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DESIGN, PREPARATION AND OPTIMIZATION OF CABAZITAXEL POLYMERIC NANOPARTICLES

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Abstract:

The present study was aimed at the design, preparation, and optimization of Cabazitaxel-loaded PLGA polymeric nanoparticles using the nanoprecipitation method to improve drug encapsulation, provide sustained drug release, and enhance formulation stability. Cabazitaxel-loaded polymeric nanoparticles were prepared using poly(lactic-co-glycolic acid) (PLGA) as the biodegradable polymer and polyvinyl alcohol (PVA) as the stabilizer. Eight formulations (F1–F8) were developed by varying the polymer concentration while maintaining a constant drug concentration. The prepared nanoparticles were evaluated for particle size, zeta potential, entrapment efficiency, surface morphology, in-vitro drug release, release kinetics, and stability. The particle size of the formulations ranged from 226 to 362 nm, while the zeta potential varied between −21 and −31 mV, indicating good colloidal stability. Drug entrapment efficiency ranged from 79.83% to 89.23%. SEM analysis of the optimized formulation confirmed the formation of spherical, smooth, and uniformly distributed nanoparticles with minimal aggregation. In-vitro drug release studies demonstrated a biphasic release pattern consisting of an initial burst release followed by sustained release over 12 hours. Among all formulations, F5 exhibited the most desirable characteristics, with a particle size of 226 nm, entrapment efficiency of 89.23%, and cumulative drug release of 98.05%. Drug release kinetic analysis revealed that the optimized formulation best fitted the Higuchi model (R^2 = 0.978), indicating diffusion-controlled drug release from the PLGA matrix. Stability studies performed under long-term and accelerated storage conditions for three months showed no significant changes in drug release, confirming the stability of the optimized formulation. The study concludes that PLGA-based polymeric nanoparticles prepared by the nanoprecipitation method are an effective carrier system for Cabazitaxel, providing high drug encapsulation, nanosized particles, sustained drug release, and good physicochemical stability. The optimized formulation has the potential to improve the therapeutic efficacy of Cabazitaxel while reducing dosing frequency and systemic toxicity.

Keywords: *Cabazitaxel, Polymeric nanoparticles, PLGA, Nanoprecipitation, Controlled drug release, Entrapment efficiency, Anticancer drug delivery.*

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INTRODUCTION:

Nanotechnology-based drug-delivery systems have emerged as promising approaches for improving the pharmaceutical and biopharmaceutical properties of poorly water-soluble anticancer drugs. Polymeric nanoparticles are submicron-sized colloidal carriers in which the drug can be encapsulated within or associated with a biodegradable polymeric matrix.[1] Polymeric nanoparticles offer several advantages over conventional dosage forms, including high surface-area-to-volume ratio, tunable particle size, controlled drug release, improved stability, and the possibility of modifying the nanoparticle surface with targeting ligands.[2] Encapsulation of cabazitaxel within a polymeric matrix may reduce direct exposure of healthy tissues to the drug, improve its apparent aqueous dispersibility, and facilitate more controlled delivery to the site of action.[3] The present study was designed to develop, prepare, and optimize cabazitaxel-loaded polymeric nanoparticles using a suitable biodegradable polymeric system.[4] The developed nanoparticles were intended to improve the delivery characteristics of cabazitaxel and provide controlled drug release.[5] Cabazitaxel is particularly important in the treatment of metastatic castration-resistant prostate cancer in patients who have previously received docetaxel-based therapy.

MATERIALS:

Cabazitaxel was procured from Hetero Labs, HYD. PLGA and Polyvinyl Alcohol were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Formulation development

Table-1: Composition of the Nanoparticles

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Cabazitaxel	20	20	20	20	20	20	20	20
PLGA	100	200	300	400	500	600	700	800
Acetone	10	10	10	10	10	10	10	10
Polyvinyl Alcohol (PVA, 1% w/v)	50	50	50	50	50	50	50	50
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Nanoprecipitation method

Cabazitaxel-loaded PLGA polymeric nanoparticles were prepared by the nanoprecipitation (solvent displacement) method. In this method, 20 mg of cabazitaxel and the required quantity of PLGA (100–800 mg according to formulations F1–F8) were accurately weighed and dissolved in 10 mL of acetone under continuous magnetic stirring until a clear and homogeneous organic solution was obtained. Acetone served as the organic solvent because of its complete miscibility with water and its ability to dissolve both the drug and polymer. Separately, 50 mL of 1% w/v polyvinyl alcohol (PVA) solution was prepared in distilled water and used as the aqueous phase. The PVA solution was stirred continuously at 800–1000 rpm using a magnetic stirrer at room temperature. The organic phase containing cabazitaxel and PLGA was then added dropwise into the aqueous PVA solution using a syringe fitted with a fine-gauge needle at a controlled rate (approximately 1 mL/min) while maintaining continuous stirring. The rapid diffusion of acetone into the aqueous phase caused immediate precipitation of the polymer, resulting in the spontaneous formation of polymeric nanoparticles. After complete addition of the organic phase, the nanoparticle dispersion was stirred continuously for 3–4 hours at room temperature to allow complete evaporation of acetone and stabilization of the nanoparticles. The resulting nanoparticle suspension was then centrifuged at 15,000 rpm for 30 minutes at 4°C to separate the nanoparticles from the aqueous medium. The collected nanoparticles were washed two to three times with distilled water to remove residual PVA and any unentrapped drug.[6]

Evaluation of Cabazitaxel loaded polymeric nanoparticles:

Particle size

The average particle size of the prepared Cabazitaxel-loaded PLGA polymeric nanoparticles were determined using Dynamic Light Scattering (DLS) with a particle size analyzer. Approximately 2–5 mg of nanoparticles were dispersed in 10 mL of distilled water or filtered deionized water. The dispersion was sonicated for 5–10 minutes to obtain a uniform suspension and prevent particle aggregation. The sample was transferred into a disposable cuvette, and measurements were carried out at 25 ± 1°C with a scattering angle of 90°**.** Each formulation was analyzed in triplicate, and the average particle size (nm) and PDI were recorded. A lower PDI value (<0.3) indicated a narrow particle size distribution and good formulation uniformity.[7]

Zeta Potential Measurement

The zeta potential of the Cabazitaxel-loaded PLGA polymeric nanoparticles was measured using a Zeta Potential Analyzer based on electrophoretic light scattering. About 2–5 mg of nanoparticles were

dispersed in 10 mL of deionized water and sonicated gently for 5 minutes to obtain a homogeneous suspension. The prepared dispersion was transferred into a folded capillary zeta cell, ensuring that no air bubbles were present. Measurements were performed at 25 ± 1°C**,** and the zeta potential was recorded in millivolts (mV). Each sample was analyzed three times, and the mean value was reported. Nanoparticles exhibiting zeta potential values greater than ±30 mV were considered to possess good colloidal stability due to strong electrostatic repulsion between particles.[8]

Scanning Electron Microscopy (SEM) Analysis

The surface morphology and shape of the prepared polymeric nanoparticles were examined using Scanning Electron Microscopy (SEM)**.** A small quantity of freeze-dried nanoparticles was mounted on an aluminum specimen stub using double-sided carbon adhesive tape. The mounted samples were coated with a thin layer of gold using a sputter coater to improve electrical conductivity and prevent charging during imaging. The samples were then observed under the scanning electron microscope at an appropriate accelerating voltage (typically 10–20 kV**)** and suitable magnifications. SEM images were recorded to evaluate the particle shape, surface characteristics, and degree of aggregation. The nanoparticles were expected to exhibit a smooth, spherical morphology with minimal aggregation.[9]

Drug Entrapment Efficiency

The drug entrapment efficiency of Cabazitaxel-loaded PLGA polymeric nanoparticles was determined by the centrifugation method**.** An accurately measured volume of the nanoparticle suspension equivalent to 10 mg of Cabazitaxel was centrifuged at 15,000 rpm for 30 minutes at 4°C**.** The supernatant containing the free (unentrapped) drug was carefully collected and analyzed using a UV–Visible spectrophotometer at the predetermined wavelength. The amount of free drug was determined from the calibration curve of Cabazitaxel. The percentage entrapment efficiency was calculated by subtracting the amount of free drug from the total drug added during formulation.[10]

Equation:
Qt=Q0+K0t
where:
QtQ_tQt = Amount of drug released at time t
Q0Q_0Q0 = Initial amount of drug
K0K_0K0 = Zero-order release constant

(b) First-Order Model
The logarithm of the percentage drug remaining was plotted against time.
Equation:
logQ=logQ0−2.303K1t
where:

- K1K_1K1 = First-order release constant

W) × 100
% Drug Entrapment = (W-w/W) × 100

In-vitro drug release studies[11]

The in-vitro drug release of Cabazitaxel-loaded PLGA polymeric nanoparticles was carried out using the dialysis bag diffusion method**.** A dialysis membrane was soaked overnight in distilled water before use. An accurately weighed quantity of nanoparticles equivalent to 20 mg of Cabazitaxel was dispersed in 2–5 mL of phosphate buffer (pH 7.4) and transferred into the dialysis bag, which was securely tied at both ends.

The dialysis bag was immersed in 100 mL of phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C under continuous stirring at 100 rpm using a magnetic stirrer. At predetermined time intervals, **5 mL** of the dissolution medium was withdrawn and immediately replaced with an equal volume of fresh prewarmed dissolution medium to maintain sink conditions. The collected samples were filtered through a 0.45 µm membrane filter and analyzed for Cabazitaxel content using a UV–Visible spectrophotometer at the predetermined wavelength. The cumulative percentage drug release was calculated and plotted against time to obtain the release profile of each formulation.

Kinetic Modeling of Drug Release[12]

The in-vitro drug release data obtained from the optimized formulation were fitted into various mathematical kinetic models to determine the mechanism of drug release from the polymeric nanoparticles.

The release data were fitted to the following kinetic models:

(a) Zero-Order Model

The cumulative percentage of drug released was plotted against time.

(c) Higuchi Model

The cumulative percentage drug released was plotted against the square root of time.

Equation:

Q=KHt

where:

- KHK_HKH = Higuchi dissolution constant

This model indicates diffusion-controlled drug release.

(d) Korsmeyer–Peppas Model

The logarithm of cumulative drug released was plotted against the logarithm of time.

Equation:

Equation: M∞/Mt=Ktn

where:

M∞ = Fraction of drug released

K = Release rate constant

n = Release exponent

The kinetic model showing the highest correlation coefficient (R^2) was considered the best fit and used to explain the release mechanism of Cabazitaxel from the polymeric nanoparticles.

Stability Studies[13]

The stability study of the optimized Cabazitaxel-loaded PLGA polymeric nanoparticle formulation was carried out according to ICH Q1A(R2) guidelines to evaluate its physical and chemical stability during storage.

The optimized formulation was filled into airtight amber-coloured glass vials and stored under the following conditions:

- **Long-term: 25 ± 2°C / 60 ± 5% RH**
- **Accelerated: 40 ± 2°C / 75 ± 5% RH**

The formulations were stored for 3 months**.** Samples were withdrawn initially (0 month) and after 1, 2, and 3 months of storage.

RESULTS AND DISCUSSION:

EVALUATION PARAMETERS

Particle size:

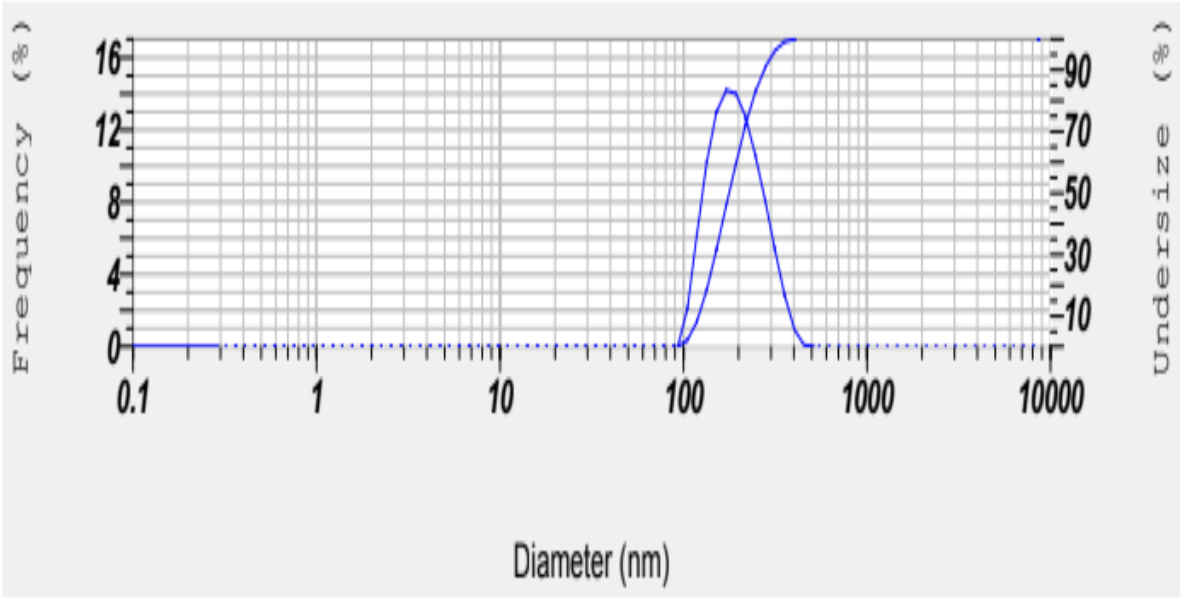


Fig-1: Particle size of Optimized formulation

Determination of Zeta potential:

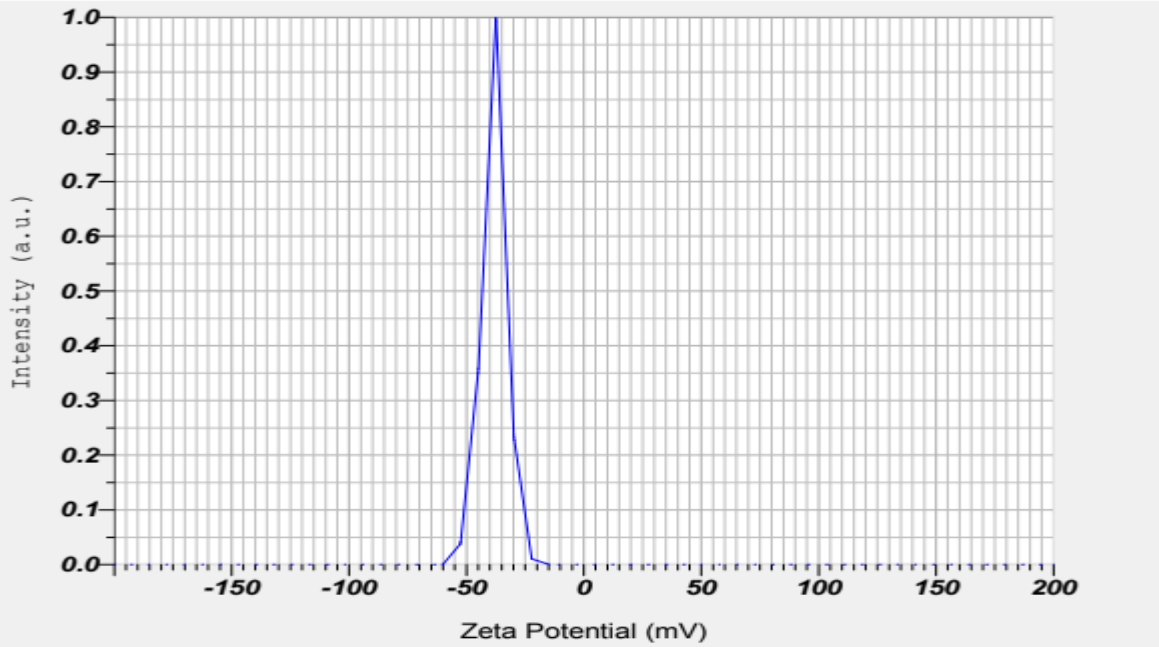


Fig-2: Zeta potential of Polymeric nanoparticles

Surface morphology:

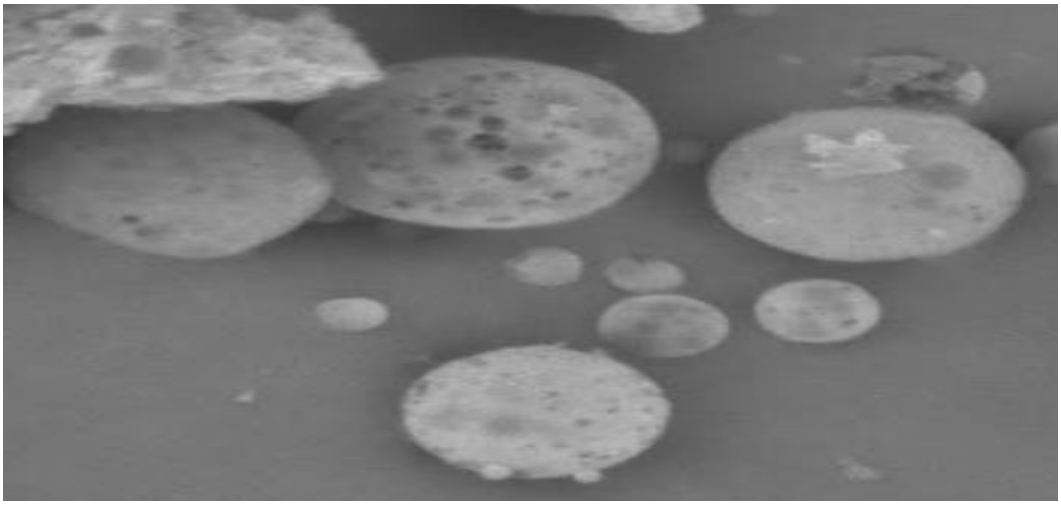


Fig-3: SEM analysis of Optimized polymeric nanoparticle

Table-2: Evaluation Studies of Prepared polymeric nanoparticles: Entrapment Efficiency and Particle size

F. No	Particle size (nm)	Zeta potential (mV)	Entrapment Efficiency (%)
F1	359	-23	81.29
F2	362	-25	79.83
F3	357	-27	83.19
F4	259	-22	85.95
F5	226	-21	89.23
F6	280	-30	87.69
F7	297	-31	85.42
F8	236	-28	84.35

Particle Size
Among all formulations, F5 exhibited the smallest particle size (226 nm), suggesting the formation of uniform nanoparticles that are expected to enhance cellular uptake and improve drug delivery.

Zeta Potential
Although F5 showed a comparatively lower zeta potential (−21 mV), it remained sufficiently stable due to the combined steric stabilization provided by polyvinyl alcohol (PVA) and the electrostatic repulsion of PLGA nanoparticles. Overall, all formulations exhibited acceptable zeta potential values, indicating good colloidal stability.

Entrapment Efficiency
Entrapment efficiency reflects the ability of the polymeric matrix to encapsulate the drug effectively. The entrapment efficiency of the formulations ranged from 79.83% to 89.23%. The lowest entrapment efficiency was observed in F2 (79.83%), whereas the highest was recorded for F5 (89.23%). The gradual increase in PLGA concentration from F1 to F5 resulted in improved drug encapsulation because a larger amount of polymer was available to entrap Cabazitaxel within the nanoparticle matrix. However, further increases in polymer concentration beyond the optimum level led to a slight reduction in entrapment efficiency in F6, F7, and F8, possibly due to increased viscosity, which hindered efficient drug diffusion and homogeneous nanoparticle formation. The high entrapment efficiency obtained with F5 demonstrates the suitability of the selected drug-to-polymer ratio for efficient drug loading.

Surface Morphology (SEM Analysis)
Scanning Electron Microscopy (SEM) analysis of the optimized formulation F5 revealed that the nanoparticles were spherical in shape with a smooth and uniform surface morphology. The particles appeared discrete, well distributed, and showed minimal aggregation, indicating successful preparation by the nanoprecipitation method. The smooth surface suggests complete encapsulation of Cabazitaxel within the PLGA matrix and the absence of surface-adhered drug crystals. The SEM findings correlated well with the particle size analysis, confirming the formation of nanosized particles with a narrow size distribution.

In vitro drug release studies

Table-3: *In vitro* drug release profiles of Cabazitaxel polymeric nanoparticles (F1-F8)

Time (hr.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0		0	0
1	17.89	18.49	16.28	18.25	19.89	15.49	16.93	17.23
2	21.19	24.56	20.25	26.49	28.15	27.48	25.48	25.87
3	33.58	32.29	30.26	32.15	37.49	35.48	36.41	34.47
4	45.79	42.58	43.15	41.15	48.12	47.96	46.82	49.75
6	56.89	55.12	61.28	63.28	69.73	65.35	59.78	64.53
8	69.18	71.10	72.35	75.19	77.82	78.18	73.22	73.22
10	83.12	81.25	83.64	85.36	86.39	87.80	84.58	86.39
12	95.10	93.15	96.35	97.49	98.05	95.18	94.48	97.40

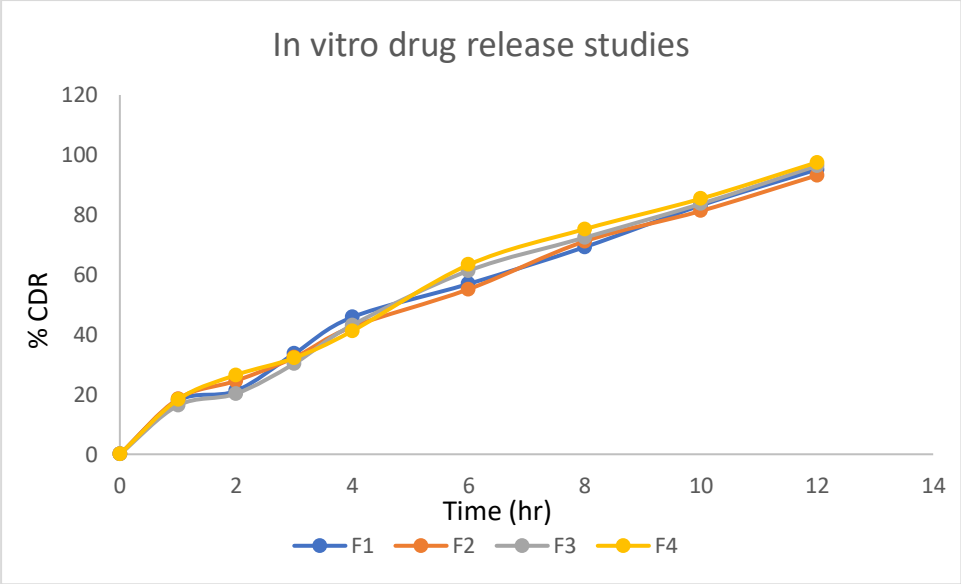


Fig-4: Drug release for (F1-F4) formulations

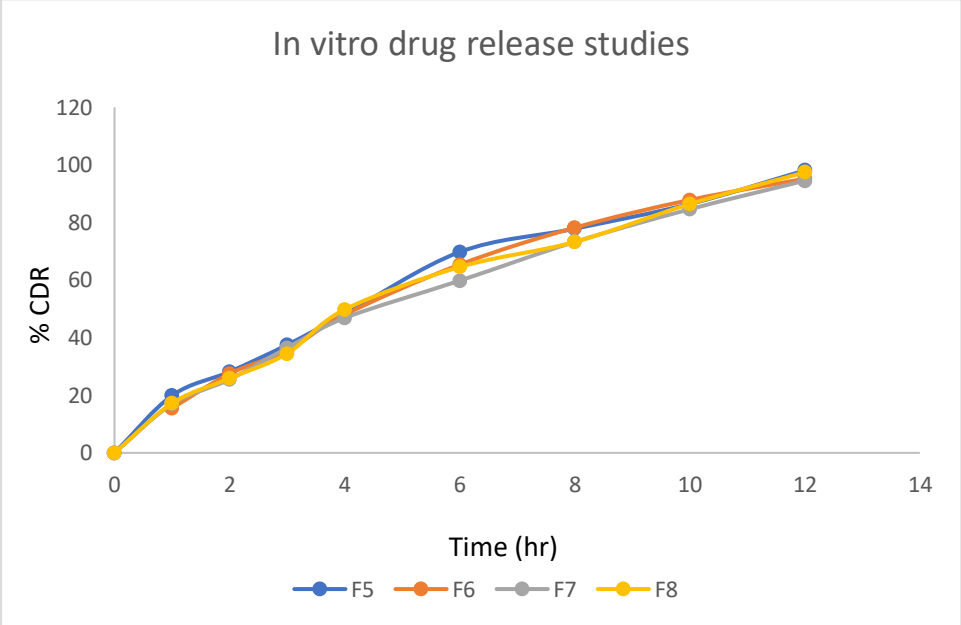


Fig-5: Drug release for (F5-F8) formulation

Discussion

At the end of 12 hours, the cumulative drug release ranged from 93.15% to 98.05%**.** Formulation F2 showed the lowest drug release **(**93.15%**),** whereas the optimized formulation F5 exhibited the highest cumulative drug release **(**98.05%**).**

The release profiles indicate that PLGA effectively controlled the release of Cabazitaxel, making the nanoparticles suitable for sustained drug delivery. The optimized formulation (F5) provided an ideal balance between rapid initial drug availability and prolonged release, which may improve therapeutic efficacy while reducing dosing frequency and minimizing systemic toxicity.

Kinetic models:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Zero order kinetics

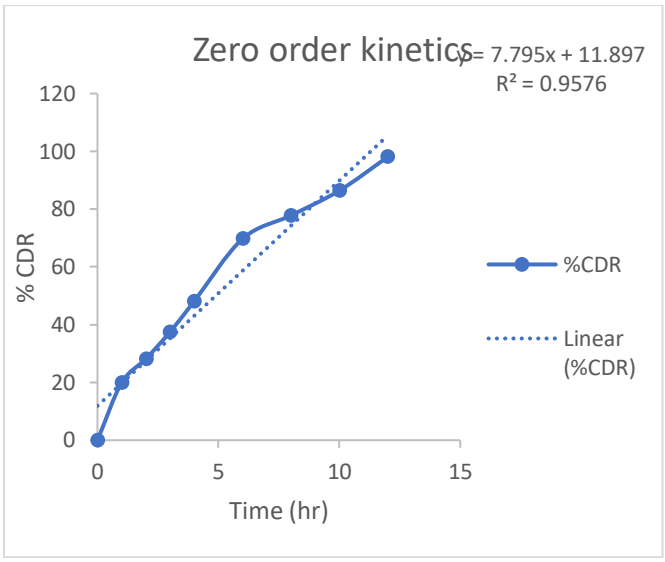


Fig-6: Zero order kinetics of optimized formulation

First order kinetics

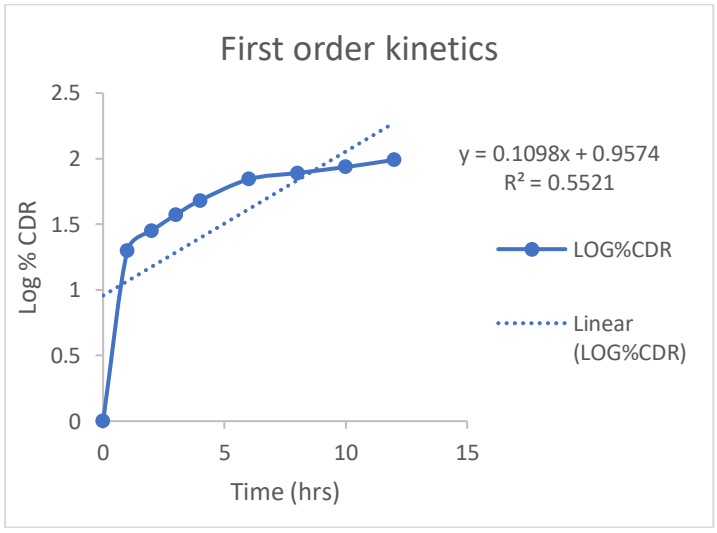


Fig-7: First order kinetics of optimized formulation

Higuchi model

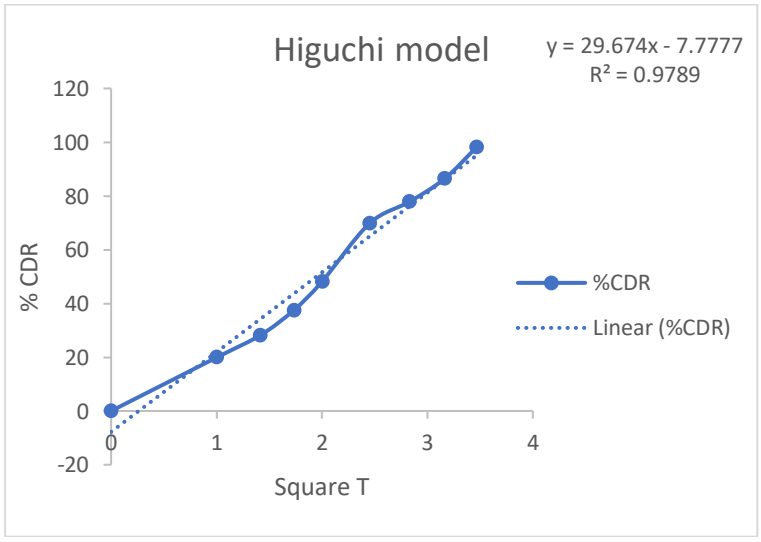


Fig-8: Higuchi model of optimized formulation

Korsmeyer peppas

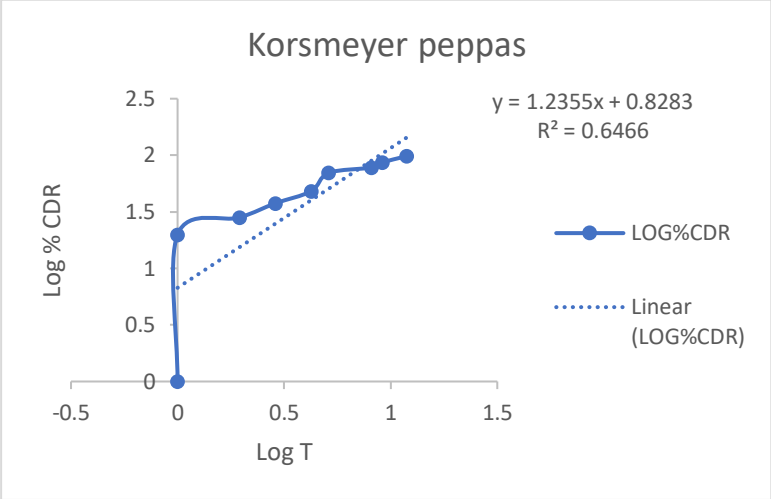


Fig-9: Korsmeyer peppas of optimized formulation

Discussion

Among the evaluated models, the Higuchi model exhibited the highest regression coefficient (R^2 = 0.978), indicating that the release of Cabazitaxel from the PLGA polymeric nanoparticles predominantly followed a diffusion-controlled mechanism. The close fit to the Higuchi model suggests that drug molecules diffused gradually through the hydrated polymeric matrix during dissolution.

Stability studies

Table-12: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Table-4: Stability studies of all formulations

F.no	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	25^{0}C/60%RH % Release	98.05	97.83	96.37	95.36	Not less than 85 %
F-5	30^{0}C/75% RH % Release	98.05	97.52	96.28	95.22	Not less than 85 %
F-5	40^{0}C/75% RH % Release	98.05	97.32	96.20	95.73	Not less than 85 %

Discussion

The stability of the optimized formulation (F5) was evaluated under 25 ± 2°C/60 ± 5% RH, 30 ± 2°C/75 ± 5% RH, and 40 ± 2°C/75 ± 5% RH for a period of three months in accordance with ICH guidelines. The cumulative drug release showed only minimal changes during storage. At 25°C/60% RH, the drug release decreased slightly from 98.05% initially to 95.36% after three months. Similarly, at 30°C/75% RH, drug release decreased from 98.05% to 95.22%, while at 40°C/75% RH, the release remained 95.73% after three months. In all storage conditions, the drug release remained well above the specified acceptance limit of not less than 85%. The slight reduction in drug release observed during storage may be attributed to minor changes in the polymer matrix caused by moisture uptake or gradual polymer aging. However, these changes were not significant and did not adversely affect the overall performance of the formulation. No visible changes in physical appearance, aggregation, or instability were observed during the storage period. The stability results confirm that the optimized formulation (F5) maintained its physicochemical properties and controlled drug release characteristics throughout the three-month study, demonstrating excellent formulation stability under both long-term and accelerated storage conditions.

CONCLUSION:

The present investigation successfully demonstrated the development of Cabazitaxel-loaded PLGA polymeric nanoparticles by the nanoprecipitation method. The formulation variables significantly influenced the physicochemical characteristics of the nanoparticles, including particle size, drug entrapment efficiency, and drug release behavior. Among the eight formulations prepared, F5 was identified as the optimized formulation because it exhibited the

smallest particle size (226 nm), highest drug entrapment efficiency (89.23%), excellent cumulative drug release (98.05%), and satisfactory zeta potential, indicating good stability. The optimized formulation exhibited a controlled and sustained release profile, with drug release predominantly governed by the Higuchi diffusion mechanism, demonstrating the effectiveness of the PLGA polymer matrix in regulating Cabazitaxel release. The stability studies further confirmed that the formulation remained stable under both long-term and accelerated storage conditions without significant changes in its release profile. Overall, the findings indicate that PLGA polymeric nanoparticles are an effective carrier system for Cabazitaxel, capable of enhancing drug encapsulation, providing sustained drug release, improving formulation stability, and offering potential advantages for targeted anticancer drug delivery. The developed nanoparticle system may contribute to improved therapeutic efficacy, reduced dosing frequency, and minimized systemic toxicity.

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