Design, Prepare, and Optimization of Cabazitaxel Polymeric Nanoparticles

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Abstract
The goal of this study was to assess the efficacy of a method based on the formulate of polymeric nanoparticles as an innovative formulation of Cabazitaxel with enhanced therapeutic efficacy. Cabazitaxel has low solubility and permeability, which result in limited and variable bioavailability; its low stability makes it difficult to develop stable aqueous liquid formulations. The Cabazitaxel Polymeric nanoparticles were created using the precipitation method. The numerous formulations with varied drug-polymer were analyzed and improved. Particle size, surface morphology by SEM, drug excipient compatibility by FTIR, and *In-vitro* drug release experiments were used to characterize the produced nanoparticles. The formulation with the best encapsulation efficiency was (F-3). A drug encapsulation effectiveness of up to 83.56 % has been attained in this study. It was discovered that the efficiency of encapsulation improved along with the polymer content. According to the results of the current investigation, the manufacture of Cabazitaxel Polymeric nanoparticles can be done using a precipitation process followed by sonication.

Keywords: Cabazitaxel Drug, Polymers, FTIR, Precipitation Method, Polymeric Nano Particles, *In-vitro* Drug Release

1. Introduction

Nanotechnology is the science of the smallest particles. Nanotechnology is a world in which new products are developed at the atomic and molecular level. It limits renewable energy sources and provides a realistic and cost-effective means of keeping the environment clean [1]. Nanotechnology is a term used to define areas of science and engineering in which phenomena occurring at nanoscale dimensions are used in the design, characterization, manufacture, and applications of materials, structures, devices, and systems [2]. The nano drugs employed have demonstrated that bioavailability is enhanced, side effects are eliminated, and therapeutic medicine is absorbed more effectively. Nanoparticles have recently been used on this membrane as a medication carrier system [3]. Particularly, nanoparticles are inhaled and cross brain membranes. The typical and traditional therapies for vascular thrombosis often have relatively limited advantages due to the short plasma half-life, many adverse effects, and fast drug wash-outs [4]. Polymeric nanoparticles (NPs) have attracted considerable interest over recent years due to their properties resulting from their small size. Advantages of polymeric NPs as drug carriers include their potential use for controlled release, the ability to protect drug and other molecules with biological activity against the environment, improve their bioavailability and therapeutic index [5]. The term “nanoparticle” comprises both nanocapsules and nanospheres, which differ with respect to their morphology. Nanocapsules are composed of an oily core in which the drug is usually dissolved, surrounded by a polymeric shell which controls the release profile of the drug from the core. Nanospheres are based on a continuous polymeric network in which the drug can be retained inside or adsorbed onto their surface. These two types of polymeric NPs recognized as a reservoir system (nanocapsule), and matrix system (nanosphere) [6]. The goal of this study was to assess the efficacy of a method based on the formulate of polymeric nanoparticles as an innovative formulation of Cabazitaxel with enhanced therapeutic efficacy.

Drug excipient compatibility studies [7]

FTIR analysis was performed in order to study the compatibility of ingredients used in the preparation of nanoparticles, using a Shimadzu FTIR spectrophotometer (Prestige21, Shimadzu Corporation, Kyoto, Japan). Cabazitaxel and Excipients their mixture with ratio (1:1) was evaluated using FTIR spectrophotometer using potassium bromide disc technique where 1mg of the sample is mixed with 100 mg of dry powdered KBr; the mixture is pressed into a transparent disc and was inserted in the apparatus for IR scan.

2. Materials and Methods

Cabaxitaxel was collected as a gift sample from Hetero labs, Hyderabad and various excipients and polymers were purchased from AR chemicals, Hyderabad.

2.1 Methodology

Formulation development

Table 1: Composition of the Nanoparticles

Ingredients	F1	F2	F3	F4
Cabazitaxel	20	20	20	20
Ethyl cellulose	100	200	-	-
Eudragit RS 100	-	-	100	200
Ethanol	10	10	10	10
PVA	1%	1%	1%	1%

Nanoprecipitation method

Dissolve the polymers in 10 mL ethanol. Add 20 mg of drug Mix thoroughly until fully dissolved. Prepare 50 mL of 1% PVA solution in distilled water (as stabilizer). Stir to ensure complete dissolution. Under moderate magnetic stirring (400–800 rpm), add the organic phase dropwise into the aqueous phase. A turbid colloidal suspension will form as nanoparticles precipitate. Stir the suspension for 2–4 hours at room temperature to allow full solvent diffusion and evaporation. Continued stirring in a fume hood, or Using a rotary evaporator. Centrifuge the suspension at 15,000 rpm for 30 min. Discard the supernatant and resuspend the pellet in distilled water. Repeat 2–3 times to remove unencapsulated drug and PVA [8].

Evaluation of Cabazitaxel loaded polymeric nanoparticles:

Zeta potential [9]

The zeta potential reflects the surface charge of the particles, which is influenced by changes in the interface with the dispersing medium, due to the dissociation of functional groups on the particle's surface or due to the adsorption of ionic species present in the aqueous dispersion medium as well as the solvation effect. This parameter is determined using Doppler techniques to measure the particle velocity as a function of voltage, thus the zeta potential is calculated from the electrophoretic mobility of particles in a solvent.

SEM analysis [10]

Scanning and transmission electron microscopy (SEM) have been widely used to obtain information regarding the shape and size of polymeric NPs. These are usually combined with cryofracture techniques to perform the NPs morphology analysis.

Particle Size and Zeta Potential [11]

The particle size of the formulation was determined by photo correlation spectroscopy with a zeta master (Malvern Instruments, UK) equipped with the Malvern PCS software. Every sample was diluted with distilled water. The surface charge (Zeta potential) was determined by measuring the electrophoretic mobility of the nanoparticles using a Malvern zeta sizer (Malvern Instruments, UK). Samples were prepared by diluting with distilled water.

Drug entrapment efficiency [12]

For determination of drug entrapment, the amount of drug present in the clear supernatant after centrifugation was determined (w) by UV spectrophotometer at 260 nm. A standard calibration curve of drug was plotted for this purpose. The amount of drug in supernatant was then subtracted from the total amount of drug added during the preparation (W). Effectively, (W-w) will give the amount of drug entrapped in the particles. Then percentage entrapment of a drug was calculated according to Equation 2

$$\% \text{ Drug Entrapment} = (W\text{-}w/W) \times 100$$

***In-Vitro* drug release studies** [13]**:**

In-Vitro dissolution of drug was carried out by the method with Dialysis bag. Dialysis membrane was used for the release study. Dialysis membrane was soaked in distilled water 24 h before the release studies. 2 mg equivalent weight of the Cabazitaxel loaded polymeric nanoparticles was incorporated into the dialysis that is tied at the two ends. 50 ml of phosphate buffer pH 6.8 was added to a beaker and the dialysis membrane was fixed in it, where the solution was stirred using magnetic stirrer at 50 rpm and the temperature was maintained at 37±0.5 °C, at the time intervals of 1, 2, 3, 4, 5, 6, 7, 8 h the sample of 1 ml was taken and same volume was added to the beaker to maintain the sync condition. Concentration of drug release from the Cabazitaxel loaded polymeric nanoparticles was calculated using UV spectrophotometer at 260 nm.

Stability studies [14]**:**

Over the course of 90 days, the stability of Cabazitaxel nanoparticle dispersion in screw-capped glass vials was assessed. Four samples were split into two groups and kept at 4°C and 25°C, respectively. At the end of the 90 days, the amount of drug leaking from nanoparticles and the average particle size of the samples were calculated.

3. Results and Discussion

FT-IR Spectrum of Cabazitaxel

Using the FTIR peak matching approach, the compatibility of the medicine with the chosen polymer and other excipients was assessed. The drug-polymer mixture showed no peaks that appeared or vanished, indicating that there was no chemical interaction between the medication, polymer and other molecules.

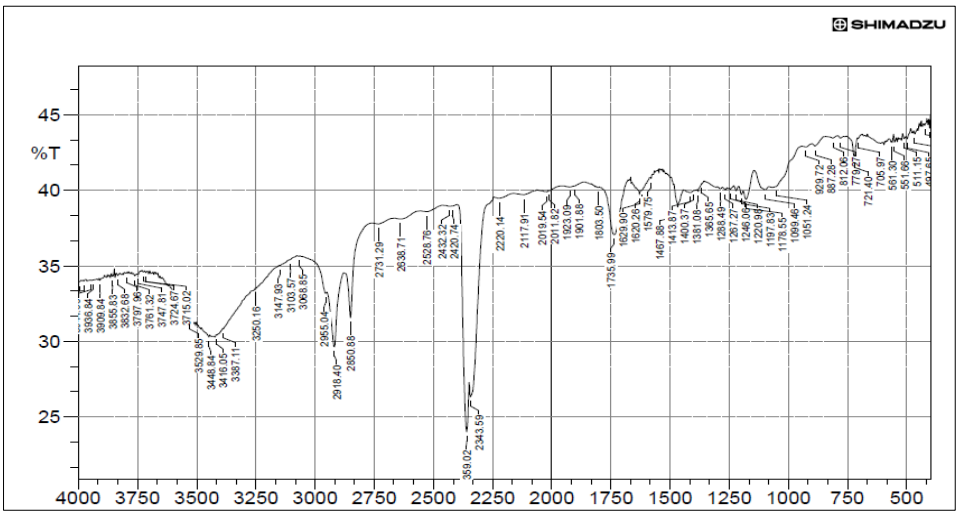

Fig 1: FTIR Spectra of Cabazitaxel

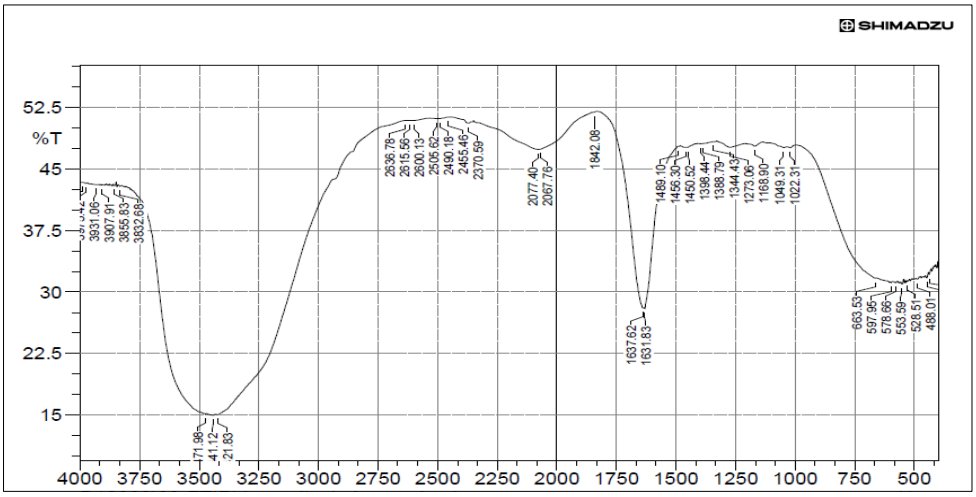

Fig 2: FTIR Spectra of Optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation Parameters

Particle size

With an increase in lipid concentration, the particle size increased. Based on entrapment effectiveness and particle size distribution.

Surface morphology

According to scanning electron microscopy (SEM), the polymeric nanoparticles were round, smooth, and free of any aggregation.

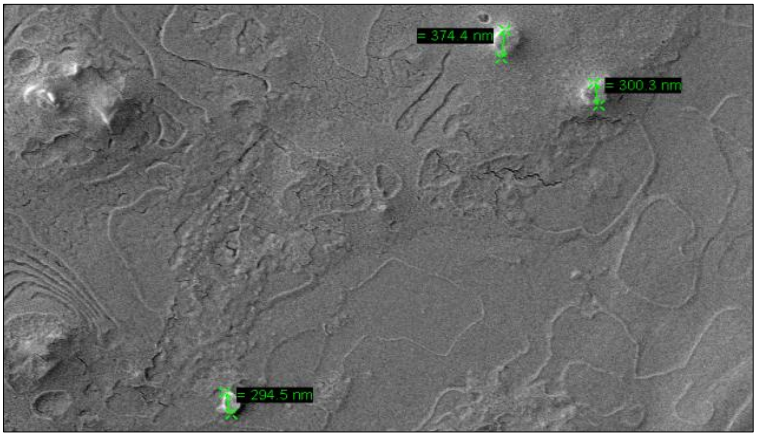

Fig 3: SEM analysis of Optimized polymeric nanoparticle

Determination of Zeta potential:

Zeta potential is a measure of charge present on the vesicle surface. It was determined by using phase analysis light scattering with Malvern zetasizer at field strength of 20V/cm in distilled water and based on electrophoretic mobility of charged particles present in the nanocrystal system. Charged particles were attracted to the electrode with the opposite charge when an electric field is applied.

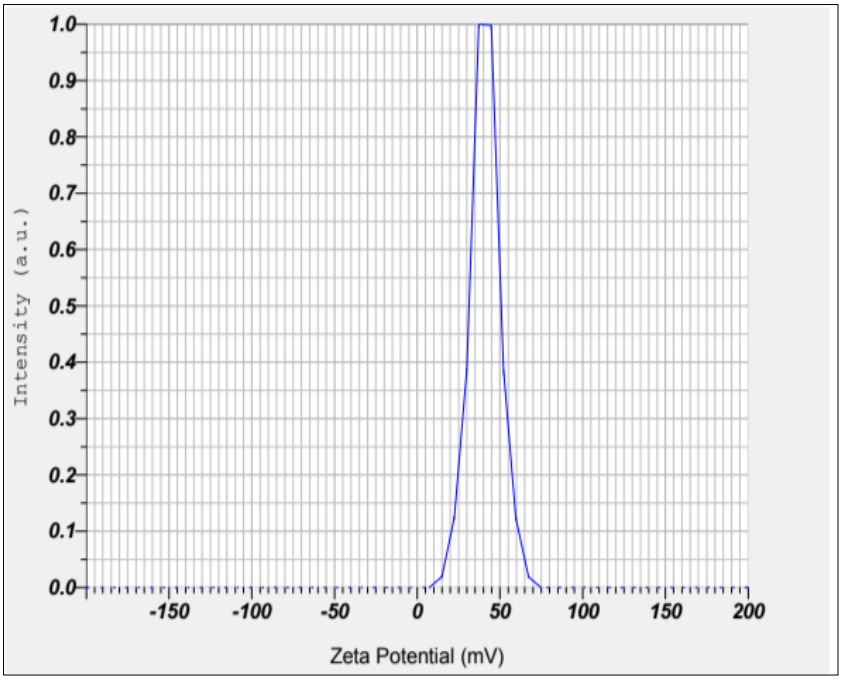

Fig 4: Zeta potential of Polymeric nanoparticles Particle size

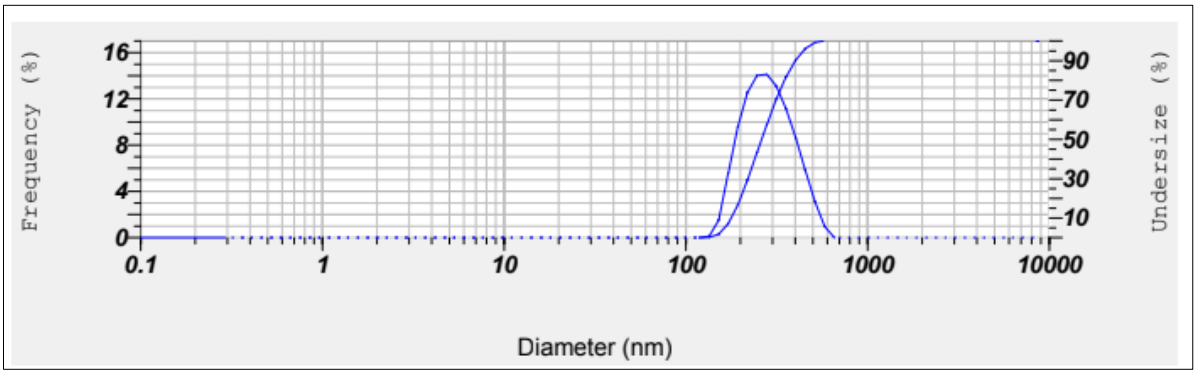

Fig 5: Particle size of Polymeric nanoparticles

The mean particle size of optimized Polymeric nanoparticles was found to be 294 nm

Drug entrapment efficiency:

Optimizing the polymer concentration to be used in the creation of polymeric nanoparticles was the first step of the work plan. Based on the particle size and entrapment effectiveness of the discovered polymeric nanoparticles, the polymer content was optimized.

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

Batch No	Particle size (nm)	Entrapment Efficiency (%)
F1	255	73.50
F2	374	80.12
F3	294	83.56
F4	300	79.62

***In-Vitro* drug release studies**

Using a dialysis membrane and a pH 7.4 buffer, the *In-Vitro* diffusion investigations were carried out for eight hours. This resulted from the drug's release from the surface of the nanoparticles. Later, for 8 hours, a consistent and gradual medication release was seen. The polymer ratio in the F3 formulation was shown to be the most effective one.

Table 3: *In-Vitro* drug release profiles of Cabazitaxel polymeric nanoparticles (F1-F4)

Time	F1	F2	F3	F4
0	0	0	0	0
1	18.10	17.68	18.53	17.24
2	27.84	30.56	32.25	29.32
3	37.96	40.25	42.58	38.56
4	47.59	53.67	55.50	48.51
5	65.81	67.89	68.33	62.34
6	72.32	76.51	77.15	73.59
7	83.52	86.95	87.90	82.50
8	92.30	94.58	96.45	95.63

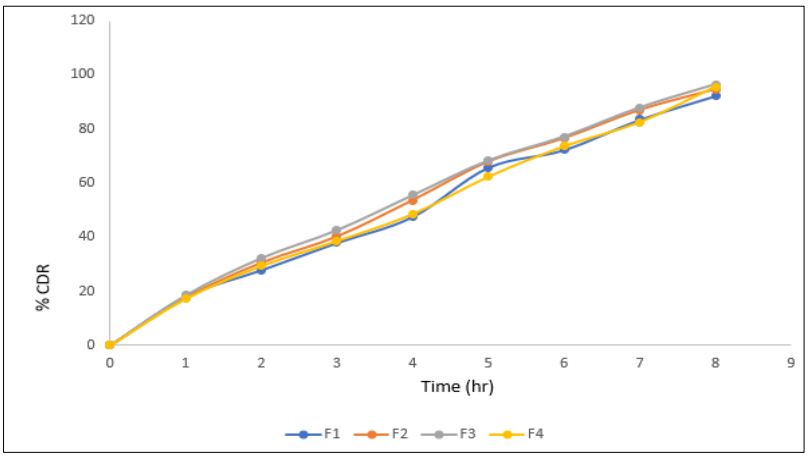

Fig 6: *In-Vitro* drug release profiles of Cabazitaxel polymeric nanoparticles (F1-F4)

Stability studies:

After three months, the physical and chemical characteristics of the nanoparticles of formulation F-3 had not significantly changed. The parameters quantified at various times were displayed.

Table 4: Results of stability studies of optimized formulation F-3

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	25^0C/60%RH	96.45	95.82	94.63	93.02	Not less than
F-3	30^0C/75% RH	96.45	95.27	94.27	93.10	Not less than
F-3	40^0C/75% RH	96.45	95.20	94.35	93.00	Not less than

4. Conclusion

The current study suggested a unique Cabazitaxel polymeric nanoparticle formulation for regulated release. Investigation into the polymeric nanoparticles' production, characterization, and *In-Vitro* release was done. The numerous formulations with varied drug-polymer and surfactant ratios were analyzed and improved. A drug encapsulation effectiveness of up to 83.56 % has been attained in this study. Cabazitaxel polymeric nanoparticles containing polymers were created using the precipitation method, then the particle size was decreased by sonication. Formulations using polymeric nanoparticles performed well in terms of medication content and encapsulation effectiveness. This shows that the formulation procedure was suitable and reproducible in nature, and it provided a good yield. The formulation with the best encapsulation efficiency was (F-3) It was discovered that the percentage of encapsulation efficiency along with the polymer concentration. According to the method described, permeation studies with dialysis membrane were conducted. The In-Vitro drug release profiles of all the formulations indicated an initial burst effect, followed by a gradual drug release. The formulations demonstrated good drug release from the polymer. These polymeric nanoparticles contained more Cabazitaxel and released it more quickly.

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