaxel solution, DXL-PhP complex PF127 micelles exhibit a higher percentage of

drug release over a longer duration.

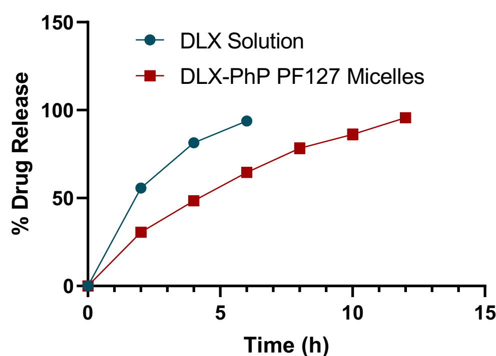


Figure 6: *In vitro* drug release from DXLPhP complex PF127 micelles

SEM study

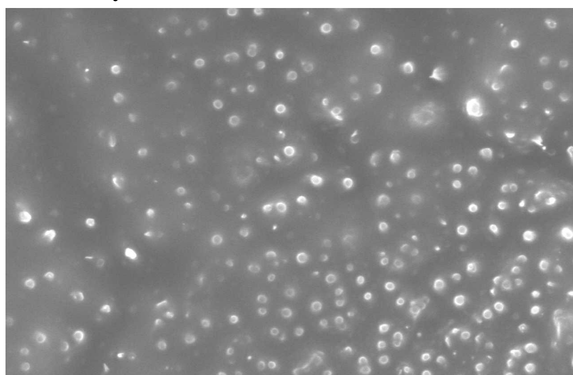
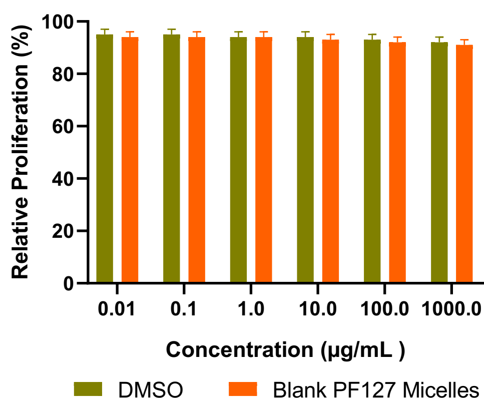


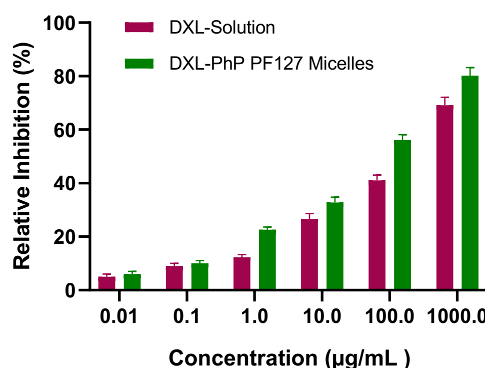
Figure 7: Scanning electron microscopic image of DXLPhP complex PF127 micelles

***In vitro* cytotoxicity study**

Using human breast adenocarcinoma MCF-7 cell lines, the MTT experiment investigated the cell cytotoxicity of Blank PF127 micelles, standard Docetaxel solution, and DXL-PhP complex PF127 micelles at different doses. Cell viability in response to DMSO, various Ccm solutions, and DXL-PhP complex PF127 micelle doses is shown in Figure 8 (A and B). At low concentrations, all three formulations demonstrated good cell viability; however, cell survival declines with increasing concentration.



(A)



(B)

Figure 8: In vitro cytotoxicity study of DXL-PhP complex PF127 micelles and Docetaxel solution for 72 h

Conclusion

A drug's water solubility, drug permeability, and metabolism all have an impact on its oral bioavailability. Drug development is hampered by poor solubility, which calls for methods like nanosization to increase bioavailability. Significant model terms and the requirement for model reduction were revealed by statistical analysis. Thermal analysis confirmed the development of DXL-PhP complex PF127 micelles with a lower particle size and showed that Docetaxel is compatible with excipients. In comparison to traditional solutions, the improved formulation demonstrated longer drug release and a higher drug encapsulation efficiency. Furthermore, in viability tests, the formulations' greater concentrations decreased cell survival. The overall outcome showed that PF127 micelles based on the DXL-PhP complex are a viable method for improving Docetaxel's solubility and effectiveness.

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