

Formulation, Central Composite Design Optimization and *in vitro* Evaluation of Folic Acid Conjugated Palbociclib Loaded Polymeric Nanoparticles

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ABSTRACT

Background: The efficacy of the anticancer agent palbociclib can be limited by its conventional release profile. Developing nano-formulations presents a viable approach to modulate its delivery for improved therapeutic outcomes. This work aimed to design, optimize, and characterize chitosan-based Polymeric Nanoparticles (PNs) for the oral delivery of palbociclib, with a specific focus on controlling particle size and surface charge. **Materials and Methods:** Palbociclib-loaded PNs were fabricated using a solvent evaporation technique. A Central Composite Design was employed to optimize the concentrations of chitosan and Polyvinyl Alcohol (PVA). The lead formulation was thoroughly characterized using FT-IR, SEM, and *in vitro* release studies, with its release kinetics modelled. **Results:** An optimized formulation was identified with a particle size of 337.8 nm and a zeta potential of 32.4 mV, which aligned closely with statistical predictions. The system exhibited high drug entrapment (81.28%) and provided a sustained release profile, with 90% of the drug released over 26.1 hr following a diffusion-erosion mechanism. This was a substantial extension over the rapid release of the pure drug. **Conclusion:** The findings confirm the successful development of a chitosan-based nanoparticle system capable of offering sustained release of palbociclib, highlighting its significant potential for enhancing oral drug delivery in cancer treatment.

Keywords: Chitosan, Drug release, Folic Acid, Kinetics Palbociclib, Particles Size, Particles Charge.

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INTRODUCTION

Nanotechnology remains an enigmatic concept for many individuals, yet it is already shaping our future and promises to have a profound impact when combined with biotechnology and information technology (Chakraborty *et al.*, 2025; Martin, 2000). Nanocapsules and nanospheres are included in the term nanoparticle and these two are identical with the exception in their morphology (Schaffazick *et al.*, 2003). Polymeric Nanoparticles (PNPs) have the ability of encapsulating various therapeutic agents, increase bioavailability, and produce controlled release which in turn, increase therapeutic efficacy and decrease the side effects (Aldaais, 2018, Amanzio *et al.*, 2020). Polymer characterization used in the production of PNPs determines directly the physicochemical nature of PNPs including their size, shape, surface charge and drug-loading capacity (Lu *et al.*, 2021). One factor that contributes significantly to the effectiveness of PNPs in targeted drug delivery is the capability of crossing

biological barriers and the capacity to release the cargo at a specific location where it is supposed to act. This requires an in-depth understanding of the physical characteristics of the polymer, its molecular weight, hydrophilicity/hydrophobicity, and its fictionalization, which all influence considerably the interaction of PNPs with a biological environment (Fang *et al.*, 2011). The technique of formulation and characterization is imperative to the performance of nanoparticle-based drug delivery systems owing to the fact that it does influence physicochemical properties of the drug delivery system that indirectly do affect therapy outcomes, targeting capabilities, and drug delivery effectiveness. Assessing the size, the shape, the surface charge and related particularities of the nanoparticles is critical in achieving maximum effectiveness of nanoparticles that is exercised in the concept of drugs delivery. The process ensures that the nanoparticles are tailored to meet specific therapeutic needs which in turn make them more efficient in delivering medicines where they are needed (Kankala *et al.*, 2021).

Pfizer came up with the drug palbociclib that will be used to treat HER2-negative and HR-positive breast cancer. It specifically suppresses two cyclin-dependent kinases, i.e., CDK4 and CDK6. Palbociclib was the first CDK4/6 to be approved as cancer



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treatment. Due to low water solubility and because of first-pass metabolism it also does not have a good oral bioavailability at 46%. Polymaer based nanoparticle can thus be regarded as an acceptable drug delivery system by enhancing poor oral bioavailability of palbociclib (Rocca *et al.*, 2017, Patra, 2018). Hence, the present study is planned to design, optimize, and characterize chitosan-based polymeric Nanoparticles (PNs) for the oral delivery of palbociclib, with an emphasis on achieving controlled particle size and surface charge.

MATERIALS AND METHODS

Materials

Palbociclib was generously provided by Natco Pharma, Hyderabad. Chitosan, Acetone, Ethanol and Polyvinyl Alcohol were perches from Loba Chemie Pvt. Ltd., Mumbai, Maharashtra, India. All Chemicals and API were passed for analytical grade.

Pre-formulation study

Preformulation studies analyze the drug's molecular and physical properties, both alone and with excipients, to guide effective and scalable formulation design (Krishnakumar *et al.*, 2011).

Drug-Excipients Interactions by Fourier Transform Infra-Red (FTIR) spectroscopy

FT-IR analysis (4000-400 cm^{-1}) was performed on palbociclib, chitosan, PVA, their physical mixtures, and lyophilized formulations (with/without drug) using a Bruker Alpha II spectrometer (1:1 sample ratio) (Krishnakumar *et al.*, 2011).

Formulation of Palbociclib polymers-based nanoparticles

To prepare PNP, the solvent evaporation technique was used. Chitosan was first dissolved in a solution of 1% acetic acid, and folic acid was then added and stirred for 2 hr. Palbociclib was dissolved in acetone, and a 2% PVA aqueous solution was made by heating water. This organic phase was sonicated into the PVA solution to create an emulsion, while folic acid and 0.3% sodium Tripolyphosphate (TDD) were added as a cross-linking agent. The solvent was evaporated with continuous stirring, and the resulting mixture was centrifuged at 15,000 rpm for 30 min. The final pellet was washed with distilled water to complete the process (Sartaj *et al.*, 2021).

Evaluation of Palbociclib Polymeric Nanoparticles

The particle size and zeta potential of palbociclib-loaded nanoparticles were measured using a Zetasizer Nano-ZS (Malvern, UK) with a 633 nm, Data analysis was performed using automated software, based on electrophoretic mobility and the Smoluchowski model (Yang *et al.*, 2010).

PNPs were centrifuged, and the supernatant was analyzed at 261 nm. The precipitate was filtered, washed, weighed, and drug loading was calculated (Liu *et al.*, 2010).

$$\% \text{ Drug loading} = \frac{\text{weight of drugs in NPs}}{\text{weight of NPs}} \times 100$$

PNPs were centrifuged, and the supernatant was analyzed at 261 nm. Entrapment efficiency was calculated from the free drug content (Mandal *et al.*, 2013).

$$\%EE = \frac{(\text{Total drug in formula} - \text{free drug})}{\text{Total drug in formula}} \times 100$$

In vitro Drug Release Studies

The drug release of Palbociclib-loaded nanoparticles and free palbociclib was studied using the dialysis bag method. A 20 mL sample was placed in dialysis bags, immersed in 150 mL of 7.4 pH phosphate buffer at room temperature with constant stirring. At set intervals, 2 mL was withdrawn and replaced with fresh buffer, then analyzed at 267 nm using a UV spectrophotometer (Yu *et al.*, 2016, Xie *et al.*, 2008).

In vitro Drug Release Kinetics

The release data was fitted to various kinetic models (zero-order, first-order, Korsmeyer-Peppas, etc.) using DD Solver software to predict the drug release process (Khan *et al.*, 2019).

Scanning Electron Microscope (SEM)

SEM (ESEM EDAX XL-30) was used to characterize polymeric nanoparticles. Freeze-dried samples were stored in a gold-coated graphite sample container. The chamber was maintained at 0.6 mm Hg pressure and 20 KV voltages. Scanning electron photomicrographs were taken at various magnifications (Yuan *et al.*, 2012).

RESULTS

Physiochemical properties of palbociclib

Palbociclib is a yellow, amorphous, and odorless powder. It is soluble in ethanol but practically insoluble in water, and exhibits limited solubility in dichloromethane and chloroform.

Preparation of the Standard curve of Palbociclib

A standard calibration curve of Palbociclib was constructed by plotting absorbance against concentration in the range of 5-40 $\mu\text{g/mL}$. A linear relationship was obtained with a regression coefficient ($R^2=0.997$), confirming adherence to Beer-Lambert's law (Figure 1).

Drug Excipients Interaction

Fourier Transform Infrared (FT-IR) spectroscopy was performed to assess potential drug-excipient interactions. Comparative spectra of Palbociclib and its physical mixture with excipients (Figures 2 and 3; Table 1) showed no significant shifts or

disappearance of characteristic peaks, indicating the absence of major chemical interactions and confirming the compatibility of Palbociclib with the selected excipients.

Design of Experiments

A statistical design of experiments approach was applied to evaluate the influence of formulation variables on particle size and zeta potential of the prepared chitosan-based Polymeric Nanoparticles (PNs). The evaluated formulations were subjected to particle size and surface charge analysis (Table 2).

Optimization of Dependant variable

Response 1 (Particle size)

The nanoparticle size, ranging from 376 to 412 nm as shown in Table 2, is primarily influenced by chitosan (Factor A), and based on the quadratic model analysis. The statistical findings indicate a strong model fit, with an adjusted R^2 of 0.8150, a predicted R^2 of 0.5476, and a p -value of 0.0035. The sequential p -value of 0.0035 and the Lack of Fit p -value of 0.7627 further reinforce the reliability of the model. The perturbation plot (Figure 4A) illustrates the significant impact of Factor A, while the contour plots (Figure 4B).

Response 2: (particle Charge)

The nanoparticle charge, which varied between 29.87 mV and 36.76 mV as shown in Table 2, was notably affected by the concentrations of chitosan and PVA, based on the quadratic model analysis. The statistical analysis revealed an adjusted R^2 of 0.6795, a predicted R^2 of 0.2222, and a sequential p -value of 0.0401, confirming the reliability of the model. Additionally, the Lack of Fit p -value of 0.7263 supports a strong fit. The perturbation plot (Figure 5A) and the contour plots (Figure 5B) provide further insight into the relationships between the factors.

Optimisation by Desirability Function

The optimization process uses the desirability function to adjust parameters within specified ranges. Chitosan (20-100 mg) and Polyvinyl Alcohol (10-20 mL) are set within limits, while MPS is minimized (376-412 nm) and ZP is maintained (29.87-36.76 mV). The goal is to find the best combination of these values for optimal outcomes. After applying the constraints, optimized values for Chitosan (62.575 mg), Polyvinyl Alcohol (16.080 mL), MPS (382.700 nm), and ZP (34.310 mV) were chosen, yielding a desirability score of 0.814 in Figure 6. These values were applied

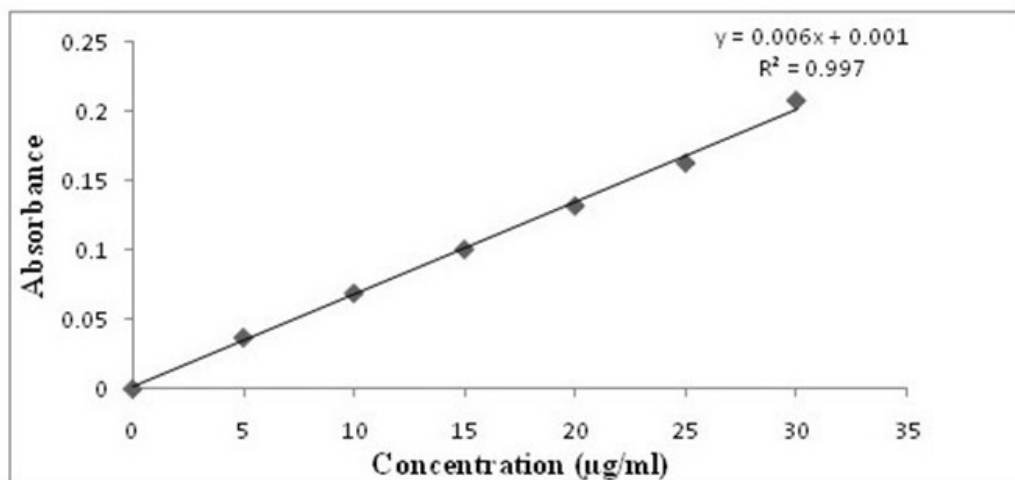


Figure 1: Graph Plot of Standard Curve of Palbociclib.

Table 1: List Absorption Readings of Standard Curve of Palbociclib.

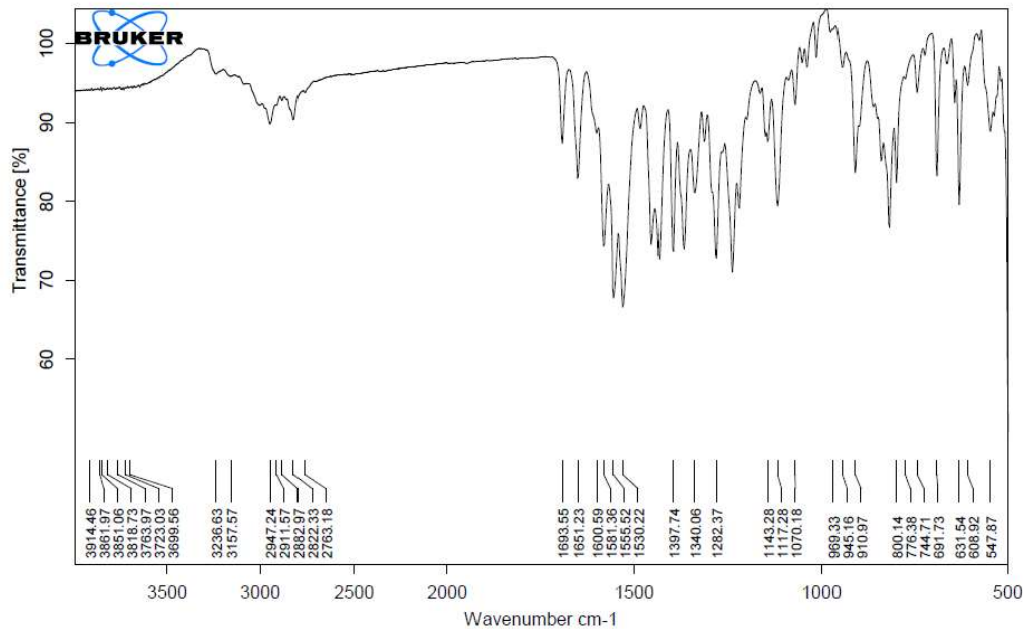
Sl. No.	Wavelength Range	Concentration (µg/mL)	I	II	III	Absorption(nm) (Mean)
0	261 nm	0	0	0	0	0
1		5	0.037	0.036	0.038	0.037
2		10	0.069	0.07	0.068	0.069
3		15	0.099	0.101	0.102	0.100
4		20	0.132	0.131	0.133	0.132
5		25	0.163	0.162	0.164	0.163
6		30	0.208	0.209	0.207	0.208

Table 2: List of Composition and Response of Palbociclib Nanoparticles.

Run	Factor A: Chitosan (mg)	Factor C: PVA (mg)	Folic Acid (mg)	Acetone 80 (mL)	Acetic Acid (mL)	Dist. H ₂ O (mL)	Response 1: MPS (nm)	Response 2: ZP (mV)
F1	100	15	10	5	10	Qs	402	34.5
F2	60	15	10	5	10	Qs	376	33.47
F3	20	10	10	5	10	Qs	412	36.76
F4	20	15	10	5	10	Qs	398	35.65
F5	60	15	10	5	10	Qs	389	34.67
F6	60	15	10	5	10	Qs	382	36.65
F7	20	20	10	5	10	Qs	411	32.41
F8	60	10	10	5	10	Qs	401	31.2
F9	100	10	10	5	10	Qs	412	29.87
F10	60	20	10	5	10	Qs	389	30.94
F11	100	15	10	5	10	Qs	399	32.12

Independent and Dependant variables in CCD

Independent Variables			Levels	
Variable	Name	Unit	Low (-1)	High (+1)
A	Chitosan	mg	100	200
B	Polyvinyl Alcohol	mg	10	20
			Goal	
Y1	Particles Size	nm	Minimum	
Y2	Particles Charge	mV	In range	



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Figure 2: FT-IR spectrums of palbociclib.

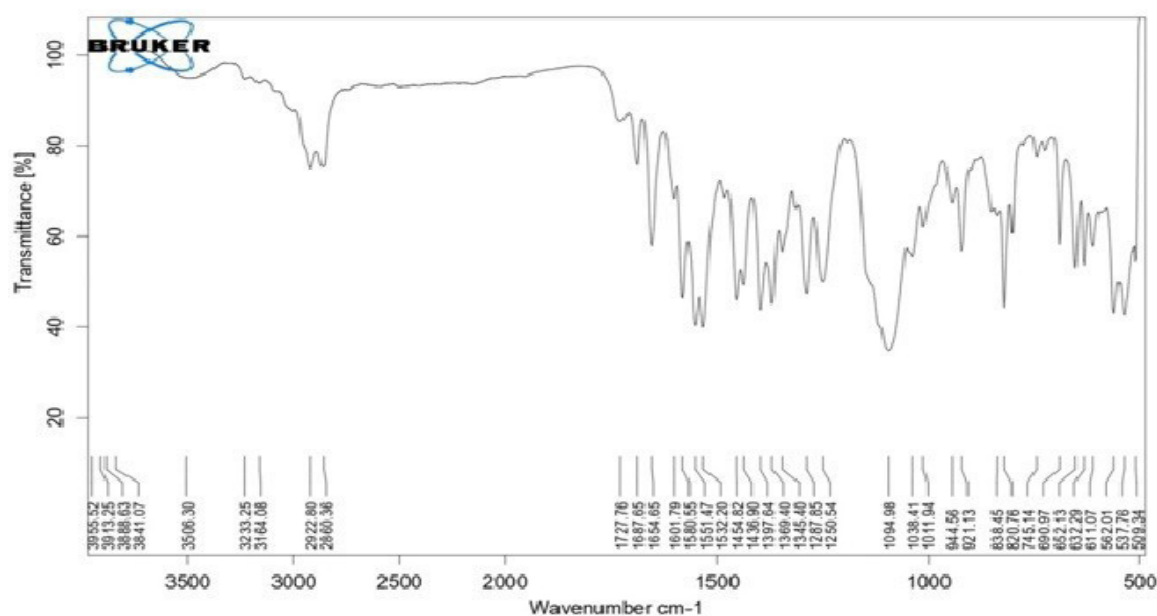


Figure 3: FT-IR spectra of Palbociclib with the excipients.

to Response 1 and Response 2, resulting in observed values of MPS at 337.8 nm (Figure 7) and ZP at 32.4 mV (Figure 8).

Drug loading and Entrapment efficiency

The percentages of drug loading and entrapment efficiency of the optimised batch were $22.96 \pm 1.23\%$ and $81.28 \pm 56\%$.

In vitro drug release study

The *in vitro* drug release profile of free drug and the palbociclib loaded polymeric nanoparticles formulation was determined by using dialysis bag method in Table 3 and Figure 9. The free drug exhibited rapid release (50% in 2 hr; 90% in 12 hr). In contrast, the nanoparticles showed a sustained profile (50% in 11.8 hr; 90% in 26.1 hr), due to the polymer matrix barrier.

In vitro drug release kinetics model

The *in vitro* drug release kinetics of the optimized formulation of Palbociclib PNS was evaluated using the “DD Solver” software shows in Table 4; Korsmeyer-Peppas model ($R^2=0.997$) and release exponent ($n=0.762$) suggests anomalous (non-fickian) transport.

Morphological Characterisation of optimised batch

The surface morphology of the optimized Palbociclib-loaded nanoparticles was examined using Scanning Electron Microscopy (SEM). The images (Figure 10) revealed uniform, spherical nanoparticles with smooth surfaces and no evidence of aggregation, confirming the homogeneity of the optimized formulation.

DISCUSSION

Palbociclib-loaded oral Polymeric Nanoparticles (PNS) were developed using a solvent evaporation method, with formulation optimization guided by a two-factor Central Composite Design (CCD) in Design Expert® software version 11 (Version 7.0, Stat Ease Inc., USA). The independent variables chitosan (100-200 mg) and PVA (10-20 mg) were systematically varied to analyze their effects on critical responses including particle size and zeta potential. Through response surface methodology and overlay plotting, the software facilitated the identification of an optimized nanoparticle formulation with desired characteristics (Sandhya, 2022).

FT-IR analysis showed minor peak shifts: C=O ($1600.59 \rightarrow 1601.79 \text{ cm}^{-1}$), N-H ($3699.56 \rightarrow 3506.30 \text{ cm}^{-1}$), and C≡N ($2947.63 \rightarrow 2922.80 \text{ cm}^{-1}$). These indicate physical interactions like hydrogen bonding but confirm no chemical incompatibility, ensuring formulation stability (Sandhya, 2022).

The nanoparticle size, ranging from 376 to 412 nm, was predominantly influenced by chitosan concentration. Statistical analysis confirmed a robust model fit (adjusted R^2 : 0.8150; p -value: 0.0035), indicating high reliability. Particle charge, varying between 29.87 and 36.76 mV, was significantly affected by both chitosan and PVA concentrations, with the model also demonstrating a reliable fit (adjusted R^2 : 0.6795; p -value: 0.0401). These results validate the quadratic model's effectiveness in optimizing both critical quality attributes (Xie *et al.*, 2008, Yang *et al.*, 2010).

The desirability function was employed for optimization, with chitosan (20-100 mg) and PVA (10-20 mL) as variables. Targets were to minimize particle size (376-412 nm) and maintain zeta

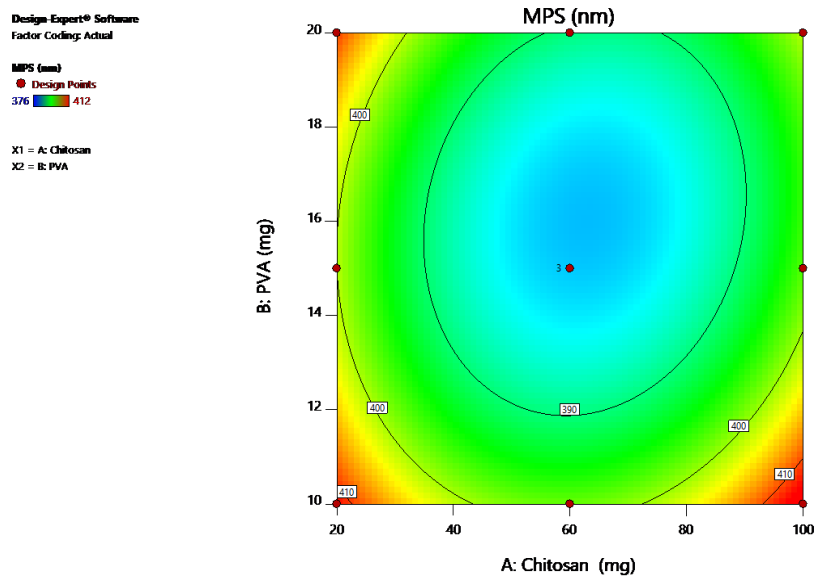


Figure 4A: Counter plot of Y1 (Particles Size).

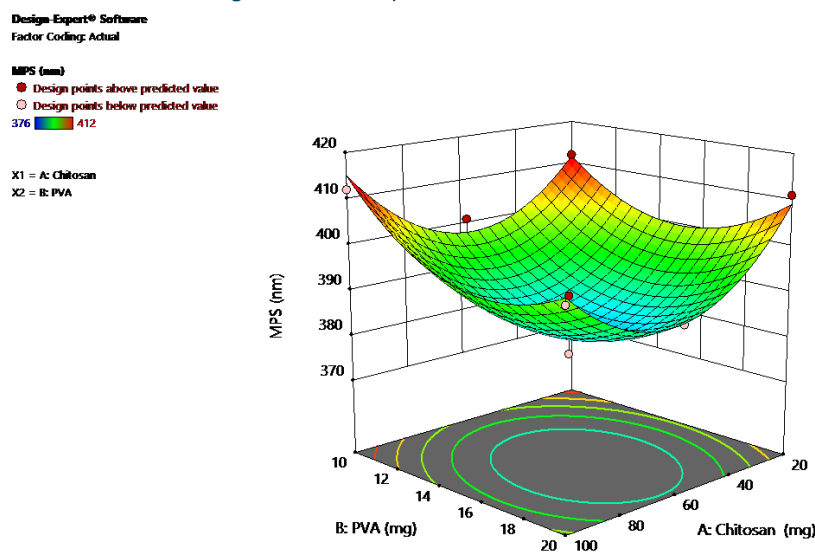


Figure 4B: 3D response Surface plot of Y1 (Particles Size).

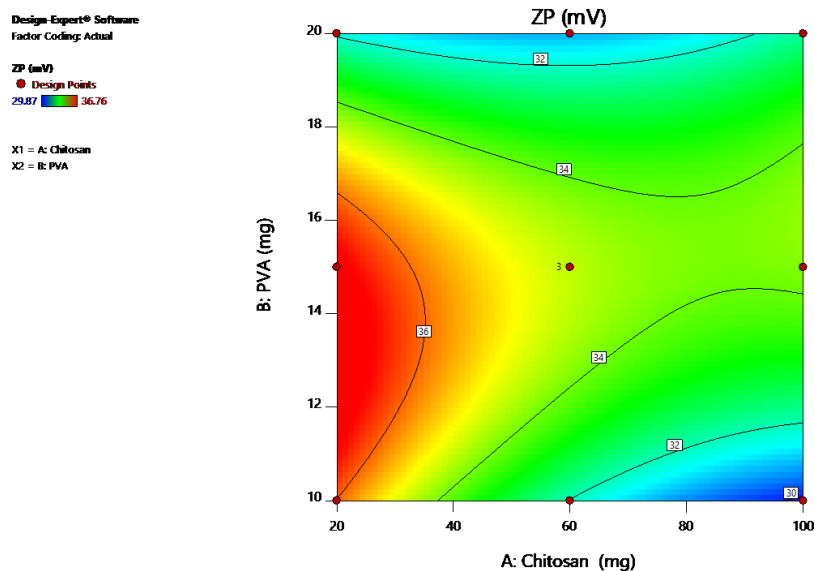


Figure 5A: Counter plot of Y2 (Particles Charge).

Table 3: List of % Cumulative Drug Release of optimize batch.

% of Palbociclib PNS Drug Release					% of Free Drug Release			
Time(hr)	R1	R2	R3	Mean±SD	R1	R2	R3	Mean±SD
0	0	0	0	0	0	0	0	0
1	8.41	7.27	9.28	8.32±1.01	30.78	32.18	33.13	32.03±1.18
2	14.55	12.62	11.63	12.93±1.49	54.87	56.69	57.74	56.43±1.45
4	20.66	21.81	19.73	20.73±1.04	72.15	74.28	74.23	73.55±1.22
6	25.61	26.33	27.64	26.53±1.03	82.41	80.55	79.47	80.81±1.49
8	34.81	35.89	36.85	35.85±1.02	86.21	84.36	83.25	84.61±1.50
12	51.05	52.12	49.13	50.77±1.52	91.51	92.52	90.53	91.52±1.00
16	63.79	61.92	63.84	63.18±1.09	94.01	95.41	96.02	95.15±1.03
20	73.78	70.89	70.75	71.81±1.71	97.43	98.46	99.45	98.45±1.01
24	81.07	79.14	82.12	80.78±1.51	98.59	98.62	99.21	98.81±0.35
26	88.28	90.42	90.97	89.89±1.42	99.79	99.81	99.84	99.81±0.03

Table 4: List of the *in vitro* Kinetics Models.

Optimized Batch	Zero Order (r2)	First order (r2)	Higuchi (r2)	Hixson-Crowel (r2)	Koysmeyer-Peppas (r2)
	0.9689	0.9848	0.9391	0.9944	0.9977

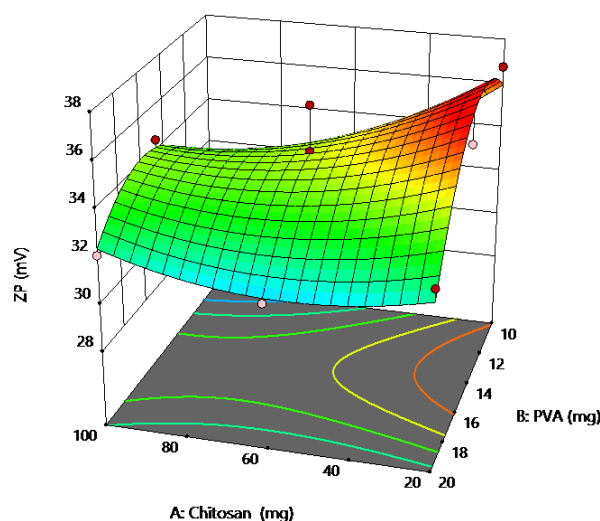
Design-Expert® Software
Factor Coding: Actual

ZP (mV)

● Design points above predicted value
○ Design points below predicted value
29.87 36.76

X1 = A: Chitosan

X2 = B: PVA

**Figure 5B: 3D response Surface plot of Y2 (Particles Charge).**

potential (29.87-36.76 mV). The optimal formulation used 62.58 mg chitosan and 16.08 mL PVA, achieving a high desirability of 0.814. Experimental validation confirmed a particle size of 337.8 nm and zeta potential of 32.4 mV, aligning well with predicted outcomes (Sandhya, 2022, Liu *et al.*, 2010).

An *in vitro* release study compared free palbociclib to polymeric nanoparticles using a dialysis method. The free drug displayed rapid release (50% in 2 hr; 90% in 12 hr), while the nanoparticles demonstrated sustained release (50% in 11.8 hr; 90% in 26.1 hr), attributed to the polymer matrix barrier (Yuan *et al.*, 2012).

DD Solver analysis indicated the release kinetics followed the Korsmeyer-Peppas model ($R^2=0.997$), with an exponent ($n=0.762$) confirming anomalous (non-Fickian) diffusion-erosion release mechanisms (Yuan *et al.*, 2012, Chakraborty *et al.*, 2025).

The optimized batch exhibited a drug loading of 22.96 ± 1.23 and an entrapment efficiency of $81.28\% \pm 0.56$, confirming efficient nanoparticle drug incorporation (Xie *et al.*, 2008).

The optimized palbociclib-loaded nanoparticles displayed a smooth, spherical morphology under SEM examination. This uniform structural characteristic supports predictable drug

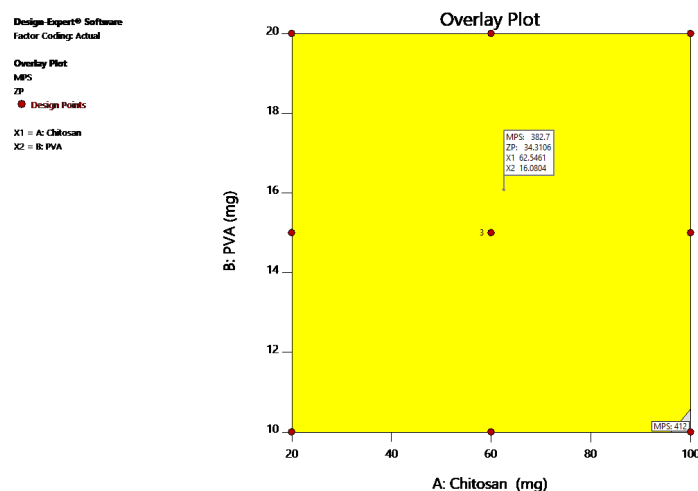


Figure 6: Optimized desirability overlay Plot.

System

Temperature (°C): 25.0 Duration Used(s): 30
Count Rate (kcps): 227.1 Measurement Position (mm): 0.85
Cell Description: Disposable sizing cuvette Attenuator: 7

Results

	Size(d.nm):	%Intensity:	St Dev (d.n.)
Z-Average(d.nm): 337.8	Peak1: 10.27	77.4	1.764
Pdl: 0.269	Peak2: 476.2	16.7	105.2
Intercept: 0.799	Peak3: 989.0	5.3	206.9

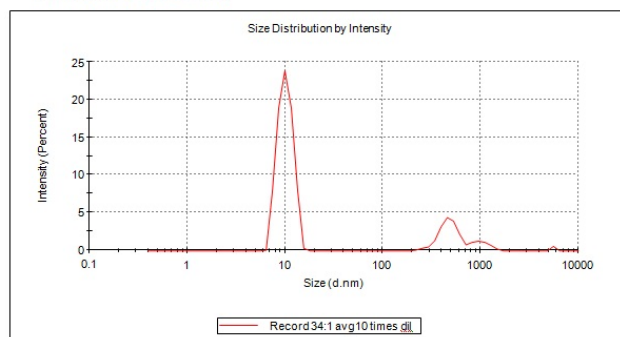
Result quality: **Good uniformity**

Figure 7: Particles size of optimized batch.

	Mean(mV)	Area (%)	Width (mV)
Zeta potential (mV) :32.09	Peak 1: 32.09	100.0	4.38
Zeta Deviation (mV) :4.36	Peak 2: 0.00	0.0	0.00
Conductivity (mS/cm) :0.0270	Peak 3: 0.00	0.0	0.00

Result quality : **Good**

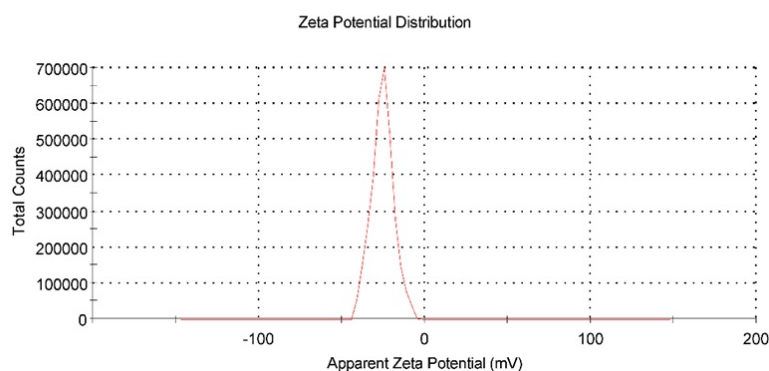


Figure 8: Particles Charge of optimized batch.

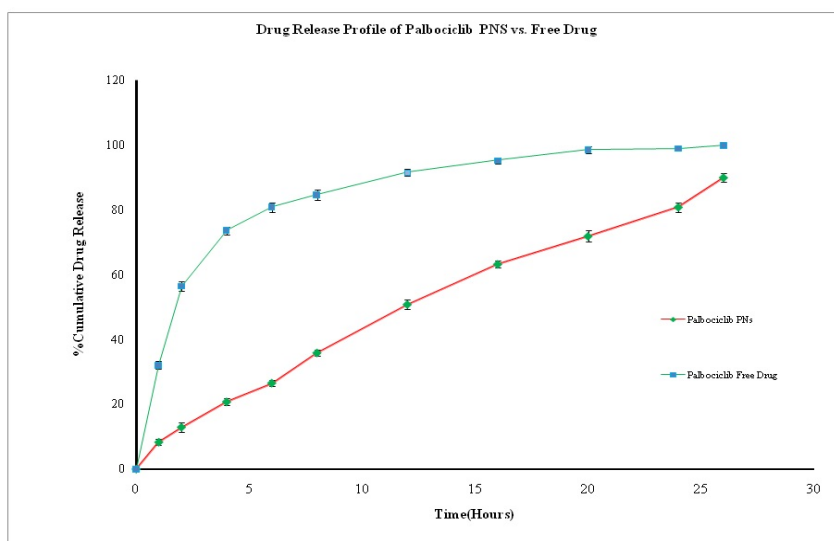


Figure 9: Graph Plot of *in vitro* % Cumulative Drug Release of Optimized batch.

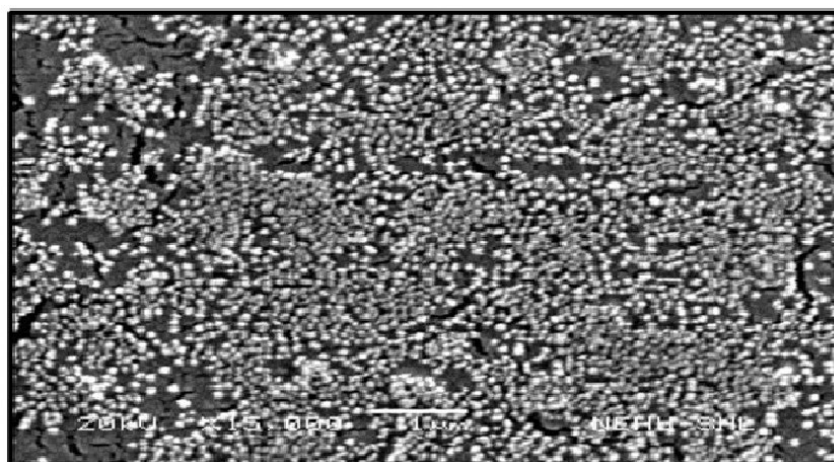


Figure 10: Image of SEM of the optimized batch.

release profiles, enhances formulation stability, and promotes efficient cellular uptake, collectively validating the effectiveness of the preparation technique (Fang *et al.*, 2011).

CONCLUSION

Palbociclib-loaded nanoparticles were successfully developed. FT-IR analysis confirmed excipient compatibility without chemical interactions. Chitosan and PVA concentrations effectively controlled nanoparticle characteristics, yielding a size of 337.8 nm and zeta potential of 32.4 mV, which aligned closely with predicted values. The formulation exhibited sustained drug release via diffusion-erosion mechanisms, high drug loading (22.96%), excellent entrapment efficiency (81.28%), and uniform spherical morphology, collectively demonstrating its suitability as an effective oral drug delivery system.

ACKNOWLEDGEMENT

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ABBREVIATIONS

CCD: Central Composite Design; **PVA:** Polyvinyl Alcohol; **PNS:** Polymeric Nanoparticles; **SEM:** Scanning Electron Microscope; **CDK:** Cyclin-Dependent Kinase.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

FUNDING

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