ISSN : 1001-1781
Journal of Clinical Otorhinolaryngology, Head, and Neck Surgery

NANOPARTICULATE SYSTEM OF NOVEL TAXANE DERIVATIVES AS IN-VITRO EVALUATION AND CHARACTERIZATION

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Abstract— a brand-new taxane derivative called cabaditaxel (CTX) is recommended for the treatment of metastatic prostate cancer that is resistant to docetaxel. CTX, like the majority of chemotherapeutic drugs, has poor physicochemical characteristics such limited water solubility and dissolution. The current commercial version of CTX (marketed by Sanofi-Aventis under the trade name "JEVTANA") comprises hazardous surfactants, polysorbate 80, and the organic solvent ethanol to increase its solubility. Nevertheless, using polysorbate 80 to increase solubility increases the risk of hypersensitivity responses, widespread erythema, hypotension, and bronchospasm, all of which can be fatal. As a result, the QbD technique was used to design CTX's nanoparticulate drug delivery system in order to circumvent the issue associated with

this standard CTX formulation. Prior study included use of QbD technique to build and optimise nanoparticulate system of CTX. Nanoscience and nanotechnology's multidisciplinary features demand a wide variety of characterisation. In fact, a broader characterisation of NPs frequently provides insight into both their in vivo behaviour and their stability throughout use. The current study places a strong emphasis on a "Molecule Centric Approach," in which the formed nanoparticulate system was assessed for drug component quantification, particle size, surface potential, solid state characterization, in vitro drug release study, compatibility study, photostability study, thermal cycling study, reconstitution stability study, and dilution stability study. In terms of in vivo performance and end-user usage, formulation has been described and assessed. Our in-vitro analysis of the nanoparticle formulation gives a hazy indication of its good robustness, market viability, and regulatory viability.

Keywords— In Vitro Evaluation, Characterization, Nanoparticulate System, Novel Taxane Derivative

INTRODUCTION

Droplet sizes of nanoemulsions are on the order of 100 nm. Oil, water, and an emulsifier are the common The most common kind of diabetes, type 2 diabetes mellitus, which accounts for 90–95% of people with the disease, is characterised by insulin resistance. The development of insulin resistance and the dysregulation of glucose and fatty acid metabolism are first brought on by impaired insulin secretion and the production of free radicals. DDA (14-deoxy-11, 12-didehydroandrographolide) is a diterpenoid derived from the annual herb Andrographis paniculata that has been used for generations in Asia to treat upper respiratory tract infections, herpes, and other disorders. Moreover, DDA has been demonstrated to have strong cardiovascular, vasorelaxant, anti-diabetic nephropathy, and antidiabetic properties in vitro (unpublished data). In recent years, interest in using biodegradable polymeric nanoparticles for hydrophobic bioactive principles in drug delivery systems has grown as a result of biomaterial research. These bioactive chemicals did not enter practical applications despite intensive study and development because of their poor solubility.

As a potential substitute for the aforementioned conventional methods, nanoparticles (NPs) have provided a powerfully innovative platform for altering physicochemical and biological properties. Colloidal dispersions or suspensions containing particles less than 100 nm are referred to as NPs. The drug candidate can be linked to a nanoparticulate system, dissolved, trapped, or encapsulated. Enhancing the biopharmaceutical properties of therapeutic molecules with limited water solubility is one of the main goals of creating NPs as a delivery mechanism. The key preferences of utilizing NPs as a drug conveyance framework incorporate a) detached medicate focusing on after parenteral organization can be accomplished when particle measure is less than 100 nm, b) the capacity to modulate the discharge profile of the medicate in support or controlled manner, c) sedate debasement can be avoided by matrix constituents, d) way better sedate tolerability and hence potentially progressed viability due to expanded dosage, and e) the nanoparticulate framework can be utilized for different routes of organizations (such as verbal, nasal, parenteral, and intra-ocular). In spite of previously mentioned advances, it is exceptionally basic and challenging to plan a nanoparticle preparation strategy that's in the long run doable at industrial/large scale. Worldwide administrative bodies such as US Nourishment and Medicate Organization (US FDA) and European Medicines

Office (EMA) are commanding to guarantee the security of inert fixings (excipients) utilized in the product. Subsequently, utilize of pharmaceutically acceptable and secure (non-toxic) excipients are nearly justified in designing nanoparticle sedate conveyance system. Recently, the improvement of sedate conveyance which delivers controlled sedate discharge at the tumor destinations risen as an attractive choice for upgrading anticancer therapeutics. Next-generation Nanotherapeutics must not contain the as it were nanoscale but ought to discover their way to the solid tumor by means of dynamic or detached focusing on. Be that as it may, successful translation of such complex details into the clinic relies on understanding basic physicochemical characteristics. These incorporate evaluation of sedate component, particle size, surface potential, strong state characterization, in vitro drug discharge ponder, compatibility think about, Photostability study and warm cycling think about. They decide the pharmacokinetics of the detailing as well as robustness and appropriateness of the definition for conclusion persistent utilize. Aim of this work is to characterize and assess cabazitaxel nanoparticulate framework. We concentrated primarily on the characterization of some parameters that will be crucial in the in vivo performance and in-use stability of the formulation in this study. Researchers have made numerous attempts to tackle the issue of CTX's poor water solubility. Markus Fusser et al. created cabazitaxel poly (2-ethyl-butyl cyanoacrylate) nanoparticles (PEBCA) to increase solubility and efficacy in a patient-derived breast cancer xenograft. Although promising therapeutic efficacy, the work had significant drawbacks, including a lack of in-use and completed product stability data, as well as a lack of in-vitro characterisation.

METHODS AND MATERIALS

(i) Chemicals- We bought polycaprolactone from Sigma-Aldrich Ltd in Bangalore. In Indore, Madhya Pradesh, India, Apeksha Research Centre Private Limited sold the drug 14-deoxy,11,12-didehydro andrographolide. Tween 20 and polyvinyl alcohol were purchased from HiMedia in Mumbai, India. Except when otherwise noted, all additional chemicals and reagents employed were of analytical grade.

(ii) Materials-Intas Laboratories Ltd. kindly provided cabzitaxel (assay 100.2%w/w) (Ahmedabad, India). We bought soy phosphatidylcholine, C18:2 (SPC) from Lipoid (Ludwigshafen, Germany). We bought sucrose with low endotoxin levels and monobasic citrate anhydrous from Merck Specialities Pvt. Ltd. in Mumbai, India. The usage of all other chemicals and reagents was unpurified and they were all of analytical grade. All studies used purified Milli-Q water from Millipore (Billerica, Massachusetts, USA) that had been degassed and filtered using a 0.45 m hydrophilic PVDF filter (Millipore Millex-HV).

(iii) DDA nanoencapsulation in PCL formulation- By using the solvent evaporation approach, four formulations of nanoparticles containing PCL-DDA conjugate (A1-A4) were created. In a nutshell, 10 ml of dichloromethane were added with known proportions of the DDA (Table 1) and PCL, and the mixture was agitated to ensure that the components were dissolved. An emulsion was created by gradually adding the organic phase to either a double emulsion with 0.5% PVA (A1), 1% Tween 20 solution (A2 and A3), or a solution with 0.5% PVA and 1% Tween 20 (A2 and A3). Using a Bandelin sonopuls sonicator (model UW2070, BANDELIN electronic GmbH & Co. KG, Berlin), this emulsion was divided into nanodroplets, which upon evaporation generated nanoparticles. A colloidal suspension of nano-DDA was left behind after

4 hours of continuous magnetic stirring at 60 rpm under ambient conditions. The precipitate was collected by centrifuging for 15 minutes at 14,000 rpm to recover the nanoparticles. The pellet was air dried and kept at 4 °C for storage.

(iv) Analytical Technique for Quantification of CTX-High performance liquid chromatography (HPLC) was employed as the analytical technique for quantifying CTX in all samples, including assay and in vitro release tests. The approach was taken from the literature and somewhat modified to meet the needs. Shimadzu's LC-2010C HPLC system, which features Chromeleon software and is outfitted with a quaternary pump, auto sampler, and UV detector, was used for the analysis. The estimation was performed using a YMC Pack Pro C18 RS 3 analytical column with ambient temperature (150 mm 4.6 mm; YMC Co. Ltd, Kyoto, Japan). A 30:70 (%v/v) ratio of water and acetonitrile made up the mobile phase, which was carried out in isocratic mode. The UV detector was set at 232 nm with a run time of 8 minutes, the injection volume was 20 L, and the flow rate was maintained at 1.2 mL/min. The results were analysed using the Chromeleon programme. According to International Council for Harmonization (ICH) guideline Q2, the procedure was only partially validated (R1).

Formulation code	DDA: PCL ratio	DDA (mg)	PCL (mg)	Surfactant	Ultrasonication time (min)
A1	1:5	2	10	0.5% PVA	4
A2	1:4	2	8	1% Tween 20	3
A3	1:5	2	10	1% Tween 20	3
A4	1:5	2	10	1% Tween 20, 0.5 % PVA (double emulsion)	3 (twice)

Table 1. Optimization of PCL vs DDA ratio

(v) Analytical Procedure for Degradation Product Analysis- For CTX-related substances (drug degradation), an HPLC-based stability indication approach was created. The Agilent 1100 Series (Agilent Technologies, California, USA) HPLC system had a UV detector, an auto sampler, and a gradient pump. Analytical column, YMC Pack Pro C18 RS 5, (250 mm 4.6 mm), YMC Co. Ltd., Kyoto, Japan, operated at 600C. As stated in Table 2 below, the mobile phase was made up of two solvent systems: water and an 80:20 v/v mixture of acetonitrile and methanol. The UV detector was set at 232 nm with a run time of 65 minutes, the injection volume was 20 L, and the flow rate was maintained at 1.2 mL/min. The results were analysed using the Chromeleon programme. The technique was validated in part in accordance with ICH guideline Q2 (R1).

Time (Min.)	*Mobile phase A%*	*Mobile phase B%*
0.0	60	40
25.0	40	60
30.1	40	60
42.0	10	90
45.0	10	90
50.0	00	100
60.0	00	100
61.0	60	40
65.0	60	40

Table 2. Gradient program for analytical method used in quantification of related substance

(vi) A Technique for Analyzing Particle Size- Since particle size is a crucial component of any nanoformulation system, it must be carefully monitored both during formulation development and stability testing. As a result, the particle size measurement device (Nicomp 380 ZLS from Particle Size Systems, PA, USA) was calibrated by gauging its accuracy and repeatability using a recognised polystyrene reference. Calibration was carried out using a Certified Polystyrene Standard with a mean diameter of 92 3 nm (NanosphereTM Size Standard, Catalogue No. 3090A, ThermoFischer Scientific, MA, USA). After a successful calibration, the mean particle size and particle size distribution of CTX NPs were determined using a detection angle of 90 degrees at a temperature of 25 degrees, with a refractive index of 1.333 and a centipoises viscosity of 0.933.

(vii) Addiction Association-The reported methodology was used to determine the percentage of drug association with the nanoparticle using size exclusion chromatography [9]. The underlying idea behind size exclusion chromatography was the molecule size. In this, whereas big molecules do not enter the pores and are eluted first in the column's empty volume, small molecules diffuse into the pores and their flow through the column is slowed proportional to their size (eluted later). In a nutshell, 500 L of reconstituted CTX NPs (2 mg/mL) were placed onto a previously equilibrated SephadexTM G-25M PD-10 column. After that, the column was eluted with a 0.9% solution of sodium chloride by taking tiny portions (about 500 L). The first 1.5 mL fraction, which constitutes the void volume, may include unentrapped medication. The volume of the fractions containing the NPs dispersions was measured (Test Sample). To achieve a concentration similar to the test sample's, 0.9% sodium chloride solution was added to 500 L of reconstituted CTX NPs (2 mg/mL) to create the control sample. The drug content of the eluted test and control samples was assessed using previously validated HPLC. The formula used to determine the percentage associated CTX was:

$$\%\text{Associated CTX} = \frac{(\%\text{ Content of CTX in Test sample}) \text{ X } 100}{\%\text{ Content of CTX in Control sample}}$$

(viii) Determination of size, shape, PDI, and zeta potential- The morphology and form of the nanoparticles were investigated using SEM. After being vigorously vortexed and put onto a double-sided adhesive carbon tape, Nano-DDA was re-dissolved in sterile water. A gold layer was applied to the samples, which were then monitored at a 5 kV acceleration voltage for 30 s. Using Image J, a SEM image was examined. To gauge how narrow the particle dispersion is, the polydispersity index (PDI) was discovered. Using a Zetasizer Ver. 7.11, zeta potential was obtained (Malvern Instruments Ltd, UK). The sample was diluted and filtered to prevent multiscattering effects. Using the built-in software and the Helmholtz-Smoluchowski equation, the electrophoretic mobility was converted to zeta potential.
(ix) Efficacy of the drug, loading, and encapsulating- HPLC was used to determine how much medication was put into the nanoencapsulation. In a nutshell, acetonitrile:water (47:53 v/v) was used as the mobile phase, and a known quantity of produced nano-DDA (5 mg/5 ml) was allowed to flow through the column after filtration through 0.22. The peak was found at 263 nm at a flow rate of 0.5 ml/min and an injection volume of 10 l. With the single point standardisation technique, the area of the primary peak was used to determine the DDA's content. At the conclusion of the formulation, the supernatant was collected by centrifugation in order to calculate the amount of free DDA. Using empty NPs as a blank, the absorbance was measured at 263 nm in the UV Spectrophotometer. The following formulae were used to calculate the encapsulation and loading efficiency.

$$\text{Encapsulation Efficiency}\,(\%) = (\text{Weight of initial amount of DDA} - \text{Weight of free DDA}/\text{Weight of initial amount of DDA}) \times 100$$

$$\text{Loading efficiency}\,(\%) = \text{Weight of initial amount of DDA} - \text{Weight of free DDA}/\text{Total Weight of nanoparticles}) \times 100$$

(x) DDA is released from nanoencapsulation in vitro- Using a dialysis bag submerged in phosphate buffered saline (PBS; pH 7.4), the in vitro release of DDA from PCL matrix was calculated. Glycerol and other metal traces were pre-treated out of a dialysis membrane with a 10,000 Da cut-off. A known quantity of nano-DDA (A1 formulation) was added to the dialysis bag along with 2 ml of pH 7.4 phosphate buffered saline (PBS). The dialysis bag was submerged in 35 ml of PBS and heated to 37 0.5 °C while being continuously stirred magnetically at 60 rpm. In order to maintain a constant volume, samples were taken at regular intervals, and fresh dissolving media of the same volume was substituted. A UV spectrophotometer set at 263 nm was used to measure the amount of medication emitted. The percentage release profile of free and nano-DDA was calculated by dividing the amount of DDA released by the total amount of drug present in the same volume of sample.

$$\text{Drug release}\,(\%) = (\text{Released DDA}/\text{Total DDA}) \times 100$$

CTX NANOPARTICULATE SYSTEM ASSESSMENT FOR VARIOUS STUDIES

(i) Investigation of In-Vitro Release- On the basis of our earlier work, an internal method for an in vitro release research was established. To evaluate the vitro release of CTX from CTX NPs, a dialysis membrane with a 110 kD cut-off (from HiMedia Laboratories Pvt Ltd, Mumbai, India) was utilised. The setup includes a USP Type- II Dissolution Test Apparatus (ElectroLab TDT-08L, Bombay, India) kept at 37°C. Orthophosphoric acid was used to make hydroxyl propyl cellulose (HPC) solution (0.005%w/v) and bring the pH level down to 4.5. The produced HPH solution (0.005% with pH 4.5) solution was combined with ethanol in a 9:1 ratio and utilised as release media to create a sink state. A solution with a CTX concentration of 0.3 mg/mL was produced by properly diluting reconstituted CTX NPs (2 mg/mL) with 5% dextrose. In order to stop any leakage from the dialysis sac, prepared samples (0.5 mL) were poured into the 7 cm long dialysis membrane and carefully sealed with a universal closure. The apparatus was started right away after fixing the universal closure with a sac and fixing the dissolving paddle with the aid of thread. Five millilitres of the sample (5 mL) were removed at time intervals of 0.5, 1, 2, 4, 8, 12, 16, 20, 24, 30, 36, and 48 hours, and fresh release medium was substituted that had been previously pre-equilibrated at 37°C. The generated CTX NPs formulation's release profile was compared to the commercial formulation (Jevtana). CTX quantification for release samples using verified HPLC is been described. Results were presented as a time-dependent cumulative CTX release percentage.

(ii) Dual Scanning Calorimetry (DSC)- On a DSC (Q2000, TA, New Castle, USA) with precision and thermal accuracy of 0.05% and 0.01°, thermograms of CTX, SPC, monosodium citrate, sucrose, and optimised lyophilized CTX NPs were taken. Each sample (2-4 mg) was heated in an aluminium pan at a rate of 1°C/min in a nitrogen environment (40 mL/min) between -20 and 240°C. The DSC was calibrated using empty pans for baseline measurements and indium for temperature and enthalpy measurements.

(iii) Polymeric nanoparticle preparation-By changing the surfactants and the ultrasonification period in different formulations (A1-A4), polymer coated DDA nanoparticles were created (Table 1). After the preparation was complete, the solvent gradually evaporated, causing the drug and polymer to precipitate, resulting in the creation of solid shell polymeric nanoparticles with an average size of 252.898 nm (Fig. 1) for the A1 formulation. The smooth surface and spherical shape of the nanoparticle were visible at higher magnification (1200). To create a prolonged drug release mechanism that would allow DDA to be employed for antidiabetic therapy, DDA was encapsulated in Polycaprolactone. A safer anti-diabetic therapy could be developed as a result of the current investigation. The formulations A2, A3, and A4 exhibited agglomeration (sonication time, drug:polymer ratio, and kind of surfactant utilised might all affect the nanoparticle's size and structure) and hence it was impossible to ascertain the particle size. The attainment of nanoparticles' distinctive qualities, such as their high encapsulation effectiveness, small size, and restricted distribution, depends on a variety of important elements. These nanoparticle characteristics play a key role in biological applications. Nanoparticles are thought to be stable in suspension if their zeta potential is greater than +/30 mV. All of the formulations' zeta potential values and polydispersity indices (PDI) were tabulated. A1 formulation alone showed potential and PDI of 38.9 0.091 mV and 0.150 0.002 respectively, among the four formulations (Table 3). The findings showed that the charge repulsion prevented any aggregation, and the material was therefore deemed stable in

suspension (38.9 mV). A homogenised particle size range is indicated by a polydispersity index 0.2. Although the study's polydispersity index was determined to be 0.150, the findings showed adequate particle homogeneity. The in vitro drug release, cellular uptake, cytotoxicity, as well as their in vivo pharmacokinetics and biodistribution, are all significantly influenced by physicochemical parameters like particle size and surface qualities.

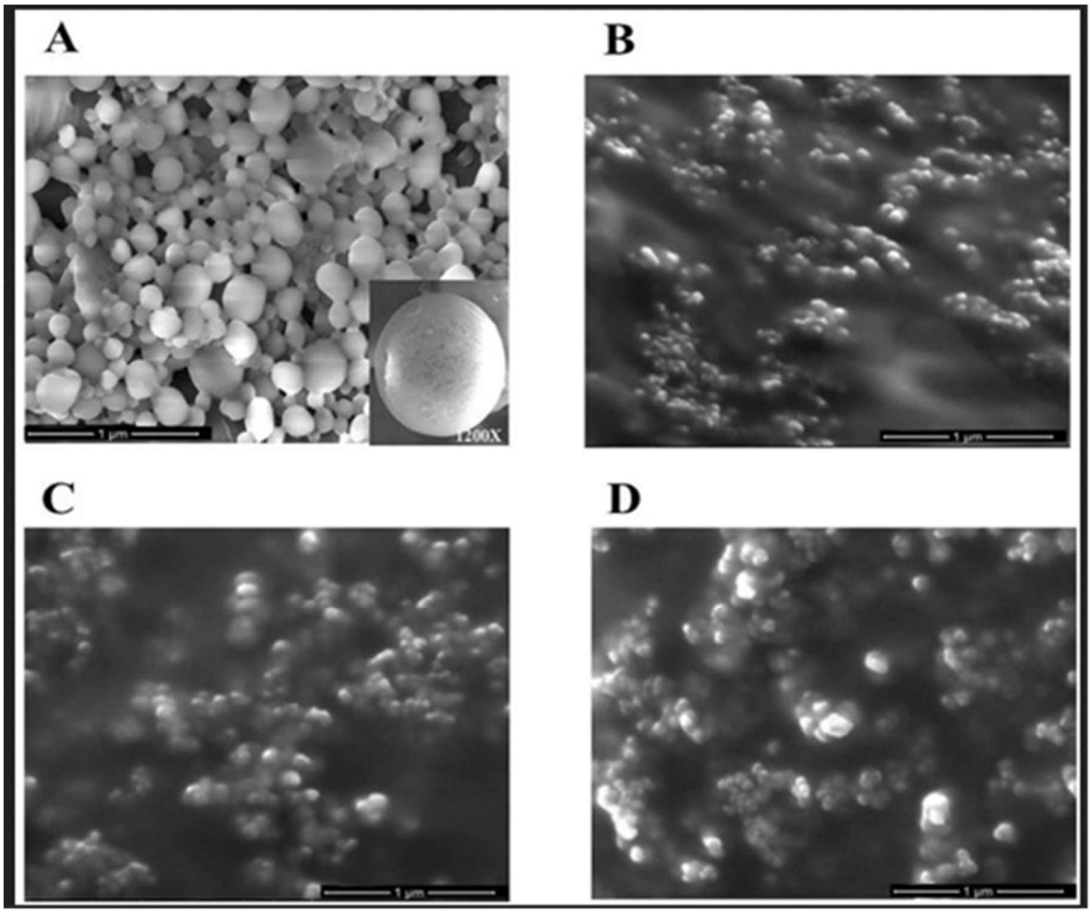

Fig.1. SEM pictures of nano-DDA in several formulations, including (A) A1, (B), A2, (C), and (D)

Formulation	Zeta potential	Polydispersity index
A1	−38.9 ± 0.091	0.150 ± 0.002
A2	−17.30 ± 0.265	0.551 ± 0.027
A3	−15.027 ± 0.449	0.651 ± 0.029
A4	−21.067 ± 0.491	0.432 ± 0.019

Zeta potential is expressed as mV. Values are expressed as mean ± SD, n = 3.

Table 3. Zeta potential and Polydispersity index of nano-DDA

S. No.	*Temperature condition*	*Time duration*	*Physical observation*
First Cycle			
1.	-20° ± 5°C	2 days	A off-white colored lyophilized cake in a clear glass vial
2.	25° ± 2°C/60% ± 5%RH	2 days	A off-white colored lyophilized cake in a clear glass vial
Second Cycle			
3.	-20° ± 5°C	2 days	A off-white colored lyophilized cake in a clear glass vial
4.	25° ± 2°C/60% ± 5%RH	2 days	A off-white colored lyophilized cake in a clear glass vial
Third Cycle			
5.	-20° ± 5°C	2 days	A off-white colored lyophilized cake in a clear glass vial
6.	25° ± 2°C/60% ± 5%RH	2 days	A off-white colored lyophilized cake in a clear glass vial

Table 4. Protocol for Freeze-Thaw study

RESULTS

CTX NANOPARTICULATE SYSTEM ASSESSMENT FOR VARIOUS STUDIES

(i) Investigation of In-Vitro Release- Fig. 3 compares the in vitro release characteristics of CTX NPs and Jevtana (a commercial formulation). More than 80% of the medicine is released within 24 hours, according to an in vitro release study that shows a sustained release pattern. In contrast, the JEVTANA formulation showed a fast release profile with a drug release of 98.2 2.1% within the first 30 minutes. Delayed drug release from a nanoparticulate delivery system has advantages over currently used conventional therapies such as passive targeting of the delivery system and accumulation in the tumour.

(ii) Characterization of lyophilized CTX NPs in the solid state- PXRD and DSC analyses were used to characterise the solid state of lyophilized CTX NPs. DSC analysis was carried out to determine the physical state of the medication (amorphous, crystallised, or semicrystalline) in lyophilized CTX NPs formulation. CTX has no strong melting peak (endotherm), indicating that it is amorphous, as validated by PXRD research. SPC DSC examination revealed strong endotherm peaks at 75.40°C and 106.02°C, indicating its crystalline composition (Fig. 4). The first endotherm in SPC is attributed to segmental motion associated with SPC fatty acid chains, but the later endotherm at 106.02°C is attributed to polar head group motion.

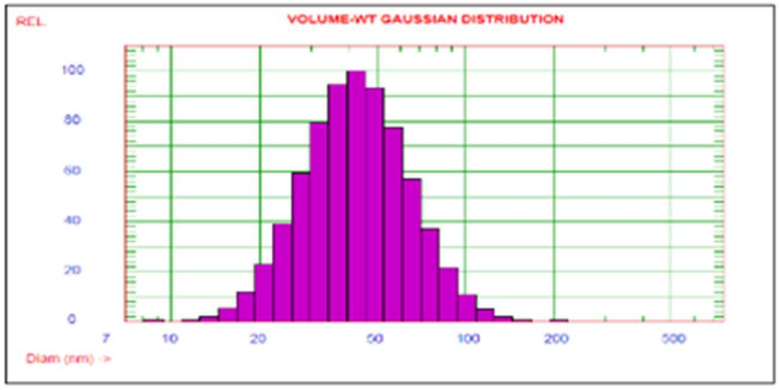

Fig. 2- Nicomp 380 ZLS particle size analysis of reconstituted CTX nanoparticles

(iii) Particle Size-A volume weighted Gaussian distribution was used to calculate the mean particle size of prepared CTX NPs, which was 40.6 5.5 nm with a PDI of 0.311 0.014. Figure 2 depicts a representative example of CTX NPs particle size distribution. Results indicate that the produced delivery system is a real nanoparticulate system. The majority of medication delivery system particles are in the nanometer range.

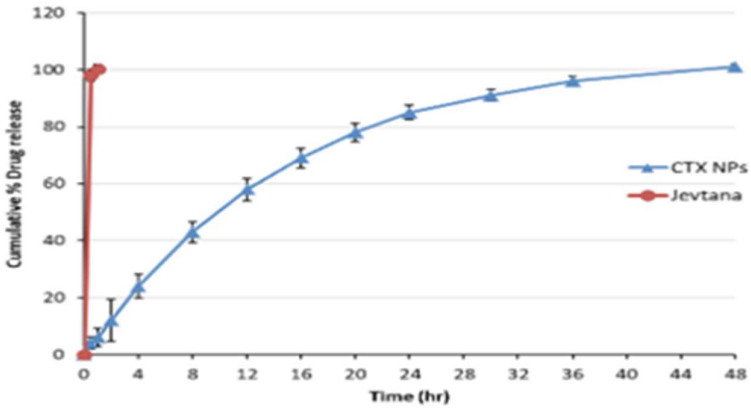

Fig. 3- Comparison of in vitro release profiles for CTX NPs and Jevtana

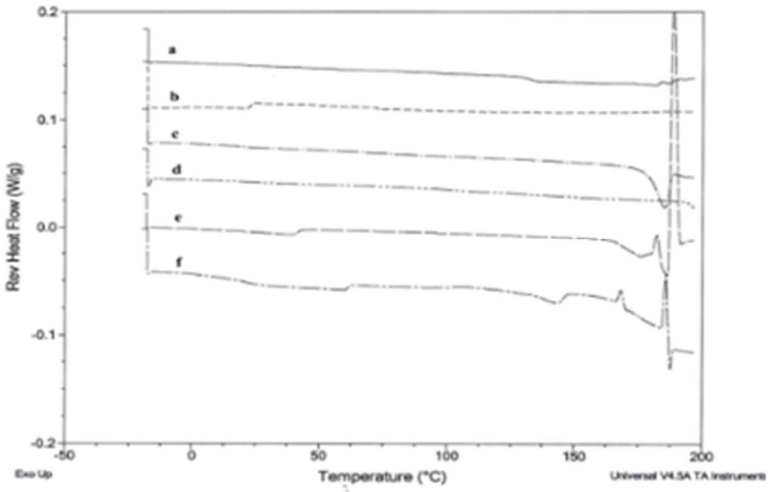

Fig. 4- DSC thermograms of (a) CTX, (b) SPC, (c) Sucrose, (d) Monosodium citrate, (e) Physical mixture, and (f) Lyophilized CTX nanoparticles

CONCLUSION

Prior research concentrated on the systemic development of CTX-loaded nanoformulations utilising the QbD method to avoid negative effects associated with conventional formulations. Using Central Composite Design, the formulation was systematically adjusted with SPC concentration, PEG 400 concentration, HPH pressure, and number of HPH passes as independent variables. Particle size and particle density index (PDI) were identified as dependent variables. The current study aimed to test the formulation and its in-process stage (bulk), as well as to assess its end-patient usage. To that end, drug component measurement, particle size, surface potential, solid state characterisation, in vitro drug release research, compatibility study, photostability study, and thermal cycling study were all carried out in either in-process bulk samples or completed dosage form. The overall findings of all research are satisfactory. All of the results fall well within the acceptance criteria specified before the study began. Such a systematic investigation and its favourable outcomes reflect the quality of the formulation that will be provided to cancer patients. The risk of giving patients low-quality medications is reduced by such high-quality formulation. This work also exemplifies the strategy to be used when a drug delivery system is supplied to an animal or a human for preclinical or clinical trials. The findings of the in vitro studies confirm earlier findings from system DoE-based research. Proper independent and dependent factor selection, as well as its level and choice of experimental design, results in a fully optimised drug delivery system, which is backed by the favourable results of a thorough in-vitro evaluation.

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