Formulation and Characterization of Docetaxel-Loaded Polymeric Nanoparticles

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Abstract:

The aim of the present study is to prepare and characterize nanoparticles containing Docetaxel using polymer. The Docetaxel loaded nanoparticles were prepared by Solvent evaporation method. Nanoparticles were prepared and characterize for process yield, Drug entrapment efficiency, particle size, in vitro drug release, kinetic studies and stability studies. The prepared nanoparticles were spherical in shape. The infrared spectra and scanning electron microscopy showed stable character of Docetaxel in the drug-loaded nanoparticles and revealed the absence of drug polymer interactions. The formulation F2 registered has best formulation. The in vitro release behavior from all the drug loaded batches were found to follow first order and provided sustained release over a period of 8 h. No appreciable difference was observed in the extent of degradation of product during 90 days in which Nanoparticles were stored at various temperatures. The best-fit release kinetics was achieved with First order followed by Higuchi plot. The release of Docetaxel was influenced by the drug to polymer ratio and particle size and was found to be diffusion controlled.

Keywords: *Nanoparticle, Polymer, Docetaxel and solvent evaporation method, In-Vitro drug Release*

Introduction:

Over the past three decades, research into particle size reduction has advanced from basic exploration to a sophisticated, commercially viable strategy for drug delivery. Among these, nanonization technologies have gained prominence due to the increasing number of pharmaceutical compounds that display low aqueous solubility. Both industrial and academic groups have contributed to the development of various nanoparticle fabrication methods. Typically, these particles consist of pure active pharmaceutical ingredients (APIs) and are stabilized by surfactants or polymeric agents to enhance performance and prevent aggregation. (1)

The Concept of "Nano"

The prefix “nano,” derived from the Latin *nanus* (dwarf) and the Greek root for “small,” refers to a scale of 10^{-9} within the SI system (2). The rapid adoption of this term across fields ranging from nanoscience and nanotechnology to nanochemistry, which illustrates the growing importance of nanoscale phenomena. At the nanoscale, atoms and molecules often behave differently than at the macroscopic level, unlocking unique physical, chemical, and biological properties. This “science of the tiny” has been integrated into a variety of product domains, especially in medicine, where traditional technologies often fall short. (3)

Nanotechnology should not be viewed as a single isolated process but as a multidisciplinary science embedded across surfaces, materials, and structures. In pharmaceuticals, nanoparticles are defined as solid, submicron drug carriers, often smaller than 100 nm, which may or may not be biodegradable. (4)

Advantages of Nanoparticles in Drug Delivery:

Nanoparticle-based drug delivery systems offer several benefits:

1. The release and degradation of drugs can be finely controlled by selecting appropriate matrix materials.
2. Drugs can be incorporated without chemical modifications, preserving their activity.
3. Site-specific targeting is achievable by attaching ligands to the nanoparticle surface or by external magnetic guidance.
4. Small-sized nanoparticles can penetrate capillaries, ensuring efficient accumulation at targeted sites.
5. They can be administered through multiple routes such as oral, nasal, parenteral, and intraocular delivery. (5,6)

Limitations of Nanoparticles:

Despite their advantages, nanoparticles present certain drawbacks. Their altered physical properties can lead to aggregation, complicating handling and stability. Their high surface area

makes them highly reactive in cellular environments, which can limit drug loading and sometimes cause burst release. (7,8)

Types of Nanoparticles:

Nanoparticles can be categorized by size, morphology, physical, and chemical properties. Common types include:

Carbon-Based Nanoparticles:

These include carbon nanotubes (CNTs) and fullerenes. CNTs are rolled sheets of graphene with extraordinary mechanical strength, 100 times stronger than steel and unique electrical and thermal properties. They exist as single-walled (SWCNTs) or multi-walled (MWCNTs). Fullerenes e.g., C-60 Buckminsterfullerene, which have a cage-like structure and are applied in fields requiring strength, conductivity, and electron sensitivity. (9-11)

Ceramic Nanoparticles:

Composed of inorganic materials such as oxides, carbides, or phosphates, ceramic nanoparticles are chemically inert, heat-resistant, and widely used in catalysis, imaging, and drug delivery. Their properties, including porosity and surface area, can be tailored for controlled therapeutic release.

Metal Nanoparticles:

Synthesized via chemical, electrochemical, or photochemical methods, metal nanoparticles (e.g., gold, silver) have high surface energy and the ability to adsorb biomolecules. They are used in biosensing, imaging, and environmental monitoring. For example, gold nanoparticles are routinely used to enhance scanning electron microscopy (SEM) imaging.

Polymeric Nanoparticles:

Polymeric nanoparticles can exist as nanospheres (uniformly distributed matrix) or nanocapsules (core–shell structure). They offer controlled release, drug protection, and biocompatibility, making them highly suitable for therapeutic and diagnostic purposes.

Lipid-Based Nanoparticles:

These spherical structures (10–100 nm) consist of a lipid core surrounded by surfactants or emulsifiers. They can encapsulate lipophilic drugs and are commonly used in oncology and RNA delivery.

Techniques for Nanoparticle Preparation:

Nanoparticle preparation involves entrapping drugs within a matrix or adsorbing them onto particle surfaces. Techniques include:

Amphiphilic Macromolecule Cross-Linking:

Proteins and polysaccharides with dual affinity for aqueous and lipid phases are aggregated and stabilized by heat or chemical cross-linking. (12-14)

Polymerization Methods:

These involve polymerizing monomers within emulsions or dispersions. Variants include emulsion polymerization, dispersion polymerization, and interfacial condensation, where polymers form at phase boundaries.

Polymer Precipitation Methods:

1. **Solvent Extraction/Evaporation**: The drug and polymer are dissolved in organic solvent and dispersed in an aqueous phase, followed by solvent removal.
2. **Solvent Displacement/Nanoprecipitation**: A lipophilic polymer solution is mixed with a miscible aqueous phase, leading to rapid precipitation.
3. **Salting Out**: An aqueous solution of stabilizer is mixed with polymer solution in acetone, inducing phase separation and nanoparticle formation. (15-17)

Separation of Unentrapped Drug:

Unencapsulated drugs must be removed to ensure uniform formulation. Techniques include dialysis against buffers, gel filtration using columns e.g., Sephadex-G-50, and centrifugation with repeated washing. (18-20)

Applications of Nanotechnology in Medicine

Nanotechnology has revolutionized diagnostics and therapeutics by operating at the biological scale. Applications include:

- **Cancer Therapy**: Nanoparticles enable targeted drug delivery to tumor cells while sparing healthy tissue.
- **Cardiovascular Treatment**: HDL-mimicking nanoparticles have been developed to reduce arterial plaque buildup.
- **Diagnostics**: Gold nanoparticles are used as probes for detecting nucleic acid sequences and improving imaging modalities.
- **Gene Sequencing**: Solid-state nanopore materials are being engineered for high-speed, low-cost genetic analysis.

- **Regenerative Medicine**: Nanotechnology is applied to bone and neural tissue engineering.
- **Vaccines**: Researchers are exploring nanoparticle-based delivery systems that could eliminate the need for needles.

The field of nanotechnology continues to expand exponentially. Its integration into medicine, materials science, and biotechnology highlights its transformative potential. With growing research into nanomedicine, nanoparticles are expected to play a crucial role in personalized therapy, advanced diagnostics, and regenerative healthcare solutions.

Despite extensive progress in nanotechnology for drug delivery, there remains a critical need for optimized formulations that ensure high entrapment efficiency, controlled release, and long-term stability of anticancer drugs. Docetaxel, though highly effective, suffers from poor solubility and systemic toxicity, limiting its therapeutic potential. The present work addresses this gap by developing and characterizing polymer-based Docetaxel-loaded nanoparticles prepared via the solvent evaporation method. This approach enables sustained and diffusion-controlled release, minimizes degradation, and enhances drug stability, thus providing a promising platform for improving the safety and efficacy of Docetaxel delivery in cancer therapy.

Methodology:

Drug Profile:

Docetaxel (Taxotere, Docecad, Docefrez) is a taxane derivative with the molecular formula C43H53NO14 and molecular weight of 807.890 g·mol−1. It is poorly soluble in water but soluble in organic solvents such as ethanol, acetone, and DMSO. Mechanistically, Docetaxel is a microtubule inhibitor that stabilizes tubulin polymerization, preventing depolymerization and leading to apoptosis of cancer cells.

Pharmacokinetic features include poor oral bioavailability, high protein binding (94–97%), hepatic metabolism via CYP3A4, and elimination predominantly in feces (~75%). The terminal half-life is ~11 hours. Clinically, Docetaxel is used in the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric cancer, head and neck cancers, and ovarian cancer (off-label).

Excipient Profile:

Tragacanth: A natural gum polysaccharide, insoluble in ethanol but swells in water to form mucilage. It is used as a binder, stabilizer, and medicinally in formulations such as denture adhesives and lotions.

Polyvinyl Alcohol (PVA): A synthetic polymer with emulsifying and stabilizing properties, commonly used as a polymeric aid and thickener.

Sodium Alginate: A polysaccharide salt of alginic acid used as a stabilizer, suspending agent, disintegrant, and viscosity enhancer in pharmaceuticals.

Materials:

Materials: Docetaxel, tragacanth, sodium alginate, polyvinyl alcohol, dialysis membranes, and buffer salts.

Preformulation Studies: (21-23)

Preformulation studies were performed to evaluate Docetaxel stability and compatibility with excipients.

- **Melting Point**: Determined using the capillary method.
- **Solubility**: Studied in DMSO, dimethylformamide, and phosphate buffer pH 7.4.
- **Compatibility**: Assessed using IR spectroscopy to evaluate drug–polymer interactions.

Preparation of Calibration Curve:

Docetaxel was analyzed using a UV–visible spectrophotometer at 230 nm in phosphate buffer (pH 7.4). A stock solution (1 mg/ml) was prepared, and dilutions ranging 10–50 µg/ml were used to construct the calibration curve.

Preparation of Phosphate Buffer (pH 7.4):

The buffer was prepared by dissolving 2.48 g disodium hydrogen phosphate, 0.19 g potassium dihydrogen phosphate, and 8 g sodium hydroxide in 1000 ml distilled water.

Preparation of Docetaxel-Loaded Nanoparticles: (24,25)

Nanoparticles were prepared by the solvent evaporation method. Appropriate amounts of tragacanth or sodium alginate were dissolved in methanol (2 ml) and dichloromethane (8 ml), followed by addition of 5 mg Docetaxel. The mixture was stirred at room temperature for 30–45 minutes with intermittent vortexing for complete solubilization.

This organic phase was poured into 5 ml of aqueous PVA solution and homogenized for 3 minutes to form an oil-in-water emulsion. The emulsion was added dropwise into 125 ml aqueous PVA and stirred for 6 hours at room temperature to evaporate the solvents, yielding a nanoparticulate suspension. The suspension was filtered, centrifuged (1000 rpm, 10 min), and ultracentrifuged (3200 rpm, 1 h). The pellet was washed twice with deionized water and resuspended to prevent aggregation.

Formulation composition: Eight batches (F1–F8) were prepared with constant Docetaxel (5 mg), variable tragacanth (50–200 mg) or sodium alginate (50–200 mg), methanol (2 ml), dichloromethane (8 ml), and PVA (125 ml).

Table 1: Composition of the Nanoparticles

Ingredients	Batch no							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Docetaxel(mg)	5	5	5	5	5	5	5	5
Tragacanth (mg)	50	100	150	200	-	-	-	-
Sodium alginate(mg)	-	-	-	-	50	100	150	200
Methanol (ml)	2	2	2	2	2	2	2	2
Dichloromethane	8	8	8	8	8	8	8	8
Polyvinyl Alcohol(ml)	125	125	125	125	125	125	125	125
Water	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s

Evaluation of Nanoparticles: (26-28)

- **Particle Size**: Evaluated microscopically by measuring nanoparticle dimensions at multiple fields.
- **SEM Analysis**: Nanoparticles were lyophilized, gold-coated, and examined by scanning electron microscopy (SEM; Philips XL30, The Netherlands).
- **Encapsulation Efficiency**: 50 mg of lyophilized nanoparticles were dissolved in phosphate buffer and analyzed by UV spectrophotometry.
- $$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount entrapped}}{\text{Total drug-loaded}} \times 100$$
- ***In-Vitro*** **Drug Release**: Conducted using a Franz diffusion cell with dialysis membrane in phosphate buffer (pH 7.4) at 37 ± 0.5 °C and 200 rpm. Samples were withdrawn at intervals (1–8 h), replaced with fresh buffer, and analyzed spectrophotometrically.

The percentage of drug release was determined using the following formula.

$$\text{Percentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Drug Release Kinetics: (29)

Drug release profiles were fitted to mathematical models to determine kinetics:

- Zero-order
  The equation for zero-order release is

$$Q_t = Q_o + K_o t$$

- First-order
  The first order release equation is

$$\text{Log } Q_t = \text{Log } Q_o + K_t / 2.303$$

- Higuchi model
  The Higuchi release equation is

$$Q_t = K_H \sqrt{t}$$

- Korsmeyer–Peppas model
  Korsmeyer –Peppas equation is

$$F = M_t / M = K_m t^n$$

The best-fit model was selected based on the correlation coefficient (R).

Stability Studies:

The optimized formulation was subjected to stability testing as per ICH guidelines under the following conditions:

- 25 °C / 60% RH for 3 months (monthly analysis)
- 30 °C / 75% RH for 3 months (monthly analysis)
- 40 °C / 75% RH for 3 months (monthly analysis)

Results And Discussion:

In the present study, 8 formulations with variable polymer concentration were prepared and evaluated for physicochemical parameters, studies of *in vitro* release, and studies of stability.

Preformulation studies:

Organoleptic evaluation:

Table 2: Organoleptic properties of Docetaxel

Properties	Results
Description	Crystalline powder

Taste	Tasteless
Odour	Odorless
Color	White

Melting Point:

The melting point of Docetaxel was found to be 232ºC meeting the standard melting point range of 230-235ºC indicating the purity of the drug.

Solubility:

Docetaxel has limited solubility in water, with a maximum solubility in plain water. It is more soluble in organic solvents such as DMSO and ethanol.

Preparation of standard curve of Docetaxel:

The regular Docetaxel curve was calculated by plotting a concentration of absorbance V / s at nm. Use of a solution prepared at 230 nm in pH 7.4. And it follows the Beer laws. The value R 2 is 0.999

Table 3: Calibration curve of Docetaxel in 7.4 phosphate buffer

S. No	Concentration (µg/ml)	Absorbance
0	0	0
1	10	0.124
2	20	0.234
3	30	0.334
4	40	0.467
5	50	0.565

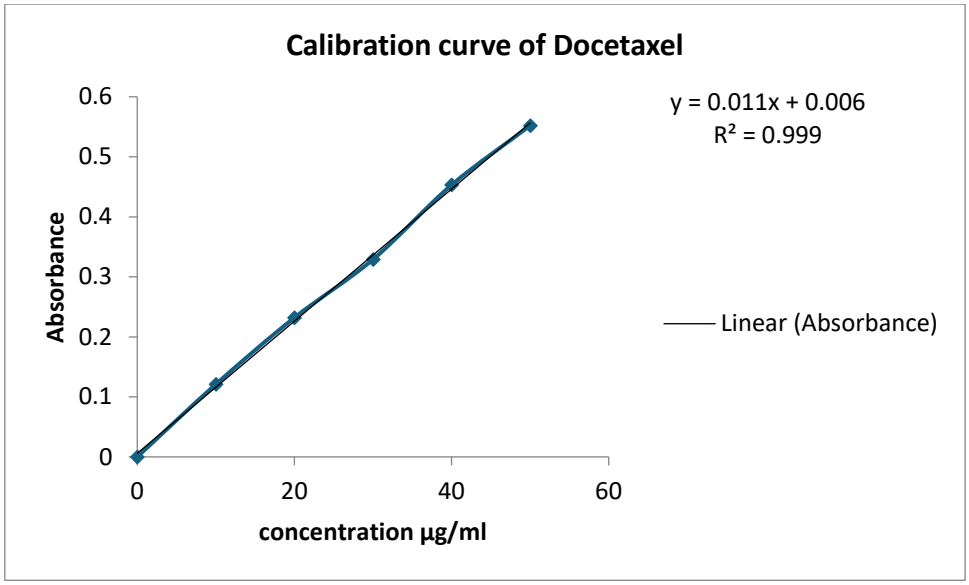

Figure 1: Calibration curve of Docetaxel

Drug - excipient compatibility studies (FT-IR):

Using the FTIR peak matching method, compatibility among the drug and the selected lipid and other excipients was assessed. The drug-lipid mixture did not display or disappear peaks, which indicated the nonappearance of slightly chemical interaction between medication, lipid, and other chemicals.

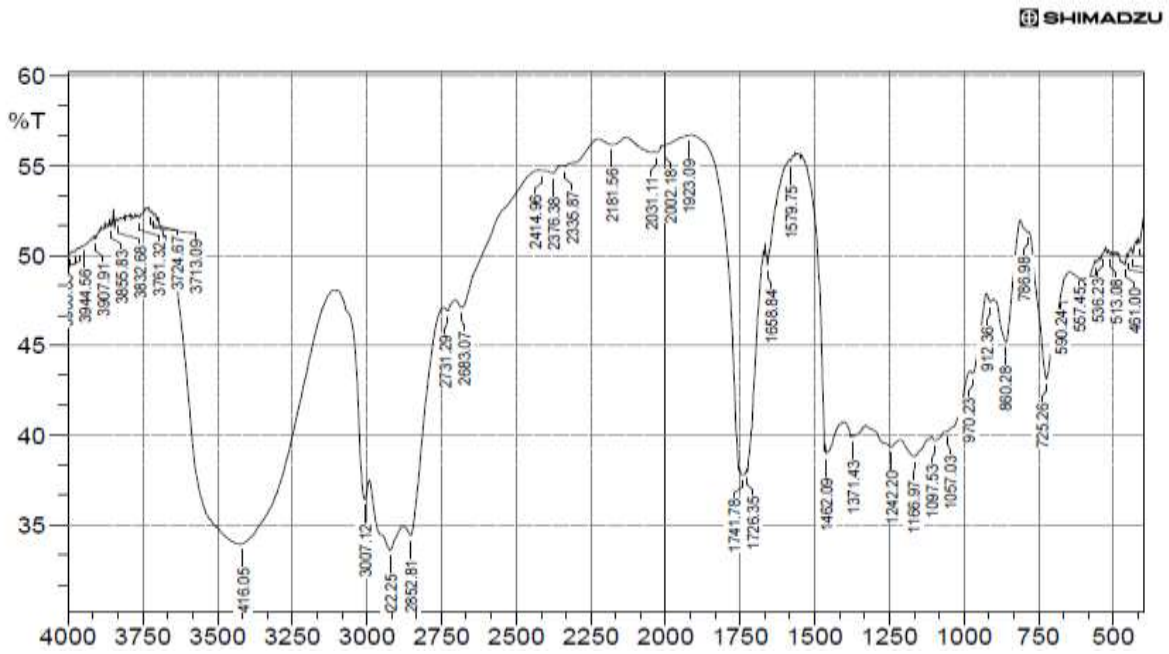

Figure 2: FTIR Studies of Docetaxel

Table 4: Characteristic Peaks for Docetaxel

S. No	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH Bending	4000-3500	3907.91
2	C-H stretching	2500-2000	2414.96
3	C=O stretching	1500-1000	1371.43

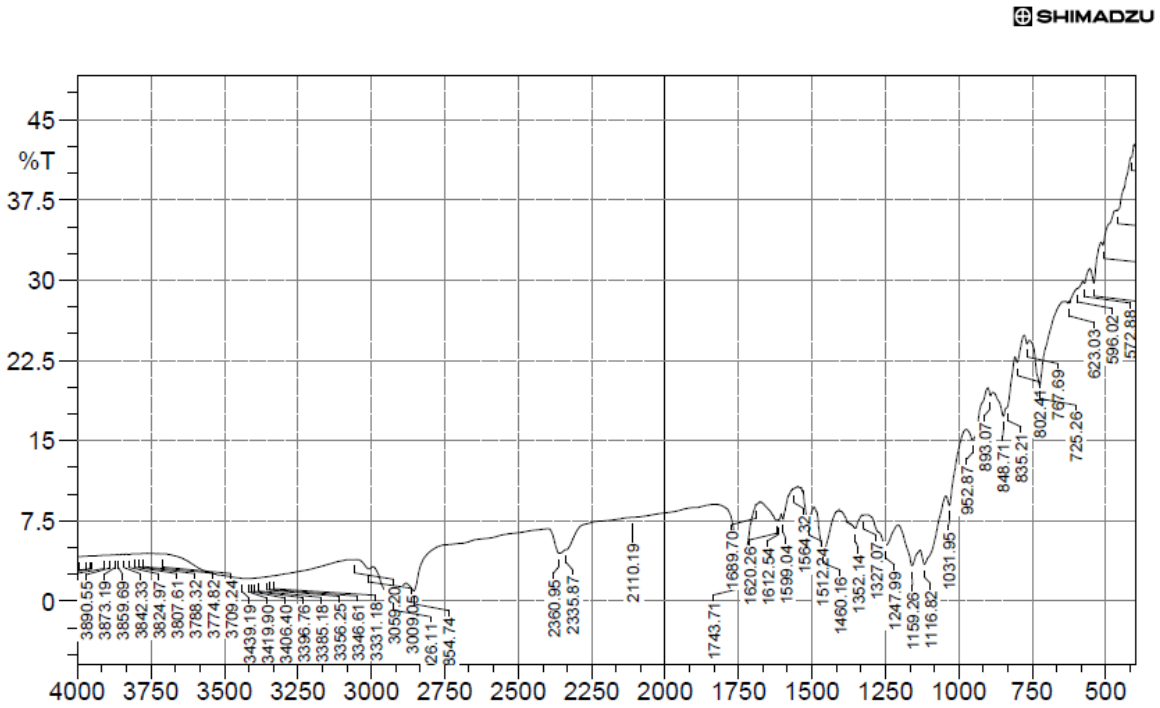

Figure 3: FTIR Studies of optimized formulation

Table 5: Characteristic Peaks for optimized formulation

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3842.33
2	OH Bending	2500-2000	2360.95
3	C=O stretching	1500-1000	1352.14

Evaluation Parameters:

The nanoparticles organized were estimated as per the following parameters-

- Entrapment efficiency

- Particle size and SEM analysis
- In vitro release study
- Drug release kinetics
- Stability studies

Table 6: Estimation Studies of Prepared Nanoparticles: Entrapment Efficiency, Particle size

Batch No	Particle size (nm)	Entrapment Efficiency (%)
F1	186	74.6
F2	173	80.25
F3	176	69.6
F4	192	75.1
F5	116	64.9
F6	132	71.6
F7	168	73.6
F8	122	70.8

Surface morphology:

Scanning electron microscopy (SEM) SEM revealed that the Docetaxel nanoparticles further confirmed spherical morphology and smooth surfaces, which are desirable characteristics for sustained and controlled drug release.

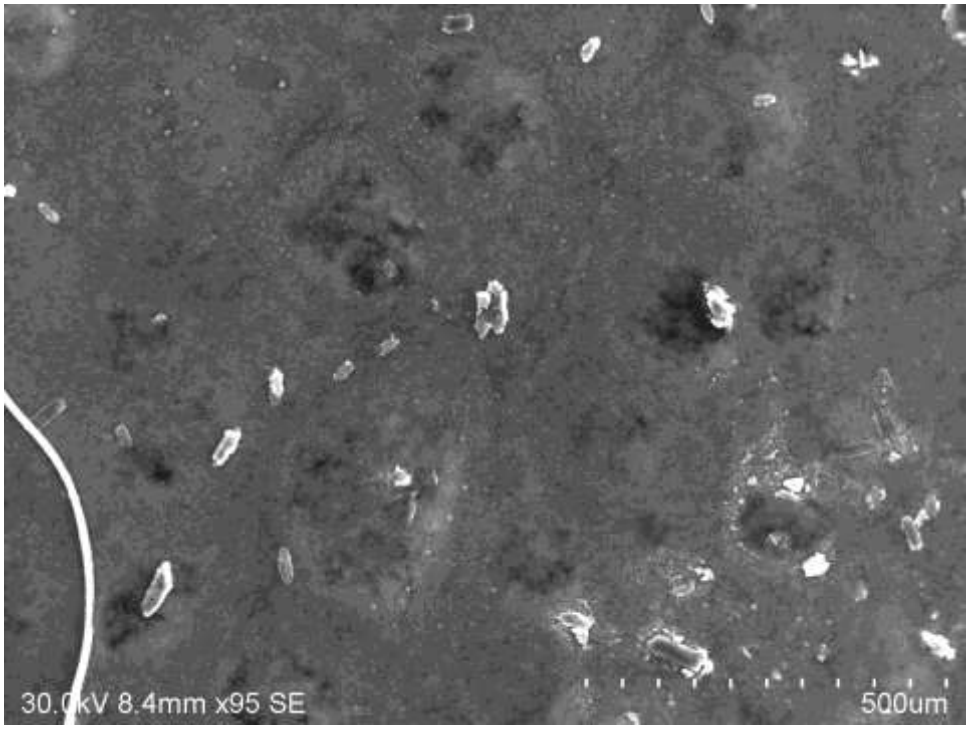

Figure 4: SEM analysis of Optimized Nanoparticles

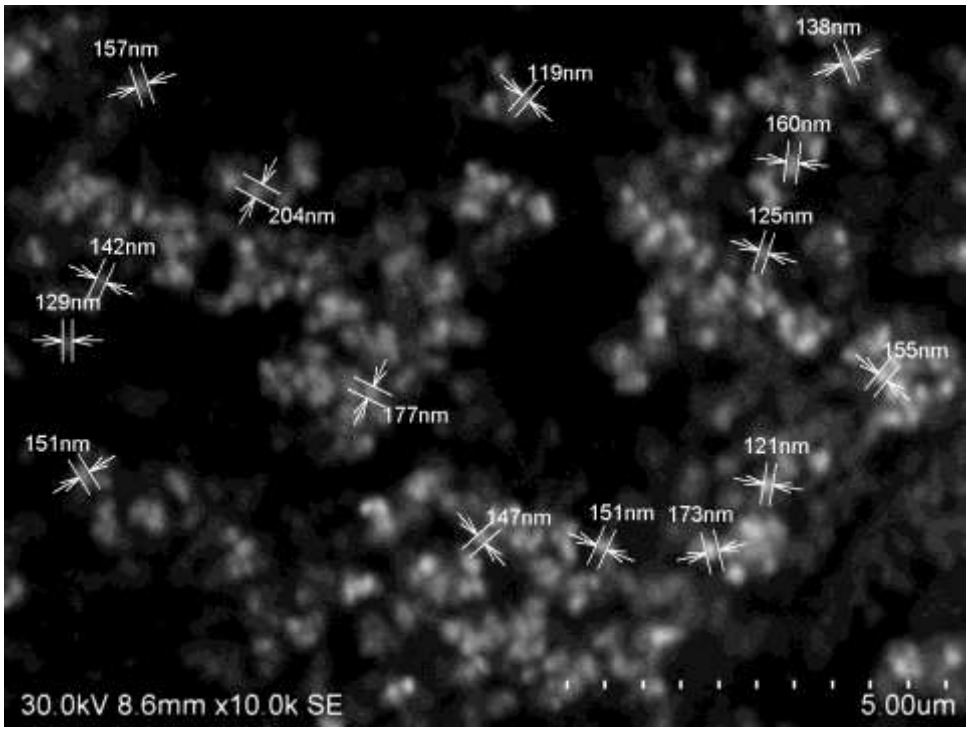

Figure 5: SEM analysis of Optimized Nanoparticles

Drug release studies:

Table 7: Diffusion study profiles for all formulations

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	23.62	22.10	21.50	22.10	29.43	28.82	24.29	29.94
2	30.25	32.59	35.89	38.90	35.69	37.18	38.10	35.58
3	49.28	42.69	47.30	42.69	41.78	39.61	40.76	45.21
4	52.35	50.25	52.36	53.65	50.7	49.20	52.32	51.87
5	62.62	61.19	61.50	61.19	59.2	55.81	66.49	61.71
6	78.56	72.91	75.47	82.91	65.3	71.76	78.77	70.86
7	82.68	82.9	89.71	82.9	83.35	83.63	85.84	88.82
8	94.82	97.26	91.80	93.64	90.3	94.32	92.24	90.12

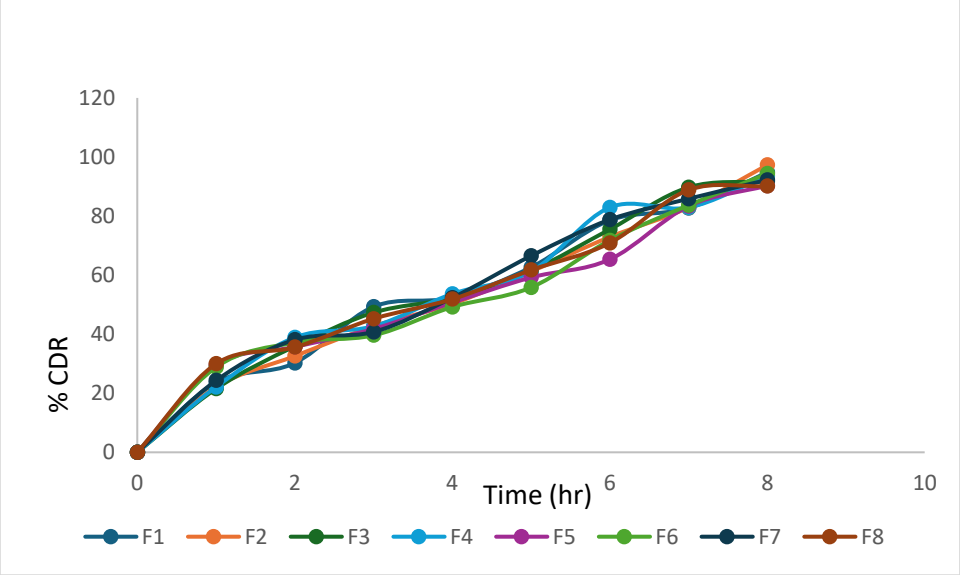

Figure 6: *In vitro* drug release studies for all formulations

In pH 7.4 buffer the in vitro diffusion experiments were performed using the dialysis membrane for 8 hours. Initially, drug release from all lots was found to be around 25-35 percent in 8 hours. It was due to the release of adsorbed nanoparticles from the soil. A continuous and slow release of drugs was observed later during 8hrs. The optimized formulation of F2 formulations which had drug-polymer tragacanth was decided.

Kinetic modeling of drug release:

All 8 formulations of Docetaxel nanoparticles prepared underwent in vitro release studies using the dissolution apparatus.

The results obtained studies on in vitro release were plotted as follows in different data treatment models:

1. Cumulative percentage of product released over time (zero command rate kinetics)
2. Log cumulative percentage of retained drug vs. time (First order Kinetics rate)
3. Cumulative percentage of drug released versus square time root (Higuchi's Classical Equation of Diffusion)
4. Cumulative percent log release Vs log time (Exponential Equation of Peppa's)

In Zero-order, first-order, and Higuchi equations the dissolution data of the above two methods is fitted. Higuchi equation was used to determine the mechanism of drug release.

Table 8: Drug Release Kinetics of Formulation F2

Time	%CDR	Log % CDR	Log T	Square T	ARA	Log % ARA
0	0	0	0	0	0	0
1	22.10	1.506505	0	1	77.9	1.8318698
2	32.59	1.5965971	0.30103	1.414214	67.41	1.7817554
3	42.69	1.7217282	0.477121	1.732051	57.31	1.6749529
4	50.25	1.7866805	0.60206	2	49.75	1.5889436
5	61.19	1.8536982	0.69897	2.236068	38.81	1.456366
6	72.91	1.9186069	0.778151	2.44949	27.09	1.2327421
7	82.9	1.9680157	0.845098	2.645751	17.1	0.8512583
8	97.26	1.9879343	0.90309	2.828427	2.74	0.4377506

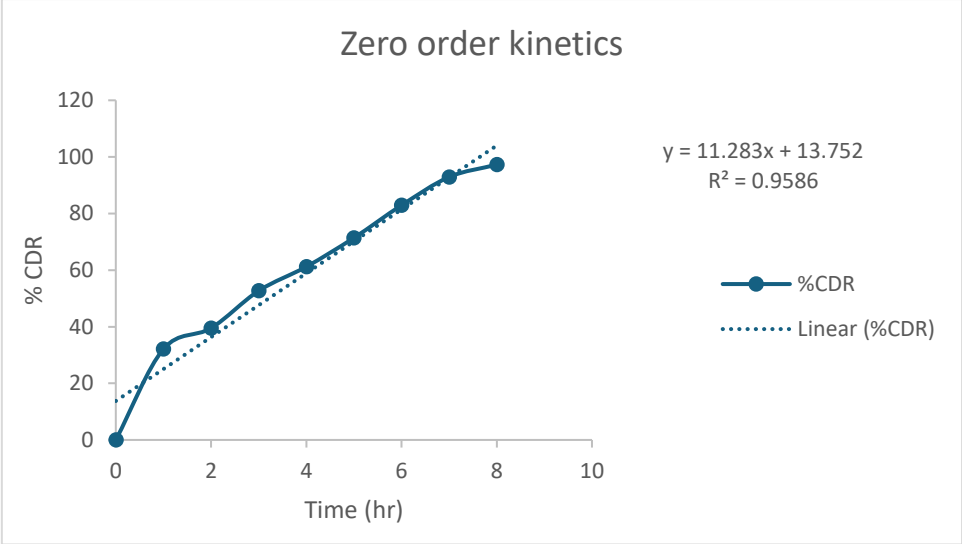

Figure 7: Zero-Order plot for optimized formula

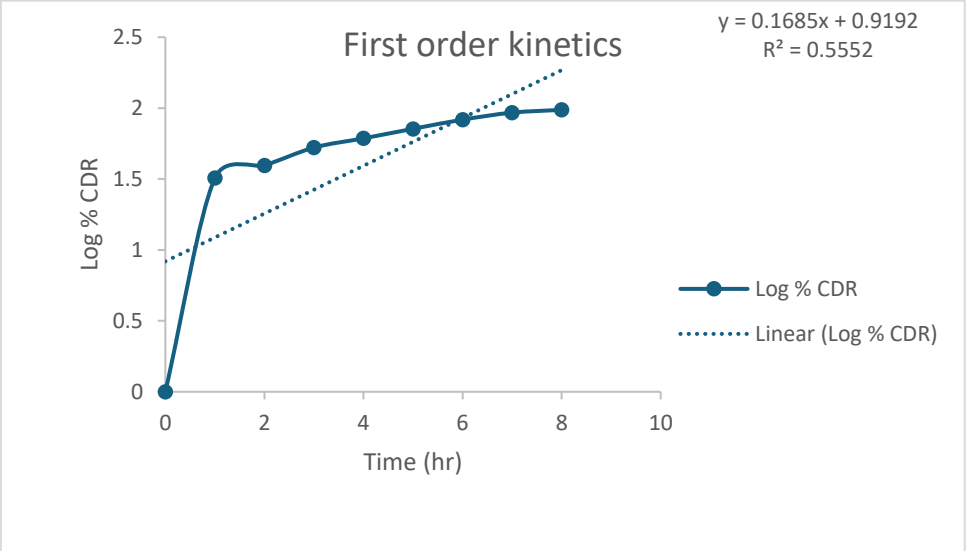

Figure 8: First order for the optimized formula

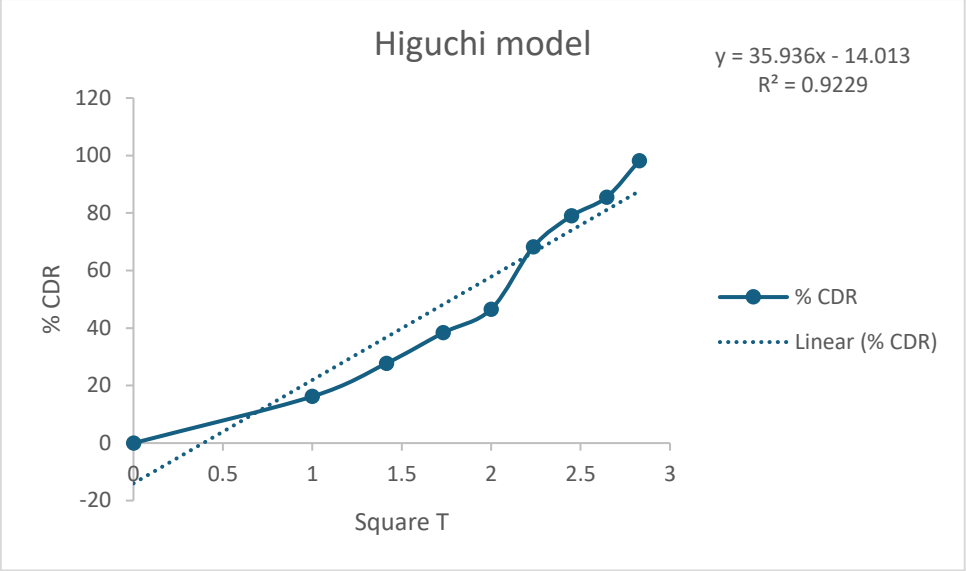

Figure 9: Higuchi plot for optimized formula

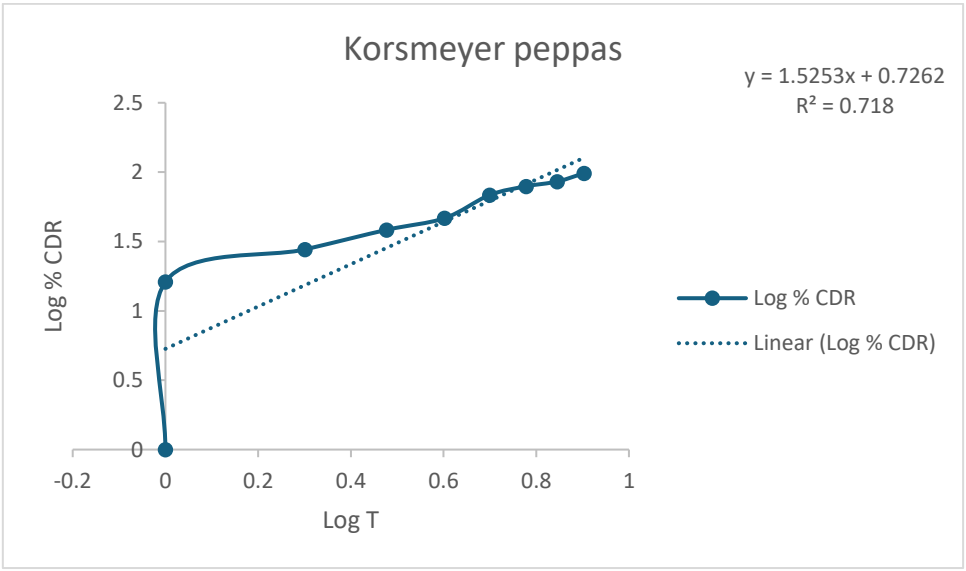

Figure 10: Korsmayer Peppas plot for optimized formula

The drug release from the nanoparticles was found to follow the release of Zero-order based on the "r" value obtained for the formulation of Zero order (0.958) and first-order (0.555). Besides, the mechanism for drug release was found to be "Diffusion" based on the "r" value of 0.984 obtained for Higuchi's plot. Similarly, the mechanism for drug release was found to have an Anomalous diffusion mechanism based on the "n" value of 0.569 obtained for Peppa's equation.

Stability Studies:

After 3 months, there was no significant change in the physical and chemical properties of the Formulation of F-2 nanoparticles. Parameters quantified were seen at various time intervals.

Table 9: Results of stability studies of optimized formulation F-2

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-2	**25^0C/60%RH % Release**	97.26	96.54	95.49	94.39	**Not less than 85 %**
F-2	**30^0C/75% RH % Release**	97.26	96.52	95.48	94.37	**Not less than 85 %**
F-2	**40^0C/75% RH % Release**	97.26	96.53	95.46	94.35	**Not less than 85 %**

Discussion:

In this study, eight formulations (F1–F8) of Docetaxel-loaded nanoparticles were successfully prepared using different concentrations of natural (tragacanth) and synthetic (sodium alginate) polymers. Preformulation analysis confirmed the drug's purity with a melting point of 232°C and solubility consistent with reported characteristics, while FTIR studies indicated no significant chemical interaction between Docetaxel and excipients, ensuring compatibility.

Entrapment efficiency ranged between 64.9% and 80.25%, with F2 showing the highest entrapment (80.25%) and a particle size of 173 nm. This suggests that polymer concentration plays a crucial role in enhancing drug encapsulation, where an optimal ratio provides improved stabilization of drug molecules within the polymeric matrix. The particle size range (116–192 nm) across formulations falls within an ideal nanoscale range, favouring cellular uptake and improved therapeutic potential. SEM analysis further confirmed spherical morphology and smooth surfaces, which are desirable characteristics for sustained and controlled drug release. *In vitro* drug release studies over eight hours revealed sustained release behaviour across all formulations. While initial release within the first two hours accounted for 25–35%, the subsequent release was gradual and continuous, reducing the risk of burst effect. Among all, F2 exhibited superior release kinetics with 97.26% cumulative release at 8 hours, aligning with zero-order release ($r = 0.958$). Additionally, Higuchi's model ($r = 0.984$) indicated that diffusion was the dominant mechanism, while the Peppas model suggested an anomalous transport mechanism. Such controlled release behavior highlights the potential of the formulation in minimizing dosing frequency and enhancing therapeutic efficacy of Docetaxel.

Stability studies conducted under ICH guidelines demonstrated that F2 retained its physical and chemical integrity over three months at varying temperature and humidity conditions, with drug release consistently above 94%, well within acceptable limits. This confirms the robustness of the optimized formulation and its potential for long-term storage without loss of functionality.

Overall, the results emphasize the successful development of a stable, controlled-release nanoparticle system for Docetaxel delivery. The optimized F2 formulation, in particular, demonstrates significant promise as an advanced platform for improving drug solubility, bioavailability, and patient compliance.

Conclusion:

The present study successfully developed Docetaxel-loaded nanoparticles using polymeric carriers through the solvent evaporation method. Preformulation studies validated the stability and compatibility of the drug with the chosen excipients. Among the eight formulations tested, F2 emerged as the most optimized formulation, exhibiting superior entrapment efficiency (80.25%), favourable nanoscale particle size (173 nm), and nearly complete sustained release (97.26%) over eight hours. The release followed zero-order kinetics and was primarily diffusion-controlled, ensuring predictable drug delivery. Moreover, stability studies confirmed the long-term robustness of the formulation under different storage conditions, with minimal degradation over three months.

The advancement of this work lies in successfully harnessing natural and synthetic polymers to achieve sustained release of a poorly water-soluble chemotherapeutic agent, thereby addressing limitations of solubility and systemic toxicity associated with conventional Docetaxel delivery. By improving encapsulation and extending drug release, this nanoparticle system can potentially reduce dosing frequency, enhance patient compliance, and increase therapeutic efficiency in cancer treatment.

Looking ahead, the findings of this study open avenues for further exploration. Future work could include in vivo pharmacokinetic and pharmacodynamic evaluations to confirm clinical efficacy, surface modification of nanoparticles with ligands for targeted drug delivery, and scaling up production for translational studies. Such advancements could eventually contribute to the development of personalized nanomedicine platforms, offering safer and more effective cancer therapies.

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