RESEARCH PAPER

Design and Evaluate Polymeric Micelles Loaded with Paclitaxel, A Chemotherapy Drug, for Breast Cancer Treatment

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Abstract
Breast cancer, particularly the aggressive triple-negative subtype (TNBC), remains a major therapeutic challenge due to a lack of targetable receptors and the severe limitations of conventional chemotherapy. Paclitaxel (PTX) is a cornerstone drug, but its clinical utility is hampered by poor aqueous solubility and severe side effects linked to its solubilizing vehicle, Cremophor® EL. This study aimed to develop a Cremophor-free, polymeric nanoparticle system to improve the delivery and therapeutic profile of PTX. Paclitaxel was encapsulated within poly (lactic-co-glycolic acid) (PLGA) nanoparticles using a double-emulsion solvent evaporation method, with polyvinyl alcohol (PVA) as a stabilizer. The optimized formulation (NP3) exhibited a high encapsulation efficiency (84.25%), a particle size of ~309 nm, a negative zeta potential, and a spherical morphology as confirmed by FESEM and TEM. FTIR and DSC studies confirmed the absence of chemical interactions and the crystalline state of the encapsulated drug. In vitro release studies demonstrated a sustained release profile over 30 days, fitting the Korsmeyer-Peppas model. Crucially, the NP3 formulation showed significantly enhanced cytotoxicity against HepG2 and Huh-7 liver cancer cell lines compared to free PTX and a commercial formulation, while blank nanoparticles were non-toxic. The results indicate that PLGA-based nanoparticulate delivery is a promising strategy to solubilize PTX without harmful excipients, provide controlled release, and enhance its anticancer efficacy, offering a potential improved therapeutic option for challenging cancers like TNBC.
Keywords: Triple-Negative Breast Cancer (TNBC); Paclitaxel; Drug Delivery; Polymeric Nanoparticles; PLGA; Cremophor EL; Sustained Release; Cytotoxicity; Nanomedicine.
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INTRODUCTION

Breast Cancer: Epidemiology, Current Therapies, and Limitations.

The most commonly diagnosed cancer and one of the principal causes of cancer-related death in women all over the world, breast cancer is a significant health burden in the world. Its epidemiology has a complicated structure of genetic, hormonal, and environmental factors, and it has been increasing with the change in lifestyle and better screening. Although the survival rates have improved significantly due to improvements in early detection and treatment, significant variability in the success of the treatment of the disease, is due to the heterogeneity of the disease. The contemporary treatment options are multimodal, depending on the subtype of cancer characterized by the expression or lack of hormone receptors (estrogen and progesterone) and human epidermal growth factor receptor 2 (HER2). In the case of hormone receptor-positive cancers, endocrine therapies (e.g., tamoxifen, aromatase inhibitors) form the centre stage treatment. Monoclonal antibodies such as trastuzumab are used to target HER2 positive cancers. Cytotoxic

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chemotherapy is a pillar in all subtypes, and particularly aggressive disease in more advanced cases. Also, surgery and radiotherapy are vital local therapies. Nevertheless, such treatments are full of restrictions [1-2]. Chemotherapy especially is afflicted with the failure of tumor selectivity which results in a high level of systemic toxicity thus reducing the quality of life of the patient as well as usually restricting dose intensity. In addition, intrinsic or acquired drug resistance is also a significant clinical challenge that causes disease progression and relapse. The issue is therefore to come up with more efficient, specific, and acceptable modes of treatment that can cut across these obstacles [3-5].

1.1.1. The Challenge of Triple-Negative Breast Cancer (TNBC)

Among the various forms of breast cancer, triple-negative breast cancer (TNBC) is a highly aggressive and clinically difficult subtype that is characterized by the absence of estrogen receptor, progesterone receptor, and HER2. The lack of receptors that are targetable in tumors makes TNBC resistant to endocrine therapy and other HER2-targeted therapy making cytotoxic chemotherapy the main systemic therapy available. TNBC has a more aggressive clinical progression, and an increased tendency towards visceral metastasis and poor prognosis than other subtypes. It is a disproportionate disease in younger women and is more common in some of the ethnic groups. The dependence of traditional chemotherapy on the treatment of TNBC worsens the situation of such treatment, as in most cases, they work well at the beginning; although they are effective, the effect is short-term then the tumor is quickly reinforced and metastatic [6-8]. In addition, TNBC microenvironment is usually immunosuppressive and very complex. This biological aggressiveness coupled with the scarcity of specific therapies available and with the high level of unmet clinical need makes TNBC an urgent target of novel treatment approaches, such as the development of comprehensive drug delivery technologies that would not only maximize drug efficacy but also reduce toxicity levels [9-11].

1.2. Paclitaxel: Mechanism of Action and Clinical Challenges

Paclitaxel (PTX) is the strong diterpenoid chemotherapy drug that was first derived in the bark of the Pacific yew tree (Taxusbrevifolia). The major mode of its activity entails assembly and stabilization of microtubules which are fundamental elements of the cytoskeleton of cells that play a significant role in mitosis and cell division. PTX is unlike other tubulin-binding agents such as vinca alkaloids; which block microtubule formation by binding to the b-tubulin subunit and hyper-stabilizing the polymerized microtubules. Such stabilization inhibits their usual dynamic disassembly and results in the cell cycle arrest at the G2/M stage, the induction of apoptosis, and eventual cell death. This powerful antitumor effect has made PTX a first-line chemotherapeutic in breast cancer including TNBC. The overwhelming clinical usefulness is however crippled by gross pharmacological difficulties based on its physicochemical characteristics and excipients involved in its preparation [12-15].

1.2.1. Poor Aqueous Solubility

The greatest problem of paclitaxel is that it is highly hydrophobic; its solubility in aqueous is inferior to 0.3 ug/mL. The inherent characteristic causes it to be incompatible with any formulation in intravenous delivery as standard aqueous vehicles and requires the use of strong, non-aqueous solubilizers to develop a dose form that can be injected [16-18].

1.2.2. Toxicity and Side Effects (Neuropathy, Hypersensitivity)

PTX system is linked with severe dose-limiting toxicities. Another frequent and frequently not reversible adverse effect that may severely affect the quality of life of patients, and may require dose decrease or cessation, is peripheral neuropathy with pain, numbness, and tingling of hands and feet. Another critical issue is myelosuppression or neutropenia. Moreover, there may be acute hypersensitivity reactions (HSRs) in the course of infusion and they include dyspnea, hypotension, and rash, which are life-threatening [19-20].

1.2.3. The Role of Cremophor® EL

To eliminate the insolubility of paclitaxel, a 1:1 Cremophor(r) EL dehydrated ethanol mixture was used to prepare the commercially available formulation (Taxol(r)). Although a good solubilizer, Cremophor EL is the cause of most of the side effects of the drug. The fact that it can cause severe hypersensitivity reactions is known and requires a long course of premedication with corticosteroids and antihistamines. It can also leech polyvinyl chloride infusion sets with plasticizers which needs special tubing with Cremophor EL. In addition, it changes the pharmacokinetic profile of PTX resulting in non-linear kinetics and adding to uncertain drug disposition. More importantly than this, Cremophor EL was found to cause neuropathy and may induce PTX to be removed in micelle-like structures into the bloodstream, which may decrease the delivery of the drug to the tumors. Thus, the vehicle itself is a significant hindrance, which creates a great need of a safer, more effective, and Cremophor-free delivery system.

1.3. Nanomedicine in Oncology: Rationale and Advantages

The use of nanotechnology in medicine, which comes as a paradigm-shifting approach to the key limitations inherent in traditional chemotherapy, is called nanomedicine. The logic is founded on taking advantage of the peculiarities of pathophysiology of solid tumors the Enhanced Permeability and Retention (EPR) effect. Tumor vasculature can appear irregular, leaky and poorly organized with the fenestrations usually being between the range of 100 to 800 nanometers. At the same time, the lymphatic drainage in the tumors is often compromised. This combination enables nano-sized particles (usually 10-200 nm) to extravasate out of the blood into the tumor interstitial space and be held in the tumor interstitial space resulting in passive, targeted accumulation. This targeted delivery has significant benefits: it may enhance the concentration of drug at the tumor subcutaneously and decrease the exposure to normal tissues, which increases the efficacy of treatment and

overall reduces systemic adverse effects. Moreover, nanocarriers help shield encapsulated drugs against early degradation and clearance by the kidneys, thereby increasing the half-life of the drugs. By delivering a high intracellular payload, they will also be able to penetrate some drug resistance mechanisms, including efflux through P-glycoprotein pumps. Nanomedicine offers aqueous formulation of hydrophobic drugs, such as paclitaxel, thus avoiding the use of solvents, such as Cremophor EL, which are harmful. This is a more efficient, intelligent, and less harmful system of delivering cytotoxic payloads [1-5].

1.4. Polymeric Micelles: A Promising Nanocarrier Platform

Polymeric micelles are among other promising and advanced nanocarriers with regard to delivering paclitaxel. They are nano core-shell structures that are created through spontaneous self-assembly of amphiphilic block copolymers in aqueous environment. Both types of copolymer contain a hydrophilic copolymer, polyethylene glycol (PEG) and a hydrophobic copolymer, poly(D,L-lactide-co-glycolide) (PLGA), poly(e-caprolactone) (PCL), or poly(lactic acid) (PLA). At concentrations beyond a critical concentration (the critical micelle concentration, CMC), such molecules assemble in such a way that the hydrophobic blocks are aggregated to create an inner core, with the structure being surrounded by a corona or shell of the hydrophilic blocks keeping the internal core outside the aqueous environment. It is an ideal architecture that can be applied to drug delivery. The hydrophobic core is used as a natural reservoir to the encapsulation of poorly soluble drugs such as paclitaxel and increases their observed solubility in water by several orders of magnitude. Steric stabilization, which is offered by the hydrophilic PEG shell, prevents aggregation and opsonization (recognition by the immune system) of the micelles to greatly extend their circulation time in the bloodstream, which is one of the essentials to exploiting the EPR effect. Polymeric micelles are commonly small (10-100 nm), which enables penetration of the tumors. Moreover, they have a highly versatile structure to incorporate an engineering of smart functions. The core may be programmed to be controlled (i.e., released in the presence of a specific stimulus e.g. the slightly acidic tumor pH) or can be stimuli-responsive (e.g. released in response to intracellular redox). To attain active targeting to overexpressed receptors on cancer cells, the micelle surface may be actively functionalized with targeting ligands (i.e. antibodies, peptides, folic acid) instead of accumulation passively using EPR. In the case of paclitaxel in particular, polymeric micelles present a triple win they allow the drug to be solubilized without Cremophor EL, protect it in vivo to avoid off-target toxicity, and direct it specifically to the tumor. This has seen them become an excellent system to repackage paclitaxel in order to optimize its treatment index in treating breast cancer, particularly in the case of challenging breast cancer cases such as TNBC where new interventions are badly desired [6-10].

Material & Methods

2.1 Preparation of Calibration Curves for Paclitaxel

In the preparation of phosphate buffered saline (PBS, pH 7.4), rodents used NaCl, Na2HPO4 and KH2PO4 in the required quantities in making the required amounts of PBS to obtain a concentration of 0.5%(w/v) sodium lauryl sulphate(SLS).In the drug release study medium, sodium lauryl sulphate(SLS) was added into the PBS to achieve the desired concentration level of 0.5%(w/v) sodium lauryl sulphate To measure the absorption maxima (lmax) of paclitaxel (PTX): A UV-visible spectrophotometer was used to scan a solution containing PTX (10 ug/ml) in the PBS-SLS medium (218 nm):To determine Drug Loading Analysis: A 10 ug/ml PTX solution was prepared in a water acetonitrile mixture (40:60). It was used as the blank to prepare serial dilutions (2-25 ug/ ml), in the same solvent. To do Drug Release Analysis: PTX (100 ug/ml) was made directly in the PBS as a stock solution with 0.5% SLS. This PBS-SLS medium (also the blank) was used as a serial dilution (2-25 ug/ml).

2.2 Preparation of Buffers for Hydrolytic Stability

Citrate Buffers (pH 3.0 and 5.0): Prepared with solutions of citric acid and sodium citrate dihydrate with final adjustment of the pH with HCl or NaOH.Bicarbonate Buffer (pH 9.2): Prepared by using designated amounts of sodium bicarbonate and sodium carbonate anhydrous and the ultimate pH regulation using HCl or NaOH.

2.3 Fourier Transform Infrared Spectroscopy (FTIR)

The samples were pure PTX, PLGA, PVA and their physical blend, blank nanoparticles, and drug-loaded nanoparticles and subjected to FTIR analysis at a wavenumber range of 4000-400Cm^{-1}.

2.4 Differential Scanning Calorimetry (DSC)

DSC studies were conducted on pure PTX and PTX-loaded nanoparticles to investigate the physical state of the drug.Samples were heated from 32°C to 310°C at a rate of 10°C per minute under a nitrogen purge.

2.5 Preparation of Nanoparticles

Paclitaxel-PLGA nanoparticles were prepared through multiple-emulsion solvent evaporation technique.A high-speed homogenizer was used to prepare an organic solution of PTX and PLGA in dichloromethane, which was then poured in a 1.5% PVA solution and mixed to create a double (w/o/w) emulsion. The nanoparticles were centrifugated, washed and frozen at -40degC followed by lyophilization.PVA was used as a stabilizer of the emulsions and also as a cryoprotectant during freeze-drying.Blank nanoparticles and fluorescent (FITC-labeled) nanoparticles were prepared in the same way.

2.6. Physicochemical Characterization of Nanoparticles

Drug Loading, and Encapsulation Efficiency: A weight known to be of nanoparticles was dissolved in water-acetonitrile mixture. The amount of PTX was assessed spectrophotometrically at 218 nm by correcting the absorbance value with blank nanoparticles. Real drug loading and loading efficiency were determined with the help of standard formulas. Percentage Yield: As a ratio of the weight of the lyophilized nanoparticles to the weight of the drug and the polymer used. Particle Size, Distribution, and Zeta Potential: The zeta potential and the distribution

of the particles will be analyzed with the help of the dynamic light scattering with the help of the Zetasizer following the dispersion of nanoparticles in Milli-Q water. Morphology on the Surface Tests Surface examined by Field Emission Scanning Electron Microscopy (FESEM) following platinum coating. Internal Morphology and Drug Distribution: Transmission electron microscopy (TEM) was used where nanoparticle suspension was deposited on a carbon gridded surface

2.7. In Vitro Drug Release and Release Kinetics

The drug release test was performed by incubating the nanoparticles in PBS (pH 7.4) containing 0.5% SLS at 37deg C. The samples were centrifuged at fixed time intervals (as long as 720 hours) and the supernatant was examined spectrophotometrically at 218 nm to determine the levels of PTX. This medium of release was replenished every time. To identify the release mechanism, the release data was modeled using different kinetic models (Zero-order, First-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell).

2.8. Hydrolytic Stability Study

Nanoparticles (NP3) and pure PTX were incubated separately in buffers of different pH (3.0, 5.0, 7.4, 9.2) at 37°C. At weekly intervals for 28 days, samples were centrifuged, washed, dried, and weighed. The percentage change in mass was calculated to assess degradation or stability.

2.9. Cancer Cell Culture and MTT Assay

Cancerous and normal cells of the human liver (HepG2, Huh-7 and normal Chang liver) were grown in media (DMEM or MEM) containing fetal bovine serum and antibiotics. In the MTT assay, cells were plated in 96-wells and exposed to different doses of free PTX, a commercial formulation of PTX, (Pacliall(r)) or the NP3 formulation in 48 hours. After incubating, MTT reagent was incorporated. Fmazan crystals formed were dissolved in the DMSO and optical density at 560nm was measured to establish cell viability.

Result & Discussion

3 Determination of Absorption Maxima

A UV/VIS spectrophotometer was used to determine the wavelength of maximum absorption of paclitaxel in two solvent systems that were necessary to analyze it later. The absorption maximum of the solution was observed to be 218 nm in phosphate-buffered saline with 0.5% sodium lauryl sulphate at pH 7.4. The same absorption maxima of 218 nm was also measured to identify using the drug in a water-acetonitrile solution in a ratio of 40: 60.

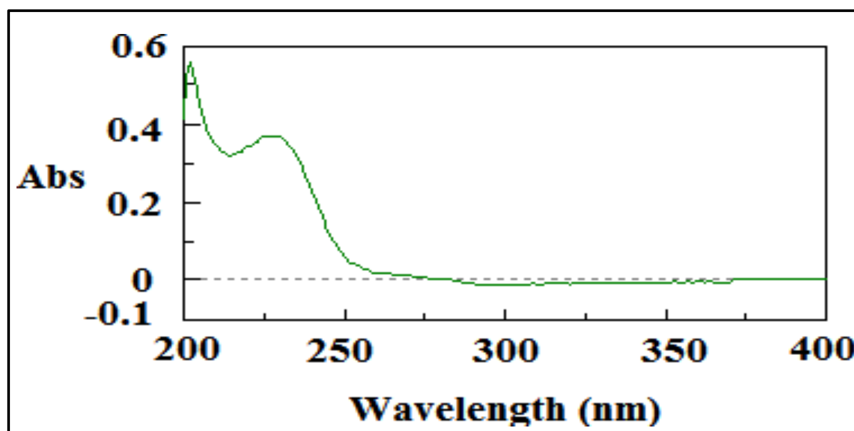


Figure 1: The absorption maxima of PTX in phosphate buffer (pH 7.4) containing 0.5% (w/v) SLS was detected at 218 nm.

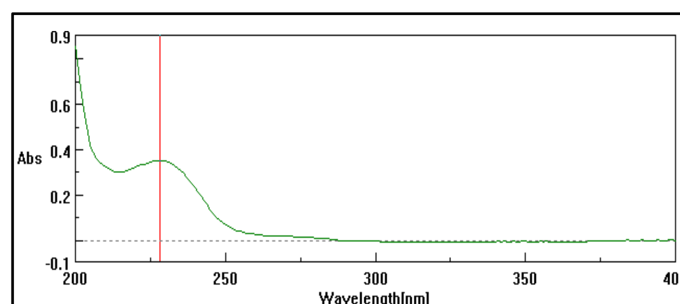


Figure 2: The absorption maxima of PTX in water: acetonitrile = 40:60 was detected at 218 nm.

3.2. Preparation of Calibration Curve

The correct analysis of paclitaxel in both analysis media was achieved through the development of standard calibration curves. At PBS pH 7.4 absorbance values rose in linear proportion to concentration over 2 to 25 ug/ml. On the same note, a linear correlation between concentration and absorbance was drawn between the water-acetonitrile mixture and the concentration range. Correlation coefficients of the two curves showed a strong linear fit that can be used in an analytical way.

Table 1: Absorbance data for calibration curve of PTXinPBS, pH7.4 at 218 nm.

SL. No.	Concentration of PTX in PBS, pH 7.4 (μg/ml)	Absorbance values*
1	2	0.0673±0.021656
2	5	0.1798±0.031749
3	10	0.3691±0.034394
4	15	0.5464±0.039051
5	20	0.7429±0.036387
6	25	0.9364±0.038223

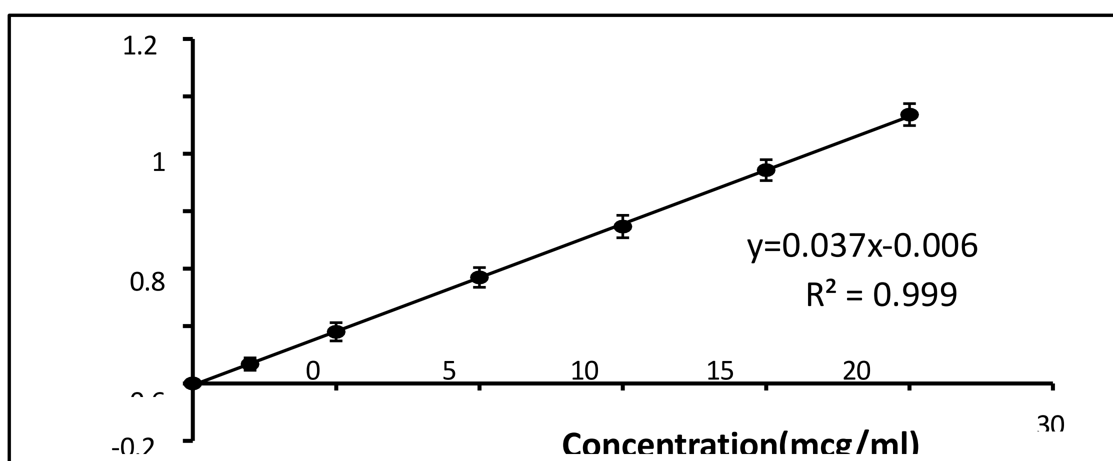


Figure 3: Calibration curve of PTX in PBS, pH 7.4 (Data represent mean ± standarddeviation, n=3).

3.3. Drug-Excipients Interaction Study

The Fourier Transform Infrared Spectroscopy analysis was carried out to determine the possibility of any chemical interactions between paclitaxel and the formulation excipients, PLGA and PVA. Their pure drug and excipients were found to have their typical functional group peaks in the spectra. The physical mixture showed the major bands of each of the components, which is the indication of the lack of a chemical interaction. Paclitaxel characteristic peaks were absent on the surface of the final nano-formulation of the non-particles. The formulation experienced slight changes in several peaks of both PLGA and PVA and this could be explained by minor physical interactions e.g. hydrogen bonding or van der Waals forces in the nanoparticle matrix.

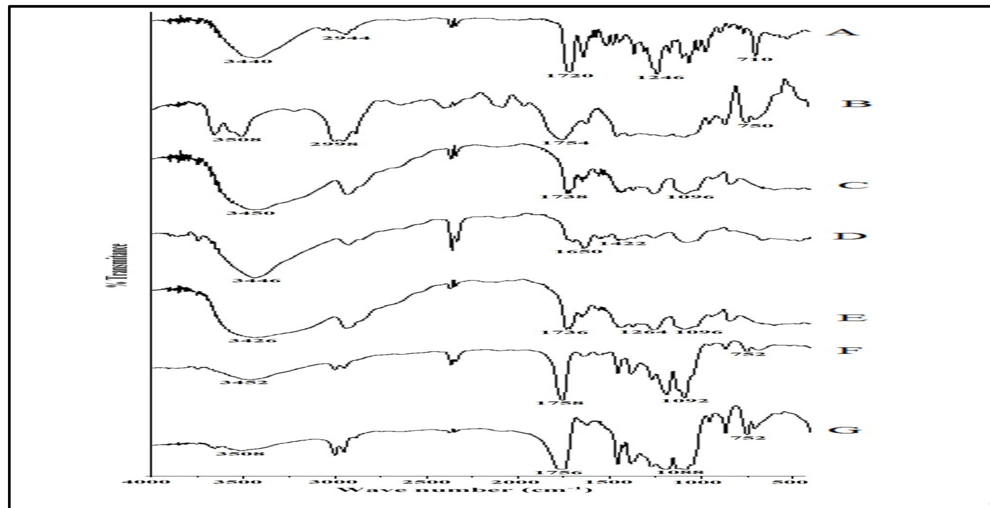


Figure 4: FTIR spectrum of paclitaxel (A), PLGA (85:15) (B), PVA(C), mixture of PLGA and PVA (D), mixture of drug, PVA and PLGA (E), blank formulation (F) and formulation NP3 (G).

3.4. Differential Scanning Calorimetry Study

Thermal analysis was done to examine the physical condition of paclitaxel in the nanoparticle system. The DSC thermogram of pure paclitaxel had a sharp melting endotherm of about 212.25degC. The thermogram of the drug-loaded nP formulation had the same endothermic peak, indicating that the paclitaxel encapsulated in the nanoparticle did not change into its amorphous form. The thermogram of the blank formulation was found to have no such peak.

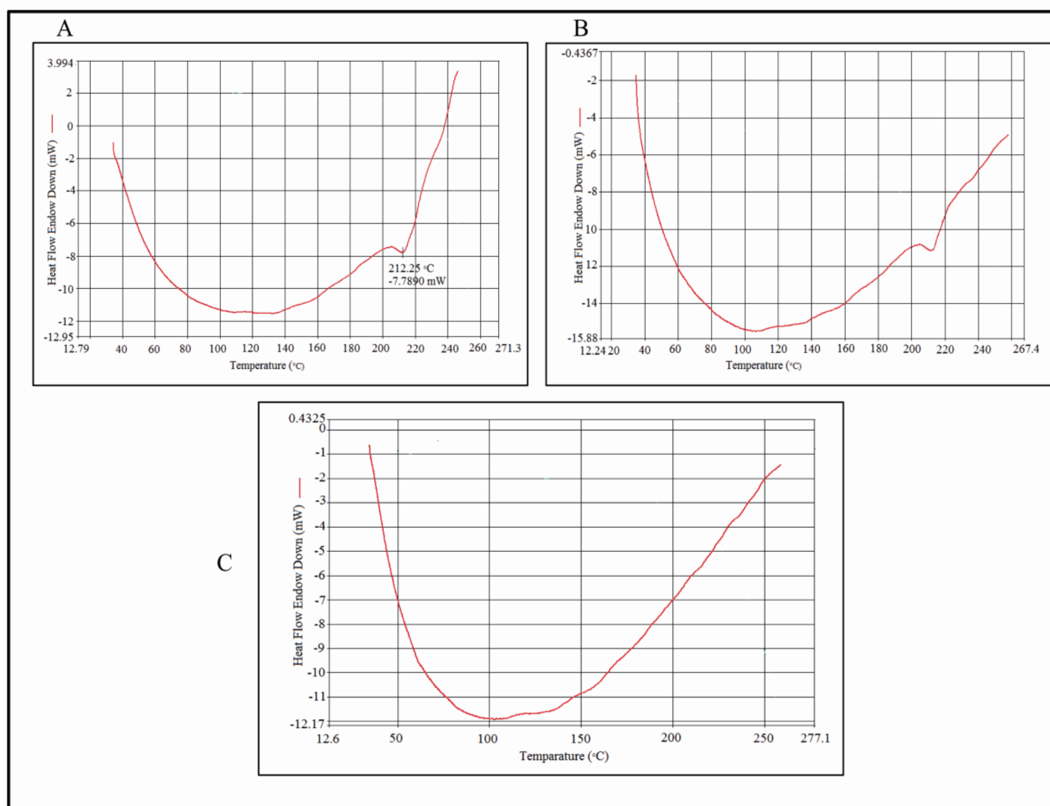


Figure 5: Differential scanning calorimetrythermogram of paclitaxel (A), NP3 (B) and blank formulation (C).

3.5. Preparation and Selection of Nanoparticles

After compatibility tests, a number of nanoparticle formulations at different loads of drug were made. The identification of the optimal batch was based on the better performance of the formulation that is NP3 with the drug to polymer ratio of 1:24 that was observed on the basis of process yield, drug loading, and encapsulation efficiency.

This expression was then chosen to be applied in all the later characterization and evaluation studies.

3.6. Drug Loading and Encapsulation Efficiency

Drug incorporation in the nanoparticles was assessed to determine its efficiency. The higher the starting rate of drug, the greater was the actual drug loading in the formulations. At 3.37 percent actual drug loading and 84.25 percent encapsulation efficiency, the NP3 formulation showed the highest actual drug loading and encapsulation efficiency respectively. The yield of the process also increased with the increase in drug content and the yield of NP3 was around 72.6.

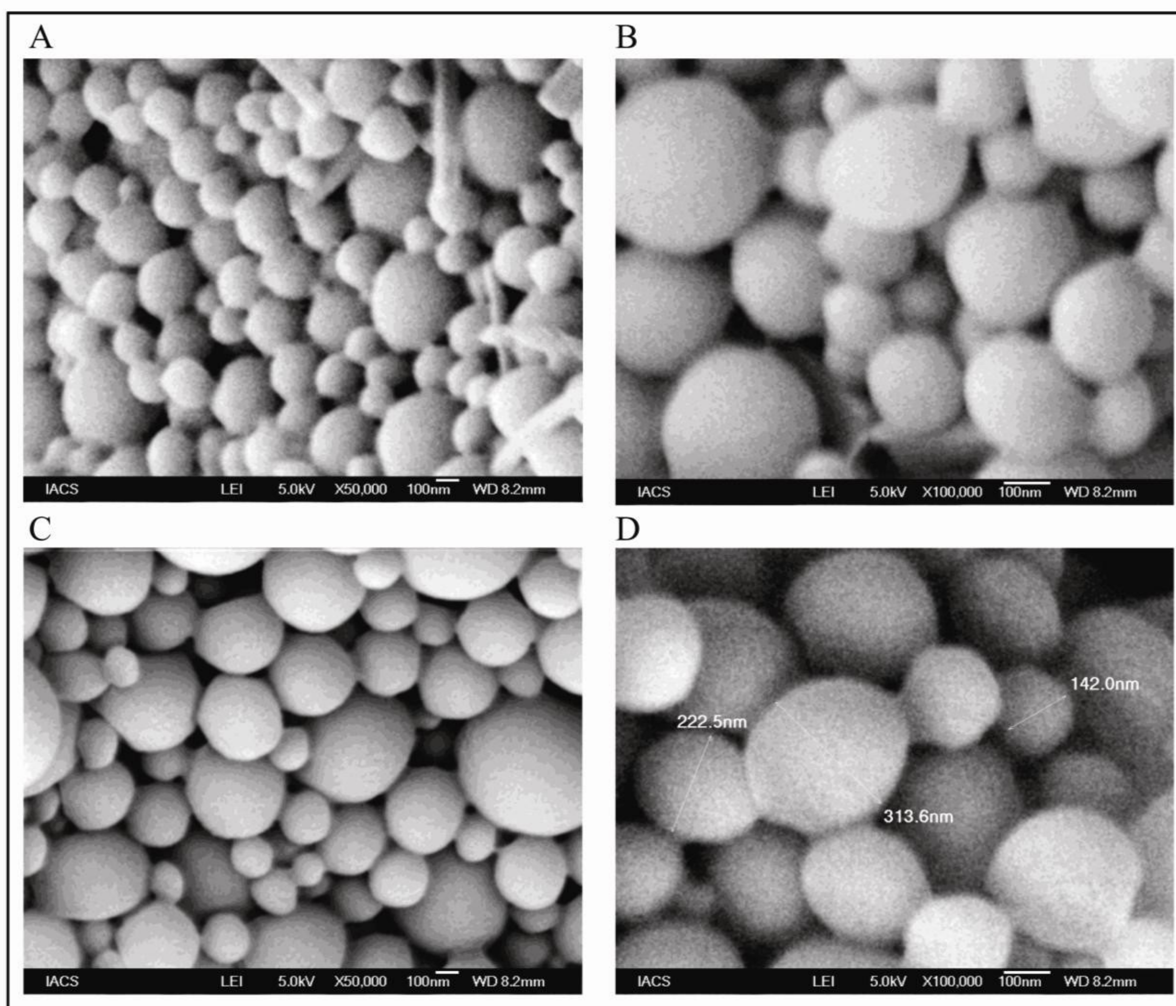
3.7. Particle Size and Zeta Potential

The formulations were of the order of 309 nm to 370 nm with the optimization NP3 giving the lowest mean particle size. The polydispersity indices were found to be moderate to wide ranging in nature. The values of Zeta potentials, denoting colloidal stability, were negative in all the formulations and negatively increased with an increase in drug load, with the NP3 having Zeta potentials of approximately -10.7 mV.

3.8. Morphological Analysis

The morphology of the nanoparticles was determined by imaging studies. Field Emission Scanning Electron Microscopy revealed that the particles were spherical having a textured surface. Unincorporated paclitaxel was sometimes found as some rod-shaped crystals. The morphology was confirmed as being spherical and with dark spots in the nanoparticles by Transmission Electron Microscopy views indicating the uniform distribution of the encapsulated drug over the polymer matrix

Figure 6: FESEM photograph of formulation NP1at50,000× (A),formulation NP2at100,000× (B), formulation NP3



at 50,000× (C) and formulation NP3 at 100,000× (D).

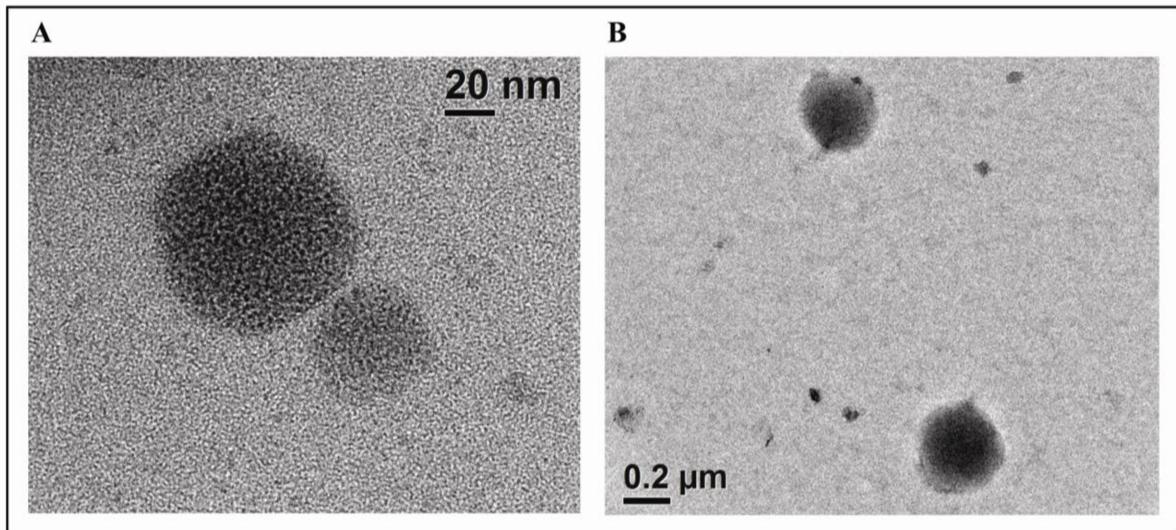


Figure 7: Transmission electron microscopic images of the optimized formulation (NP3); smallsize particles (A) and large size particles (B).

3.9. In Vitro Drug Release and Kinetics

The release profile of the drugs including the nanoparticles was such that there was an initial burst release in the first 8 hours then a slow prolonged release profile of 30 days. This release was greatest during this time in NP1 and least in NP3 meaning that NP3 offered maximum release. Kinetic evaluation of the release showed that the release of drug in formulation NP1 and NP3 was most appropriate to fit in the Korsmeyer-Peppas model, whereas the release of drug in formulation NP2 was most suitable to the Higuchi model. The values of the release exponent indicated a drug release process with a preferred Fickian diffusion.

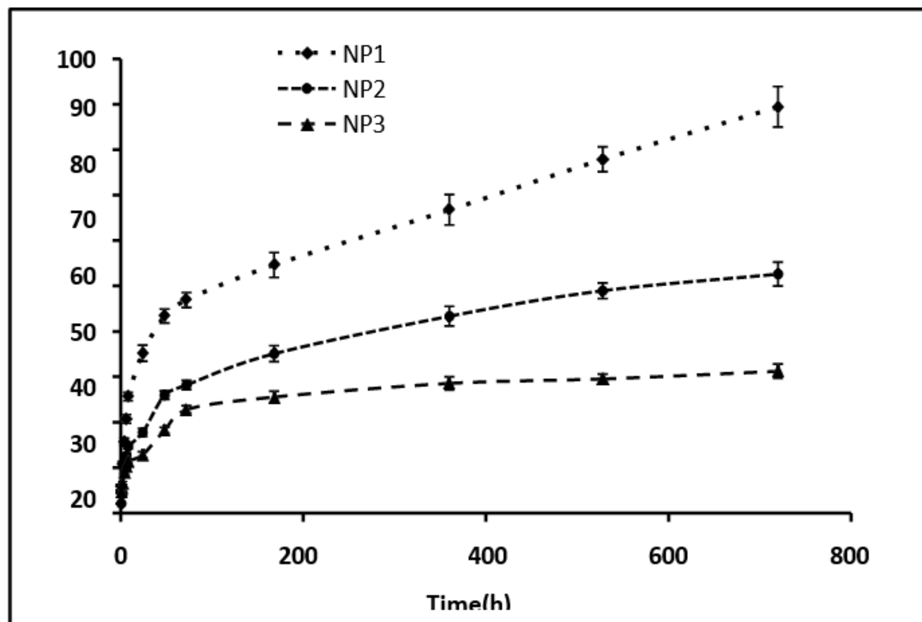


Figure 8: *In vitro* release profiles of PTX from NP1, NP2 and NP3 in phosphate buffer, pH 7.4. Data show mean ± standard deviation of three different experiments in triplicate.

3.10. Hydrolytic Degradation Study

Mass loss was used to measure the degradation of the PLGA nanoparticles in varying pH regimes after four weeks. PH was also a major factor affecting the rate of hydrolysis and more acidic conditions had a higher rate of degradation. Weaker pH gave maximum mass loss, whereas the degradation was minimum at pH 9.2. Conversely, mass loss under any pH condition was not significant in the pure paclitaxel.

3.11. In Vitro Cytotoxicity Assessment

The optimized NP3 formulation was tested in its anti-proliferative effective activity in relation to liver cancer cell lines and comparing it to free paclitaxel and a commercial formulation. The MTT assay showed that cell death was

dose-dependent in all the treatment methods in cancer cells. The NP3 formulation had the highest potency, and the values of IC50 in both HepG2 and Huh-7 cell lines were much lower than the free drug and the commercial product. In addition, the cytotoxicity of all active treatments to the .

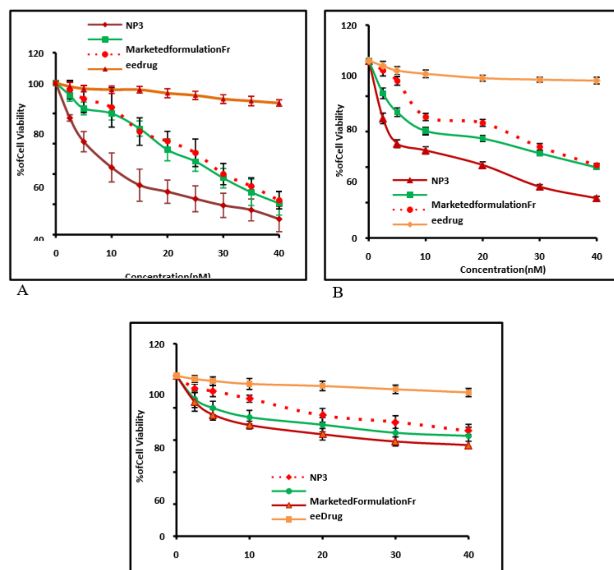


Figure 9: Cell viability study by MTT assay of free drug, marketed formulation, NP3 and blank formulation in HepG2 Cells (A), in Huh-7 cells (B) and in Chang Liver cells (C). Data show mean ± standard deviation of three different experiments.

Conclusion

This study successfully developed and characterized a PTX-loaded PLGA nanoparticle system designed to overcome the significant pharmacological challenges associated with conventional paclitaxel therapy. The optimized formulation (NP3) effectively encapsulated the hydrophobic drug, providing a stable, nanosized carrier with a sustained release profile. The absence of chemical interactions and the preserved drug crystallinity within the nanoparticles underscore the formulation's stability. The most compelling finding was the superior *in vitro* cytotoxic activity of the nanoparticle formulation against cancer cell lines compared to both free drug and a commercial preparation, while demonstrating safety in normal cells and with blank nanoparticles. This enhanced efficacy, coupled with the elimination of the toxic Cremophor EL vehicle, addresses the dual challenges of toxicity and solubility inherent to paclitaxel. The developed PLGA nanoparticle system represents a significant step toward a more effective and tolerable chemotherapeutic strategy. Future work should focus on *in vivo* pharmacokinetic, biodistribution, and efficacy studies in relevant animal models, particularly for TNBC, to further validate this platform's potential for clinical translation.

cancer cells was higher than in the normal liver cells. As mentioned, the blank nanoparticles had no cytotoxic effect and that the activity observed was because of paclitaxel and not the excipients

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