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Original Article

Formulation, Optimization and Characterization of PLGA-Chitosan Nanoparticles Containing Vinorelbine Ditartrate

Varsha Bandil[1,*], Jeetendra Kumar Gupta[1], Manoj Kumar Goyal[2]

[1]Department of Pharmacology, Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, INDIA.
[2]Departmentof Pharmaceutics, Shri Ram Nath Singh Mahavidhalaya Pharmacy, Gormi, Bhind, Madhya Pradesh, INDIA.

ABSTRACT

Background: The prime objective of our investigation was to optimize PLGA-chitosan nanoparticles containing vinorelbine ditartrate. **Materials and Methods:** The Vinorelbine ditartrate nanoparticles were formulated using emulsion method followed by probe sonication to reduce the size. A three factor three level Box-Behnken Design has been implemented to optimize chitosan, Poloxamer 188 and sonication time (independent variables) for particle size, polydispersity index and entrapment efficiency (%) as the measured responses. Particle size, zeta potential, surface morphology, entrapment effectiveness, and *in vitro* drug release were all evaluated for the optimised formulation. **Results:** The optimized PLGA-chitosan nanoparticle exhibited particles size of 161.22 nm with polydispersity index of 0.229 and zeta potential value of 10.99 mV. The formulation exhibited 78.9% entrapment of vinorelbine ditartrate. The nanoparticle was able to sustain the release of vinorelbine for more than 140 hr in the *in vitro* release studies. **Conclusion:** From studying the obtained results, it could be concluded from the investigation that PLGA-chitosan nanoparticles could be good approach to improve the bioavailability of the entrapped drug.

Keywords: Nanoparticles, Vinorelbine ditartrate, Particle size, Optimization, *in vitro* drug release.

Correspondence:
Mrs. Varsha Bandil
Department of Pharmacology, Institute of Pharmaceutical Research, GLA University, Mathura-281406, Uttar Pradesh, INDIA.
Email: varshabandil98765@gmail.com

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INTRODUCTION

Over the last few decades, the development of nanotechnology and its application to various domains has witnessed a rising popularity.[1] The biodegradability, biocompatibility, availability of several methods of formulation and the scope to incorporate a wide variety of drugs have made the polymeric nanoparticles as a very promising drug delivery approach.[2,3] The use of these polymeric carriers offers dual benefit of controlled release as well as imparting targeting ability in the delivery system.[4,5] Poly (Lactic-co-Glycolic Acid) (PLGA) is FDA-approved synthetic polymer that has been widely investigated for formulation of nanoparticles.[6] PLGA offers advantage of controlling the release of the incorporated drug along with achieving a very small particle size. Chitosan has been effectively incorporated as drug delivery agent to improve therapeutic efficacy of drugs.[7]

Vinorelbine Ditartrate (VD) is a semi-synthetic vinca alkaloid that exhibits a significant antitumor activity by disruption of microtubule. VD has been active in wide type of tumors and is primarily used for the treatment of advanced breast cancer and non-small cell lung cancer.[8] It is available as intravenous formulation that causes venous irritation and phlebitis.[9] Hence strategies like formulation of liposomes[10] or solid lipid nanoparticles[11] or folate conjugated bovine serum nanoparticles[12,13] to overcome the limitations of the intravenous formulation have been reported.

The commonly used approach to optimize the variables for formulation involves studying one variable at a time to relate it to a desired response. This empiric approach is uneconomic, time-consuming and might fail to establish a proper relation between the effect and factors.[14] With the advent of modern technologies, quality by design has become an important tool to optimize the factors that affect the desired responses.

In the present study we aim to develop and optimize PLGA-chitosan nanoparticles loaded with VD using the principle of quality by design principles.

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MATERIALS AND METHODS

Materials

Vinorelbine Ditartrate (VD) was purchased from Clear synth Lab Ltd., Mumbai, India. Poly-Lactide-co-Glycolic Acid (PLGA) and chitosan was procured from Merck, and Poloxamer 188 was purchased from Sigma Aldrich. Acetone (analytical grade) and glacial acetic acid were obtained from Central Drug House (P) Ltd., (New Delhi, India), and deionized water (HPLC grade) was purchased from Merck Millipore. Any other reagent, chemical or solvent employed throughout the study was either of analytical or HPLC grade.

Methods

Preformulation Studies

The preformulation studies were performed to determine the physicochemical properties of the drug as it effects the development and performance of the delivery system.[15]

Solubility and organoleptic features

The physical solubility of VD was assessed using water, ethanol, acetone, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4 as the solvents by shaking 1 mg of the drug in 1 to 5 mL of solvent. The organoleptic features (color, odor and appearance) were also assessed.[15]

Melting Point

Melting point was determined by a gradual increase in the temperature of the melting point apparatus holding a capillary tube containing small amount of drug. The temperature range over which melting of the drug commenced and completed was recorded.[15]

Partition coefficient

A 1:1 ratio of n-octanol and water (10 mL) was placed in a separatory funnel and 1 mg of VD was added to the mixture. The separating funnel was supported on wrist action shaker and shaken for 2 hr to attain equilibrium. The two phases were let to separate by keeping undisturbed for 24 hr. The aqueous phase was sensibly collected and the amount of VD in the aqueous phase was determined by measuring the absorbance at 268 nm using UV-spectrophotometry.[16] The partition coefficient was determined using the formula,

$$Ko/w = \frac{Amount\ of\ \text{VD}\ \ in\ octanol\ phase}{Amount\ of\ \text{VD}\ \ in\ aqueous\ phase}$$

Fourier Transform Infra-Red (FT-IR) Spectroscopy

The qualitative identification of VD was done using FT-IR Spectroscopy. The FTIR investigation was conducted by pressing 1mg of the drug in KBr pellet and recording the spectrum over 400 to 4000 cm^{-1}. The FTIR study was also conducted for assessing the compatibility amongst the drug and the polymers (PLGA, chitosan and Poloxamer 188) by obtaining the spectra of VD and the physical mixture of VD with Poloxamer 188, chitosan and PLGA.[17]

Formulation of nanoparticles

PLGA and VD were dissolved in acetone (10 mL) to obtain a ratio of 1:20 (w/w) of VD to PLGA. The aqueous phase was prepared by dissolving Poloxamer 188 in acetic acid (4 mL) and chitosan in deionized water (400 mL). The organic phase was added drop wise to the aqueous phase under sonication and further sonicating the mixture using probe sonicator for specified time. The mixture was centrifuged at 15000 rpm for 15 min and the supernatant was discarded. The nanoparticles (sediment) were collected and washed twice with deionized water. The resulting particles were freeze dried and subjected to further characterization.[18]

Design of Experiment for optimization of nanoparticle formulation

A three-factor, three level Box-Behnken Design (BBD) was utilized for optimizing the process variables to be used for formulation of VD loaded PLGA chitosan NPs. The BBD included 17 experimental runs using chitosan concentration (X_1), Poloxamer 188 concentration (X_2) and sonication time (X_3) as the independent factors. Each of these factors were varied at three levels: low (-1), medium (0) and high (+1), keeping the concentration of PLGA and VD constant in each trial. Particle size, polydispersity index (PDI) and entrapment efficiency (EE) were selected as the dependent responses (Table 1).

Optimization of variables

The linear scale desirability function was used to simultaneously maximise the three independent parameters. Based on the achievement of the minimal particle size and PDI, as well as the maximum EE%, the best formulation was carefully selected (Table 1).

Particle Size and PDI

Using dynamic light scattering technique, the formulations' PDI and particle size were evaluated utilizing a Malvern Zetasizer by diluting the nanoparticles in distilled water (200-fold dilution). The zeta potential of the formulations was also measured.

Scanning Electron Microscopy (SEM)

Using scanning electron microscopy, the nanoparticles' surface morphology and form were investigated. The surface of particles was coated by sputtering with gold film before examination.

Entrapment Efficiency (EE)

An indirect estimation technique was used to determine the amount of drug entrapped in the core of the nanoparticles. Briefly, freshly prepared nanoparticle solution was centrifuged

Table 1: Experiment design in Box-Behnken Quadratic Model.

Independent Factors	Level			Optimization controls
	-1	0	+1	
X_1 (Chitosan, mg)	40	100	160	-1 to +1
X_2 (Poloxamer 188, %w/v)	0.2	0.3	0.4	-1 to +1
X_3 (sonication time, min)	5	10	15	-1 to +1
Selected Responses				
Particle size (nm)				Minimum
PDI				Minimum
EE (%)				Maximum

Table 2: Absorbance data for calibration curve of VD.

Concentration of VD in sample (µg/mL)	Absorbance Obtained
10	0.104
20	0.224
30	0.352
40	0.489
50	0.632
60	0.772
70	0.909
80	1.027

at 15000 rpm for 15 min and the supernatant was assayed for the amount of VD present using spectrophotometric method to calculate the amount of free drug using the calibration curve of VD. The percent EE was calculated using the following formula,

$$EE\ (\%) = \frac{VD\ (total) - VD(free)}{VD(total)} x100$$

In vitro release study

The quantification of VD released from the nanoparticle formulation was done in Phosphate Buffer pH 7.4 (PBS) as the dissolution medium by loading the formulation in dialysis bag. The dialysis bag containing the nanoparticles was immersed in a beaker containing 100 mL of PBS and the contents were stirred continuously using magnetic stirrer, maintaining the temperature at 37±1°C. A fixed volume of sample (2 mL) was withdrawn from the beaker at definite time intervals and sink conditions were maintained using PBS. The sample was quantified using UV-spectrophotometry at 268 nm post appropriate dilution. A release curve was plotted taking time as one coordinate.[19]

RESULTS

Physical characteristics of VD

Vinorelbine ditartrate was assessed for its texture, odor and color and the purchased powder of VD was found to be yellowish white, odorless and amorphous in nature. The melting of VD was observed in the range of 181-183°C, consonant with the reference literature.[20] VD exhibited a partition coefficient of 0.36 and solubility in water, ethanol, acetone and phosphate buffer. Hence acetone was used as the solvent to prepare the internal phase containing VD and PLGA.

Absorption maxima and calibration curve of VD

The UV-absorption maximum of VD in phosphate buffer pH 7.4 was obtained to be 268 nm (Figure 1). This wavelength was used for construction of calibration curve by measuring the absorbance of 10 to 80 µg/mL solution of VD (Table 2). The linearity of the calibration curved depicted a R^2 value of 0.9994 (Figure 2).

Optimization of experimental conditions for nanoparticle formulation

The experimental milieu obtained through the trial runs of the optimization of the independent factors and selected results is shown in Table 3. The particles size (Y_1) of the formulations ranged from 378.68 to 163.46 nm and the PDI (Y_2) ranged from 0.229 to 0.540. The EE (Y_3) of the trial formulations was found to be in the range of 64.00 to 80.81 %. The p value of the models obtained for all the three responses were <0.0001 and the R^2 values were 0.9913, 0.9736 and 0.9780 for Y_1, Y_2 and Y_3 respectively (Table 4). So, it may be said that every response fits the model very well. The derived quadratic model is provided below in terms of coded values:

$$Y = \beta0 + \beta1X1 + \beta2X2 + \beta3X3 + \beta4X1X2 + \beta5X2X3 + \beta6X1X3 + \beta7X12 + \beta8X22 + \beta9X32$$

where Y represents the response, β_0–β_9 represent the regression coefficients and X_1, X_2, X_3 represent the independent factors.

The following models were obtained for the measured responses.

$$\text{Particle Size} = 246.29 + 98.3862 * X_1 + 10.05 * X_2 + -0.88125 * X_3 + -0.1 * X_1X_2 + -3.2475 * X_1X_3 + 0.025 * X_2X_3 + 2.92125 * X_1^2 + 19.6987 * X_2^2 + 15.1062 * X_3^2$$

$$PDI = 0.243 + 0.01025 * X_1 + 0.0045 * B + -0.096 * C + -0.00025 * X_1X_2 + 0.00075 * X_1X_3 + -0.00925 * X_2X_3 + 0.002375 * X_1^2 + -0.007625 * X_2^2 + 0.194875 * X_3^2$$

Table 3: Experimental matrix and obtained response from trial runs by BBD.

	Independent Factor			Dependent Response		
Run	Chitosan (mg)	Poloxomer 188 (% w/v)	Sonication time (min)	Size (nm)	PDI	EE (%)
1	100	0.3	10	248.26	0.239	80.53
2	40	0.3	5	163.46	0.53	63.88
3	160	0.3	5	363.72	0.552	66.5
4	100	0.3	10	239.81	0.24	79.79
5	40	0.2	10	158.97	0.229	78.56
6	160	0.3	15	358.68	0.352	72.81
7	40	0.4	10	179.07	0.229	76.56
8	100	0.3	10	247.48	0.24	78.99
9	100	0.2	15	268.43	0.339	69.86
10	100	0.4	5	293.71	0.54	64.98
11	160	0.2	10	358.95	0.247	80.59
12	100	0.3	10	248.4	0.251	80.56
13	100	0.3	10	247.5	0.245	81.08
14	160	0.4	10	378.65	0.246	80.81
15	40	0.3	15	171.41	0.327	68.56
16	100	0.4	15	288.78	0.339	67.84
17	100	0.2	5	273.46	0.503	64

Table 4: Statistical Analysis of the observed responses.

	Source	Sequential *p*-value	Lack of Fit *p*-value	Adjusted R^2	Predicted R^2	
Size	Linear	< 0.0001	0.0038	0.9550	0.9428	
	2FI	0.9852	0.0019	0.9424	0.8953	
	Quadratic	< 0.0001	0.4879	0.9974	0.9913	Suggested
	Cubic	0.4879		0.9974		Aliased
PDI	Linear	0.1630	< 0.0001	0.1587	-0.2679	
	2FI	0.9991	< 0.0001	-0.0914	-1.8271	
	Quadratic	< 0.0001	0.0781	0.9953	0.9736	Suggested
	Cubic	0.0781		0.9983		Aliased
EE	Linear	0.7129	0.0002	-0.1120	-0.6270	
	2FI	0.9956	0.0001	-0.4365	-2.5148	
	Quadratic	< 0.0001	0.7729	0.9895	0.9780	Suggested
	Cubic	0.7729		0.9857		Aliased

$$EE=80.19 + 1.64375 * X_1 + -0.3525 * B + 2.46375 * C + 0.555 * X_1X_2 + 0.4075 * X_1X_3 + -0.75 * X_2X_3 + 0.10375 * X_1^2 + -1.16375 * X_2^2 + -12.3563 * X_3^2$$

The 3D-surface response plots (Figure 3) make it evident that an increase in the X_1 and X_2 increases the particle size whereas the variable X_3 has a typically multimodal effect on the particle size. All the three variables affected the PDI in multimodal manner with the lowest PDI being exhibited at mid-level of X_3. The entrapment efficiency was found to be lower with higher ratio of X_1 and X_2. The optimized variables with lowest particle size, PDI and highest entrapment efficiency was predicted to be 45.735 mg X_1, 0.263 % w/v X_2 and 10.468 min X_3. The predicted response variables and the actual values obtained on formulating the nanoparticles with the optimized conditions are presented (Table 5).

Particles size, zeta potential and surface morphology

The optimized formulation revealed particle size of 161.22 nm having PDI of 0.229 (Figure 4). The formulation exhibited a zeta potential value of 10.99 mV. The positive value of the zeta potential reflects the presence of chitosan on surface of the nanoparticles

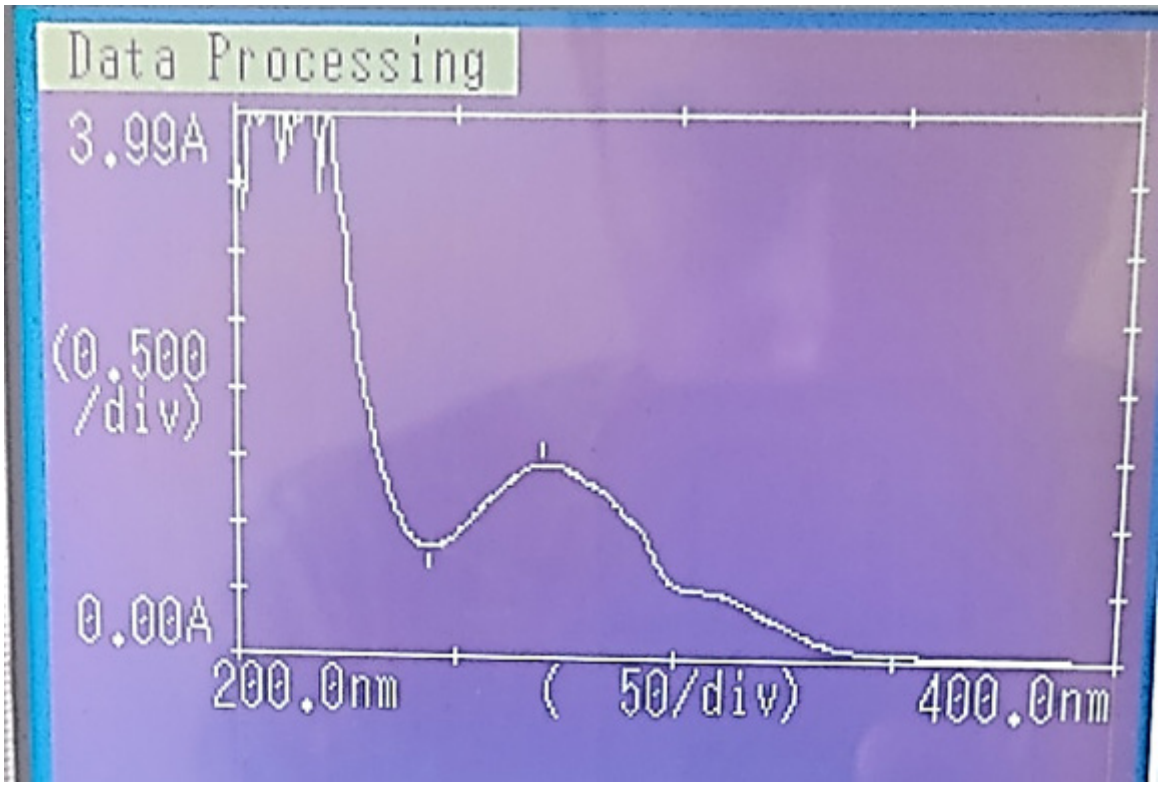

Figure 1: UV-absorption spectrum of VD in phosphate buffer pH 7.4.

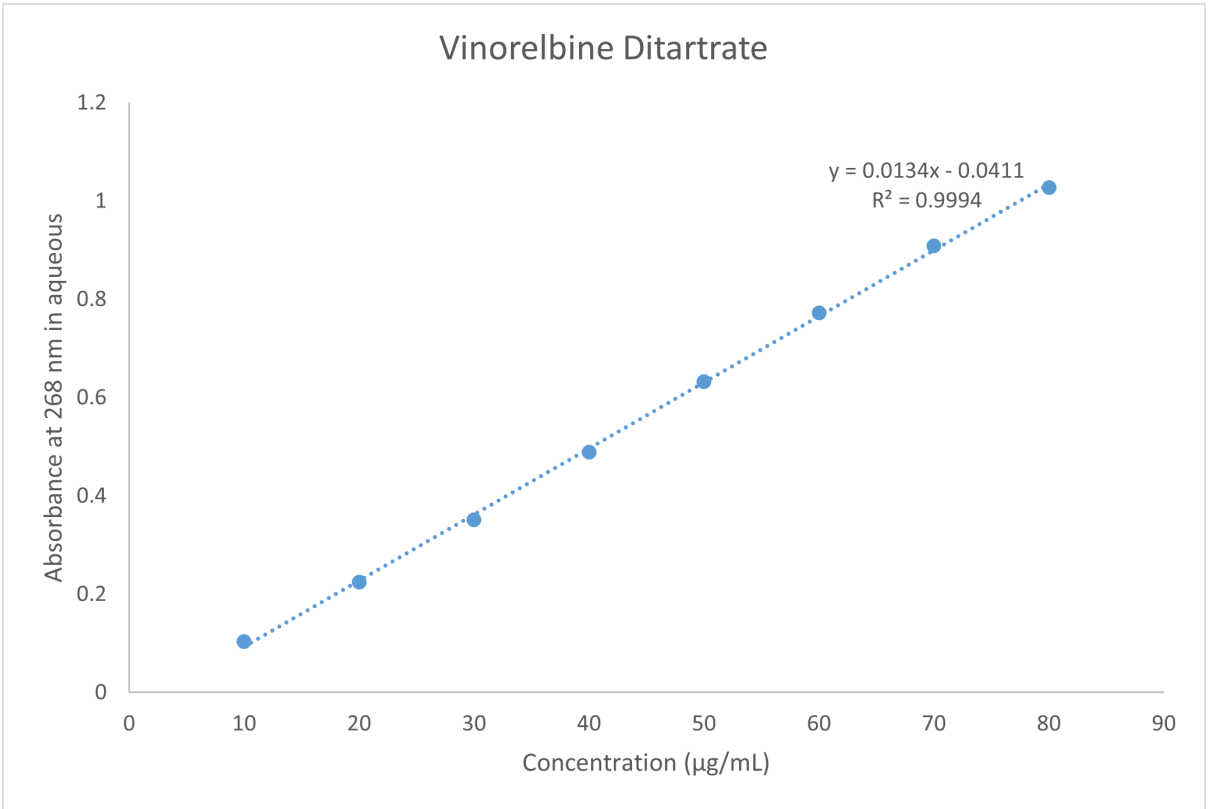

Figure 2: Calibration curve of VD in phosphate buffer pH 7.4.

(Figure 5). The SEM images of the nano formulation depicts smooth surface with cluster of particles. Individual particles were seldom visible in the SEM image (Figure 6).

FTIR Spectral studies

The FTIR spectrum of pure VD exhibited characteristic stretching vibrations at 3432 cm^{-1} (O-H stretching), 2927 cm^{-1} (C-H stretching), 1736 cm^{-1} (C=O stretching of ester), 1623 cm^{-1} (C=C stretching), 1438 cm^{-1} (N-O stretching), 1232 cm^{-1} (C-N stretching) and 746 cm^{-1} (C-Cl stretching). Occurrence of all these peaks in the physical mixture of the polymers and VD led to the conclusion that no drug-excipient interaction occurs on using the components together (Figure 7). This demonstrates the compatibility of VD with poloxomer 188, chitosan and PLGA.

In vitro drug release study

Dialysis bag method was used to determine the *in vitro* release of VD from the optimized nanoparticles in pH 7.4 phosphate buffer. The cumulative release of VD from nanoparticles was compared with that to plain VD release from the dialysis bag. The plain VD exhibited biphasic release pattern with an initial burst release for upto 6 hr followed by steady state release and thereafter a

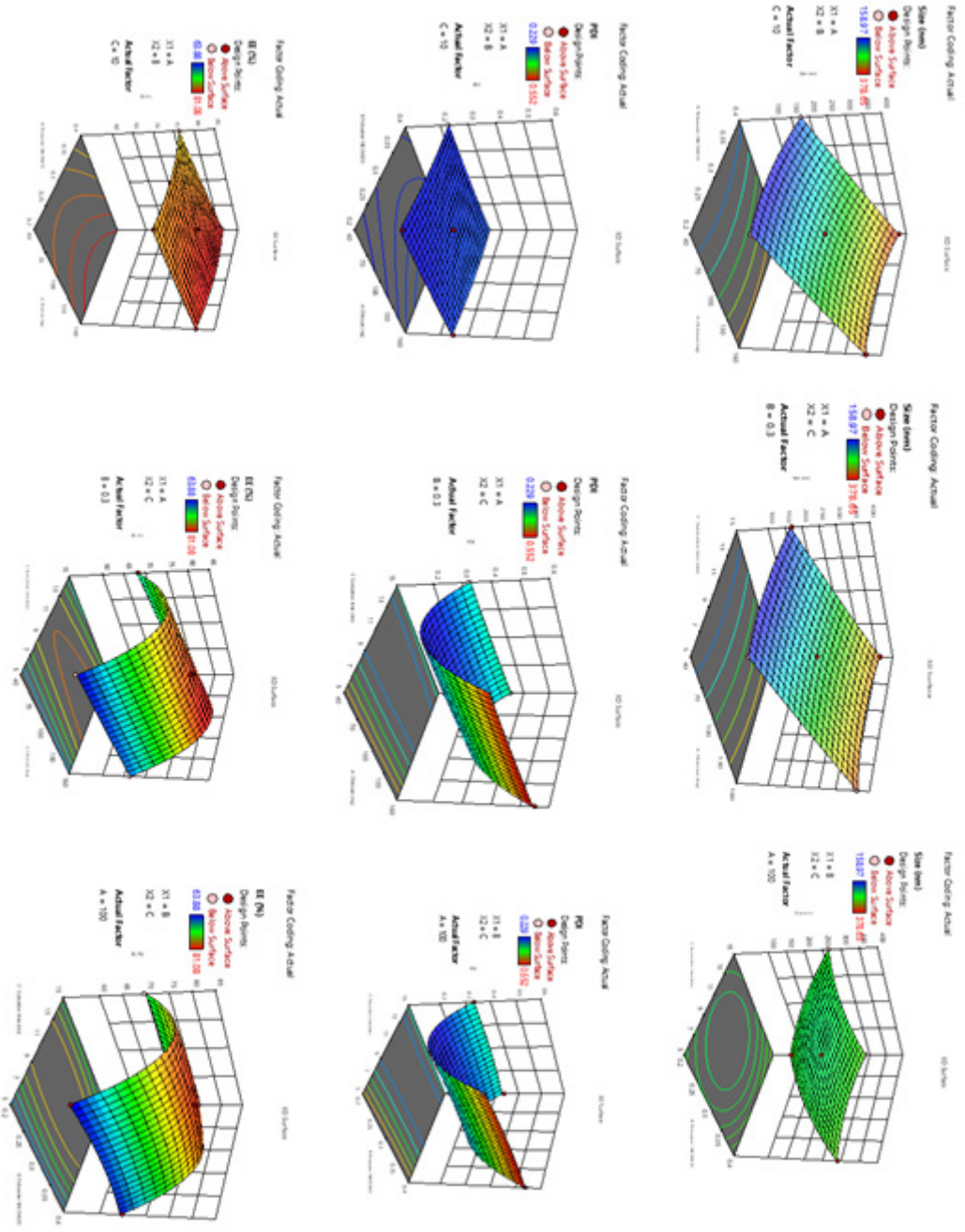

Figure 3: 3D-contour plots showing the effect of chitosan, Poloxamer 188 and sonication time on Particle size, PDI and Entrapment Efficiency.

Results

		Size (d.n...	% Number:	St Dev (d.n...
Z-Average (d.nm): 161.22	**Peak 1:**	169.09	97.2	8.703
PdI: 0.229	**Peak 2:**	42.8	3.9	132.1
Intercept: 0.864	**Peak 3:**	0.000	0.0	0.000

Result quality Good

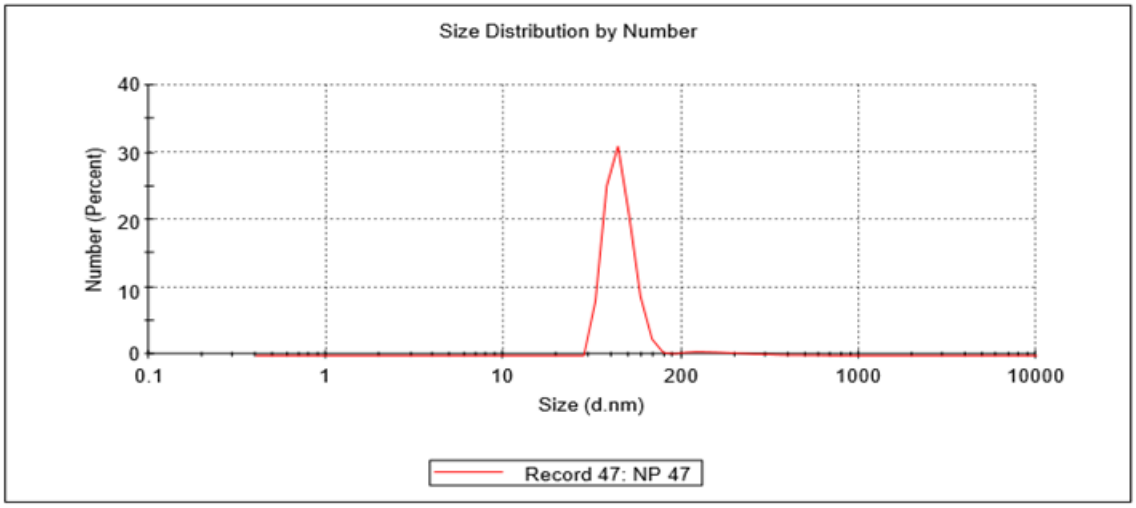

Figure 4: Particle size and PDI of the optimized nanoformulation.

Results

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): 10.99	**Peak 1:**	10.99	100.0	4.72
Zeta Deviation (mV): 4.72	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm): 0.0303	**Peak 3:**	0.00	0.0	0.00

Result quality : See result quality report

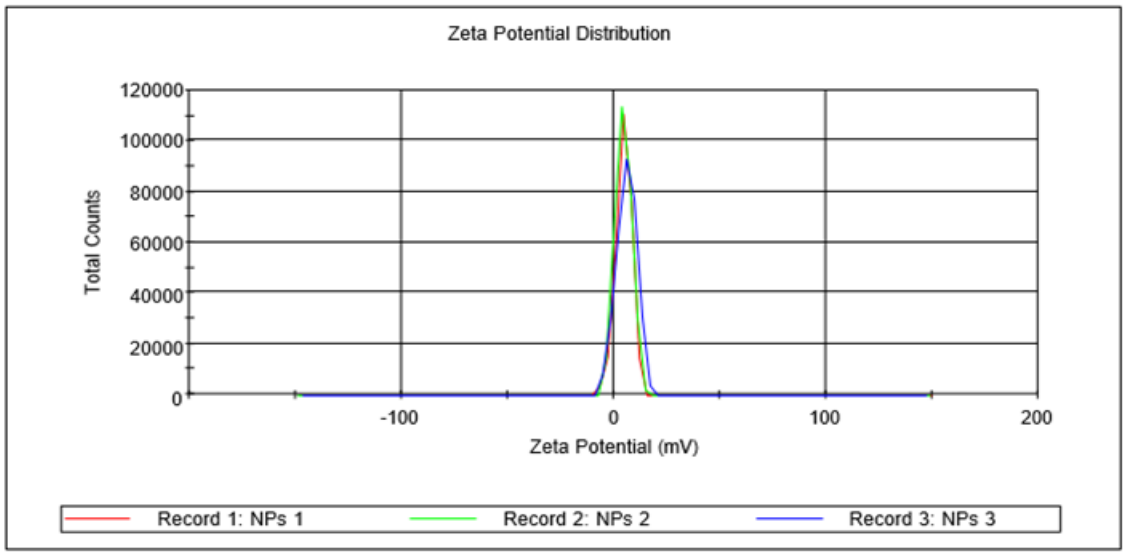

Figure 5: Zeta potential of the optimized nanoformulation.

Table 5: Comparison of predicted responses and the practically observed responses.

Chitosan (mg)	Poloxomer 188 (% w/v)	Sonication time (min)	Particle Size (nm)	PDI	Entrapment Efficiency (%)
Predicted Formulation					
45.735	0.263	10.468	158.970	0.226	79.059
Actual formulation with optimized variables					
45.735	0.263	10.5	161.22	0.229	78.962

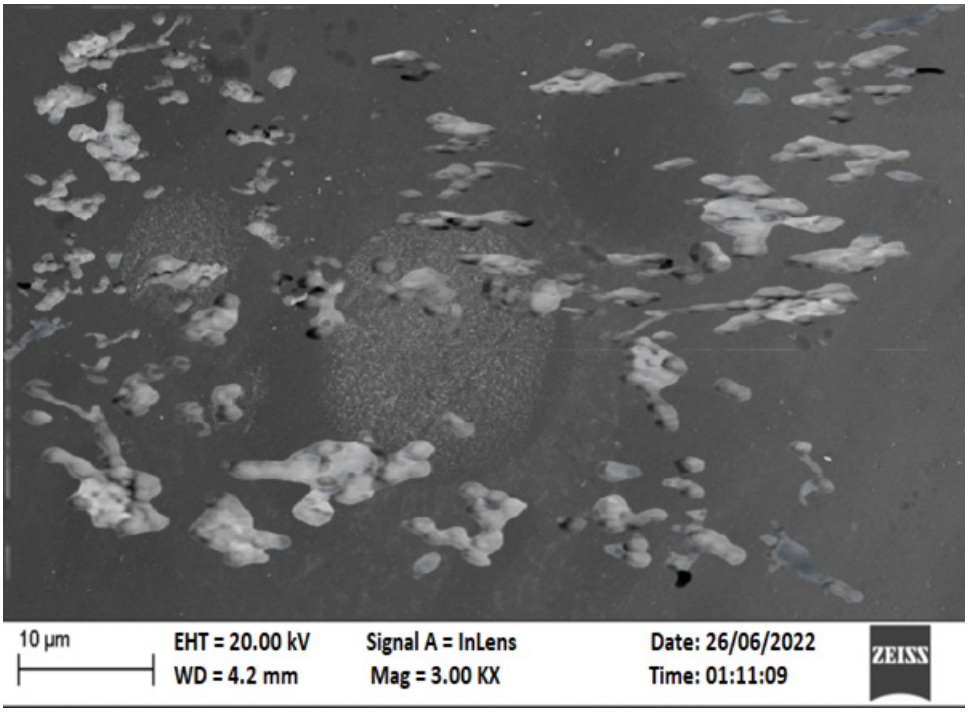

Figure 6: Scanning electron microscopic image of the optimized nanoformulation.

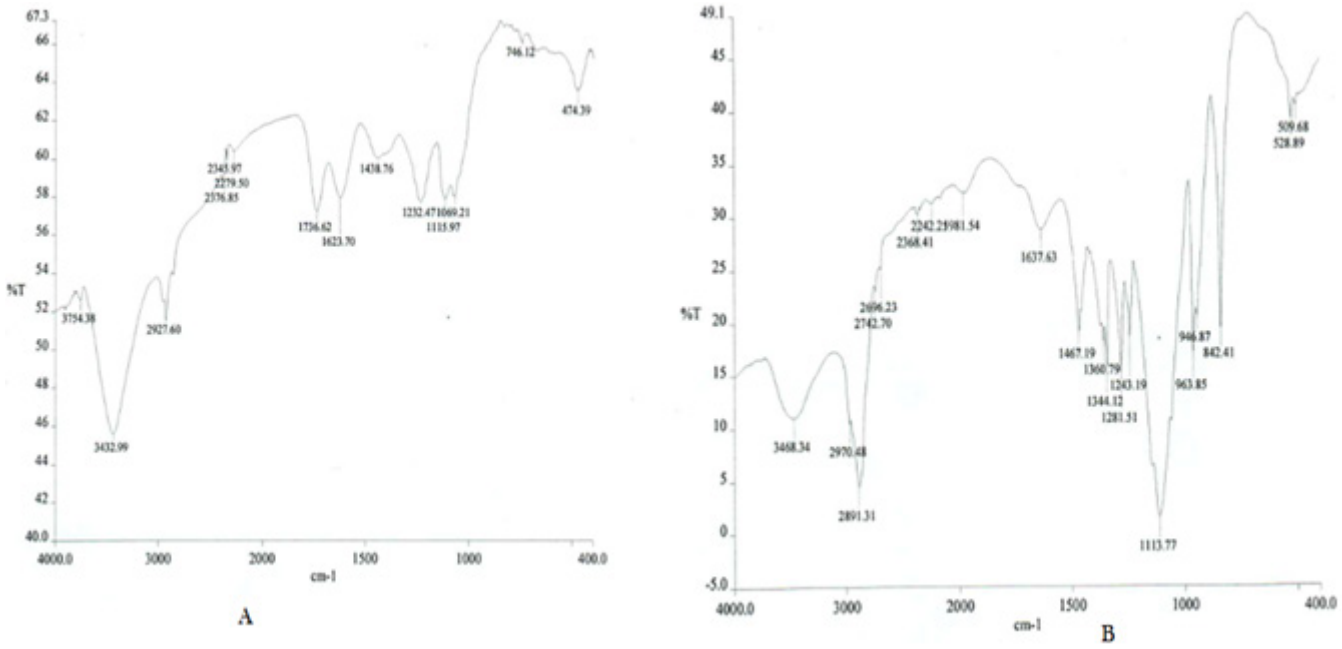

Figure 7: Infrared spectrum of (A) Vinorelbine ditartrate; (B) physical mixture of VD and excipients.

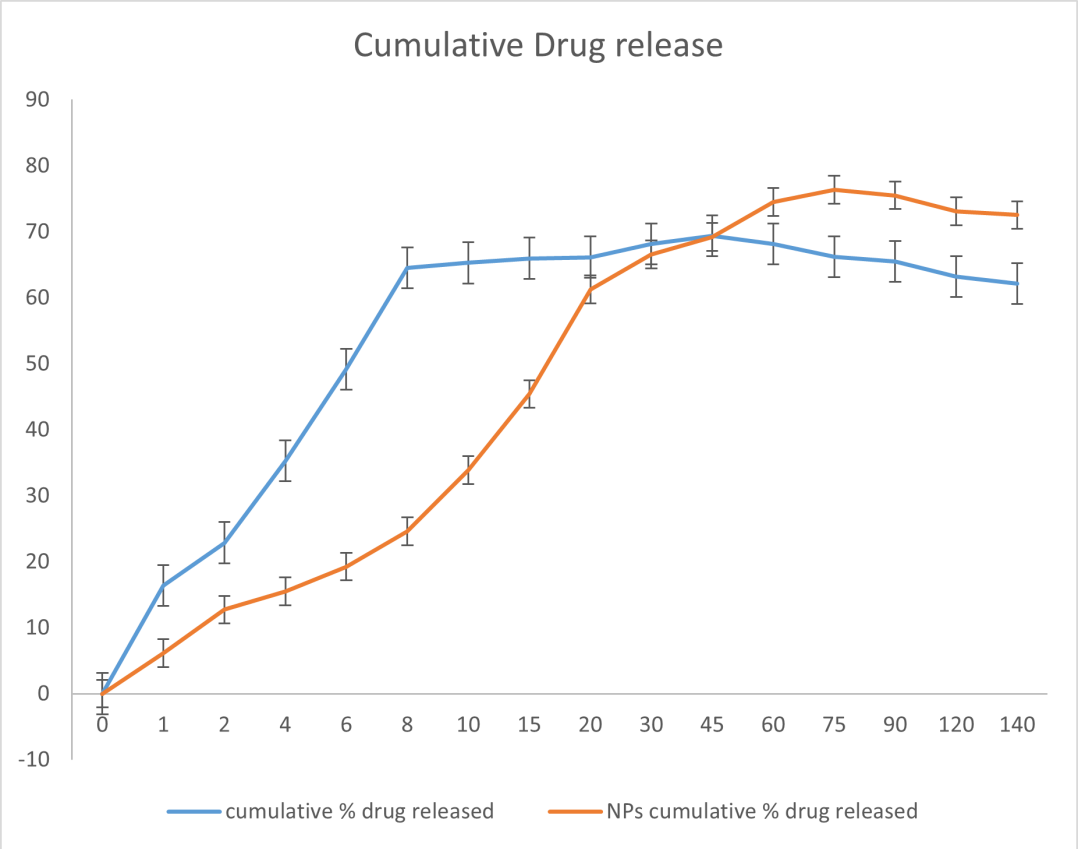

Figure 8: Comparative release curve of VD from plain drug and Nanoparticles.

decline in concentration after 60 hr. On the other hand, VD from the nanoparticle formulation released at a steady rate for more than 75 hr. A decline in concentration of VD release from the nanoparticles was visible after 90hr with maximum release of 75.51±2.13 % (Figure 8).

DISCUSSION

For optimization of the experimental conditions, computer assisted processing with Design-Expert software was done. It was observed that the obtained results were fitted in quadratic model and the significance of the models was confirmed through one-way ANOVA. The compatibility of VD with the excipients was confirmed by the infrared spectra of the mixture which revealed the presence of all characteristic functional groups of the VD. The average particle size of the nanoparticle was found to be 161.22 nm which is comparable to a previous study in which VD was loaded in nanoparticles composed of Bovine Serum Albumin (BSA) and conjugated with folate.[12]

The formation of agglomerates as visible in SEM images might be a result of the lower value of the zeta potential of the particles, limiting repulsion thereby leading to agglomeration.

The *in vitro* release of 75% drug in 90 hr displays a sustained release. A release of 75% drug steadily from 25 to 140 hr was found in the BSA nanoparticles. BSA possesses the capability to trigger antigenic response[21] and hence a chitosan-based nanoparticle definitely possesses advantages over it.

CONCLUSION

The present investigation was aimed to produce controlled release nanoparticle formulation incorporated with vinorelbine ditartrate. The nanoparticles were formulated using PLGA and chitosan as the polymeric matrix and poloxomer 188 as the stabilizing surfactant by emuslion method followed by probe sonication. The nanoparticles were optimized using Box-Behnken Design involving three factor three level design. The optimized VD nano formulation displayed particle size, PDI and entrapment efficiency within the acceptable premises of the predicted values using the software. The formulation was able to sustain the release in a steady manner for more than 90 hr and maintained drug concentration up to 140 hr during the *in vitro* study. The study led to the conclusion that PLGA-chitosan blend nanoparticles can be effective approach to improve the bioavailability of the incorporated drug.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PLGA: Poly (lactic-co-glycolic acid; **FDA:** Food and Drug Administration; **VD:** Vinorelbine Ditartrate; **UV:** Ultraviolet; **BBD:** Box-Behnken Design; **NP:** Nanoparticle; **PDI:** Polydispersity index; **SEM:** Scanning Electron Microscopy; **EE:** Entrapment Efficiency; **FTIR:** Fourier Transformed Infrared.

SUMMARY

In this work PLGA-chitosan nanoparticles containing vinorelbine ditartrate were formulated using Box-Behnken Design and characterized for particle size, polydispersity index, entrapment efficiency (%), SEM and *in vitro* release. The optimized PLGA-chitosan nanoparticle exhibited particles size of 161.22 nm with polydispersity index of 0.229 and zeta potential value of 10.99 mV. The formulation exhibited 78.9% entrapment of vinorelbine ditartrate. The nanoparticle was able to sustain the release of vinorelbine for more than 140 hr in the *in vitro* release studies.

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