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Original Article

Design and Characterization of Camptothecin Loaded Colloidosomes for the Effective Treatment of Lung Cancer

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ABSTRACT

Background: Among the various cancers, lung cancer is the second leading cause of mortality after the breast carcinoma. Camptothecin (CPT) has broad spectrum anticancer potential used in the effective management of cancer including lung cancer. However, the therapeutic applications of CPT in the clinics are restricted due to its poor water solubility, low bioavailability and severe toxicities. Therefore, current research work was aimed to develop, optimize and characterize colloidosomes for safe and efficient delivery of CPT against lung cancer. **Materials and Methods:** Colloidosomes were prepared by using oil-in-water emulsion-based method and optimized using 3^2 Factorial design using sodium alginate as emulsifier and calcium carbonate as stabilizer. The optimized CPT Colloidosomes were lyophilized using freeze dryer and characterized for morphology by Transmission Electron Microscope (TEM), crystallinity by X-ray Diffraction (XRD), *in vitro* release, *in vitro* cytotoxicity, apoptotic potential etc. **Results:** The batch S9 has displayed high % entrapment efficiency (95±1.49%) and less particle size (327±9 nm and PDI: 0.267±0.019); therefore, it is selected as optimized batch. Besides, colloidosomes exhibited zeta potential of -24.5±3.2 mV revealing better stability. Further, the surface morphology results confirmed the self-assembling nature of colloidosomes which are spherical in shape. Moreover, lyophilized CPT Colloidosomes displayed sustained and maximum release of CPT (98±4.5%) after 8hr in PBS (Phosphate buffer solution) pH 7.4. Furthermore, the colloidosomes demonstrated significantly (p<0.01) higher *in vitro* cytotoxic and apoptotic activity against lung cancer (A549) cells after 48 hr of incubation. **Conclusion:** Results obtained revealed the remarkable *in vitro* anticancer potential of CPT in the form of colloidosomes which can further alleviate the side effects caused by systemic therapy of CPT. However; further *in vivo* animal studies are required to establish its efficacy treatment of lung cancer.

Keywords: Apoptosis, Camptothecin, Colloidosomes, Cytotoxicity, Lung cancer, Optimization.

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INTRODUCTION

Carcinoma is a chief health concerns and leading cause of mortality worldwide. Amongst the different cancers, lung cancer is one of the leading cancers causing the highest death after breast cancer.[1] Moreover; the outcomes are among the poorest of all tumor types, with five-year survival of 10-20%. Lung cancer is a very aggressive and highly prevalent disease worldwide, with an estimated 2.2 million new cases and 1.8 million deaths in 2022. Globally, lung cancer is the leading cause of cancer mortality in men and is the second highest cause of cancer death in women.[2] Tobacco exposure is by far the main risk factor for lung cancer worldwide; however, environmental exposures (such as biomass fuels, arsenic, radon, industrial carcinogens and air pollution), which can vary substantially by country, also contribute to lung cancer incidence and mortality trends.[3] Among the available treatment modalities, chemotherapy is used as a first line treatment strategy alone or in combination with other strategies.[4,5] Camptothecin (CPT) is a topoisomerase-I inhibitor predominantly inhibit S phase of cell cycle and showing anticancer potential against various cancers including

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lung cancer.[6] Camptothecin (CPT), is a phytoconstituent with a multitude of pharmacological activities documented, including antiviral,[7] HIV,[8] Antibacterial, Antifungal,[9] Colorectal cancer, Cancers, Ovarian cancer[8] and Breast cancer.[9] Broad-spectrum anticancer action is shown by CPT. It is well documented that human DNA topoisomerase-I is their molecular target. By preventing the rejoining phase of topoisomerase-I's process, CPT inhibits topoisomerase-I. This then leads to the accumulation of a covalent reaction intermediate called the cleavable complex. The key mechanism by which CPT kills cells is S-phase-specific mortality via potentially lethal collisions between topoisomerase-I cleavable complexes and advancing replication forks. It has also been shown that collisions with the transcription apparatus initiate the long-lived covalent topoisomerase-I DNA complexes, which enhance CPT cytotoxicity and are largely accountable for the wide spectrum of anticancer action.[10] However, the clinical applicability of CPT was limited due to its poor aqueous solubility, short half-life and low bioavailability. Besides, the chemotherapy with CPT is associated with nonspecific distribution, severe toxicities and lack of selectivity. Therefore, to overcome the above drawbacks in the delivery of CPT, Advanced Drug Delivery Systems (ADDS) plays an imperative role. ADDS (liposomes, niosomes, transferosomes and colloidosomes) have shown promise in the delivery of anticancer therapeutics in the treatment of variety of cancers.[11] Out of these vesicular drug delivery systems, colloidosomes is found to be highly potential because of its various benefits such as high versatility, biocompatibility, high drug loading efficiency, targeting ability, controlled release of drugs. Besides, colloidosomes are able to control size, permeability and mechanical strength.[12] colloidosomes and can be used for encapsulation of biologically sensitive materials has hydrophilic drugs, pesticides, proteins and fragrances.[13] Colloidosomes is an advanced tool in drug delivery. Itis novel class of microcapsules whose shell consists of coagulated or fused colloid particles at interface of emulsion droplet. The particles self-assemble on the surface of droplets to minimize the total interfacial energy forming colloidosomes.[14] Colloidosomes are based on Pickering emulsions. Emulsion droplet stabilized by colloid particles at interface of colloidal particles, which are then locked in place on the droplet surface by sintering or some colloidalinstability.[15] Colloidosomes are mostly based on the self-assembly of colloidal particles at the interface between two immiscible liquids, typically water and oil. The initial self-assembled structures are known as pickering emulsions[16] and have been recognized for over a century. Different examples of colloidal particles such as silica solution6-7. and polystyrene latexes have been shown to be effective pickeringemulsifiers.[17] According to their elasticity of tuning the permeability over a broad size range, colloidosomes, microcapsules developed by shells of close-packed colloidal particles, have recently been recognized as promising probable vehicles.[18] Till date very few reported studies have been utilized nanoparticles and gels as novel drug delivery strategy for CPT to control the carcinomas.[19] However, the development of CPT loaded colloidosomes as novel drug delivery for the effective management of lung cancer has not been reported. Therefore, current research work was aimed to design, optimize and characterize CPT colloidosomes for effective treatment of lung cancer.

MATERIALS AND METHODS

Materials

Camptothecin (CPT) was procured from Clearsynth Pvt. Ltd., Mumbai. Sodium alginate was obtained from Sigma Aldrich, Mumbai. Calcium carbonate obtained from Molychem, Mumbai, Sunflower oil purchased from Gemini seeds Pvt. Ltd., Ethanol, methanol and distilled water were procured from Loba Chemical Pvt. Ltd., Mumbai. All other chemicals and reagents used in present research work were of analytical grade.

Drug-excipients compatibility study

Fourier Transforms Infrared (FTIR) analysis

The FTIR analysis of plain CPT, plain sodium alginate and CPT and formulation excipients of colloidosomes (physical mixture; in 1:1 weight ratio) was carried out to evaluate CPT and excipients compatibility using a Bruker, Alpha-T FTIR spectrophotometer.[20,21]

Differential Scanning Colorimetry (DSC) analysis

The DSC analysis of plain CPT, plain sodium alginate and physical mixture of CPT with formulation excipients (1:1 weight ratio) of colloidosomes was performed to assess the compatibility of CPT-excipients and any changes in the physical state of CPT on entrapment in colloidosomal by differential scanning calorimeter (DSC-60, Shimadzu, Japan). The analysis was carried out at 30°C to 300°C; a scan rate of 10°C/min in a dry nitrogen atmosphere.[22,23]

Preparation and optimization of CPT-loaded colloidosomes

The colloidosomes formulation was developed and optimized by employing 3^2 Factorial designs with Design-Expert® software (Version 12.0, Stat-Ease Inc., USA). Eleven diverse formulations as insinuated by design at three different coded levels (-1, 0 and +1) of concentration of calcium carbonate (X1) and ratio of oil to water specifically volume of water (X2) was designed (Table 1). All the batches were prepared and optimized based on particle size (Y1) and percent entrapment efficiency (Y2). Colloidosomes were prepared by using oil-in-water emulsion-based technique. Briefly, CPT (200 mg) was dissolved in sunflower oil and typical fabrication $CaCO_3$ micro particles were dispersed in sunflower oil through stirring for 1hr. Aqueous solution of sodium alginate (500 mg) was added into oil and stirred continuously for several minutes that leads to formation of oil-in-water emulsion (IKA

Ultraturrax T-18). The formed emulsion was shaken for 2 hr and allowed to left for 48 hr. Then, the obtained colloidosomal dispersion was added to ethanol (non-aqueous phase) and supernatant was separated following centrifugation. The resultant oil core colloidosomes were washed with ethanol and finally re-dispersed in water.[24,25]

Characterization of CPT-loaded colloidosomes

Particle size and PDI

The particle size of CPT-colloidosomes was determined using a Malvern Zeta-sizer. The particle size distributions of each sample were investigated in triplicate and the mean value was calculated.[26,27]

Zeta potential

The CPT-colloidosomes zeta potential was evaluated using the Malvern Zeta-sizer, UK, which consisted of appropriate software. Three different samples were tested at 25°C using a cell drive that was kept at 150 mV. The dispersion medium's dielectric constant and viscosity were used to translate electrophoretic mobility into zeta potential values.[28,29]

% Entrapment Efficiency (%EE)

For the determination of %EE of all batches of colloidosomes, initially the colloidosomes were alienated from the aqueous medium by centrifugation (10,000 rpm for 1 hr). Then, the amount of free CPT in the buoyant was determined by UV spectrophotometry at 225 nm after suitable dilution with methanol.[30] The CPT entrapped in the Colloidosomes was calculate using formula:

$$\% \text{ Entrapment Efficiency} = \frac{\text{Tp} - \text{Tf}}{\text{Tp}} \times 100$$

Where, Tp is the total CPT used to prepare the Colloidosomes and Tf is the free CPT in the supernatant.

Freeze drying and characterization of lyophilized colloidosomes powder

The optimized colloidosomes with trehalose cryoprotectant (at varying weight ratios) were lyophilized via Martin Christ freeze dryer. The lyophilized powders were then subjected for different characterization.[31]

Process Yield of Freeze-Drying Process

The amount of product obtained after completion of process is determined by process yield. Briefly, powder obtained from lyophilized (Martin Christ Lyophilize) was collected and product yield was calculated from following equation.[32]

$$\% \text{ Process yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Surface Morphology by TEM

After discarding the excess fluid, "a carbon-coated copper grid having mesh size of 300 was used to deposit 5 µL of CPT-Colloidosomes on the grid and then fix the grid. The grid was then air-dried before being stained with uranyl acetate stain at a conc. of 1% for 3 to 5 min with a transmission electron microscope (JEOL-JEM 1400 USA).[33,34]

Powder X-ray Diffraction (P-XRD)

CPT and Lyophilized colloidosomes were subjected for XRD analysis (Shimadzu XRD-6000, Japan). X-ray particle Diffractions (XRD) were acquired by employing Cu-Kα radiation using graphite monochromator.[35]

In vitro release study

In vitro release of optimized lyophilized colloidosomes was done using USP Type-I (Basket) dissolution test apparatus and was compared with plain CPT. Briefly, the lyophilized CPT Colloidosomes equivalent to 200 mg of CPT and plain CPT (200 mg) were filled in to tea pouch and kept in the flask of dissolution apparatus. Initially, 0.1 N HCL was employed as a dissolution fluid (for 1st 2 hr), later then the medium was changed to Phosphate Buffer Solutions (PBS) of pH 7.4 and maintained 37°C at a 50 rpm and drug release was studied for further remaining hours. Then aliquots (1 mL) were withdrawn at predetermined time intervals and substituted utilizing exact quantity of fresh medium (PBS pH 7.4). The samples were assayed spectrophotometrically at 225 nm and the percentage drug release was calculated.[36,37]

In vitro cytotoxicity

The survivability of CPT and CPT-colloidsomes on lung carcinoma cell lines (A-549) was investigated using an MTT dye reduction test. Cells were placed in a 96-well plate and left overnight at 37°C. The cells were cultivated for 48 hr at different doses of the test compound. Following the withdrawal of test solutions, 100 µL of MTT (6 mg/10 mL in PBS) was added to every well. The plates were then incubated for 4hr in a similar setting. After eliminating trash, 100 µL of DMSO was injected to dissolve the formazan crystals produced by living cells. The solution absorbance was assessed at 570 nm using a microplate reader. Values of IC_{50} were then determined using dose-effect relationship curves.[38]

Apoptosis by Flow cytometer

The cells were added in a 24-well micro plate and incubated overnight at 37°C. The cells were then incubated with 50 µg/mL of plain CPT and optimized lyophilized colloidosomes for 24 hr. After the incubation, cells were harvested and centrifuged for 5 min at 4°C and cell pellet was collected. The resultant pellets were washed repeatedly using a 2 mL of 1X PBS and supernatant was discarded. Then 1 µL of annexin V-FITC solution and 5 µL PI was added and mixed gently and tubes were reserved on ice.

Table 1: Full factorial Design matrix summarizing the levels, factors and responses of 09 runs for optimization of CPT loaded colloidosomes.

Batch code	Factor X_1	Factor X_2	Particle size (nm) *	PDI *	% Entrapment Efficiency *
S1	200	1:5	412±7	0.328±0.024	85.75±2.43
S2	200	1:4	480±9	0.350±0.026	76.06±3.28
S3	100	1:5	755±6	0.410±0.033	84.23±1.65
S4	300	1:4	584±9	0.376±0.027	78.62±2.78
S5	300	1:5	538±10	0.387±0.031	88.12±1.86
S6	200	1:5	418±6	0.312±0.027	86.72±3.21
S7	100	1:4	924±8	0.412±0.032	55.62±2.21
S8	200	1:5	416±5	0.344±0.030	86.08±2.70
S9	300	1:6	327±9	0.267±0.019	94.25±1.49
Factor (Independent variables)			Actual levels		
			Low (-1)	Medium (0)	High (+1)
X1: Calcium Carbonate (mg)			100	200	300
X2: Oil: Water			1:4	1:5	1:6
Dependent variables or Responses			Constraint		
Y1: Vesicle size (nm)			Minimize		
Y2: Entrapment efficiency (%)			Maximize		

* Values are mean±SD (n=3).

Finally, the 400 µL of ice-cold 1X binding buffer was added into the tubes incubated in dark for 15 min and were analyzed by flow cytometry within 30 min.[39,40]

Apoptosis by DAPI staining

In a CO_2 incubator, 1×10^4 cells were seeded in a 24-well plate and incubated overnight at 37°C. The following day, the cells were treated with CPT and CPT-Colloidosomes at concentrations below 50 µg/mL. After 24 hr of incubation in the CO_2 incubator, the cells were rinsed with PBS for 30 min in preparation for staining. A 20 µL aliquot of DAPI staining solution (0.1 µg/mL) was then added to the cells, which were subsequently incubated in the dark. Apoptotic cells were quantified by randomly sampling and counting cells that exhibited signs of apoptosis under microscopic observation.[41]

Stability study

According to ICH guidelines stability study of lyophilized CPT colloidosomes was performed temperature 40±2°C and RH-75±5% for 3 months and its physical stability was estimated by parameters like drug content, percent drug release after 1, 2 and 3 months.[42]

Statistical analysis

The data are expressed as the mean±Standard Deviation (SD) derived from three independent experiments to ensure reliability and reproducibility. Statistical analysis was performed using GraphPad Prism software version 8 (GraphPad Software, Inc., La Jolla, CA, USA). The obtained results were subjected to one-way Analysis of Variance (ANOVA) to determine statistical significance. A p-value of less than 0.05 ($p<0.05$) was considered indicative of a statistically significant difference, highlighting the effects observed in the experiments.

RESULTS

Drug-excipients compatibility study

FTIR Study

The FTIR spectral analysis was employed to ascertain compatibility between the CPT and excipients of colloidosomes. The FTIR spectra of pure CPT, plain sodium alginate and physical mixture of formulation excipients of colloidosomes are shown in Figure 1. FTIR spectra of CPT (Figure 1A), showed characteristic peaks at wave number of 3433.41 cm^{-1}, 1440.87 cm^{-1} and 1041.60 cm^{-1} are attributed to the characteristic peaks of -OH, C=N and C-O of CPT respectively. Besides, the peak at 1649.19cm^{-1} is corresponding to the C=O and C=C functional groups of CPT. FTIR spectra of sodium alginate showed principle peaks at 2926.61 cm^{-1} and 1416.03 cm^{-1} which are peak corresponding to C-H stretch and C=O stretch of sodium alginate. Moreover, the peak at 1620.54 cm^{-1} is attributed to the peak of O-C=O (Figure 1B). The FTIR spectra of physical mixture of CPT and formulation excipients of colloidosomes (Figure 1C), showed functional groups peaks of -OH at 3433.41 cm^{-1}, C=C at 1637.62 cm^{-1}, C=N at 1442.80 $cm^{-1}$and C-O at 1041.60 cm^{-1}. The principal peaks of CPT are retained in the FTIR spectra of CPT Colloidosomes. Thus, obtained results

clearly revealed compatibility (no chemical interaction) between CPT and formulation excipients of colloidosomes.[43]

DSC Studies

Differential scanning calorimetry is a distinctive method used to determine the compatibility between the CPT and colloidosomes excipients. Figure 2 displays the DSC thermograms of pure CPT, pure sodium alginate and a physical mixture of CPT with excipients of colloidosomes. The Differential Scanning Calorimetry (DSC) thermogram of pure CPT (Figure 2A) exhibited a peak at 285°C, while the thermogram of pure sodium alginate (Figure 2B) displayed a peak at 256°C, both corresponding to the respective substances. The DSC thermogram of the physical mixture of CPT and excipients of colloidosomes (Figure 2C) shows an endothermic peak at 286°C, which is similar to the peak reported for CPT. The results obtained showed that the integrity of CPT was maintained when combined with colloidosome excipients, indicating compatibility between CPT and the formulation excipients.[44,45]

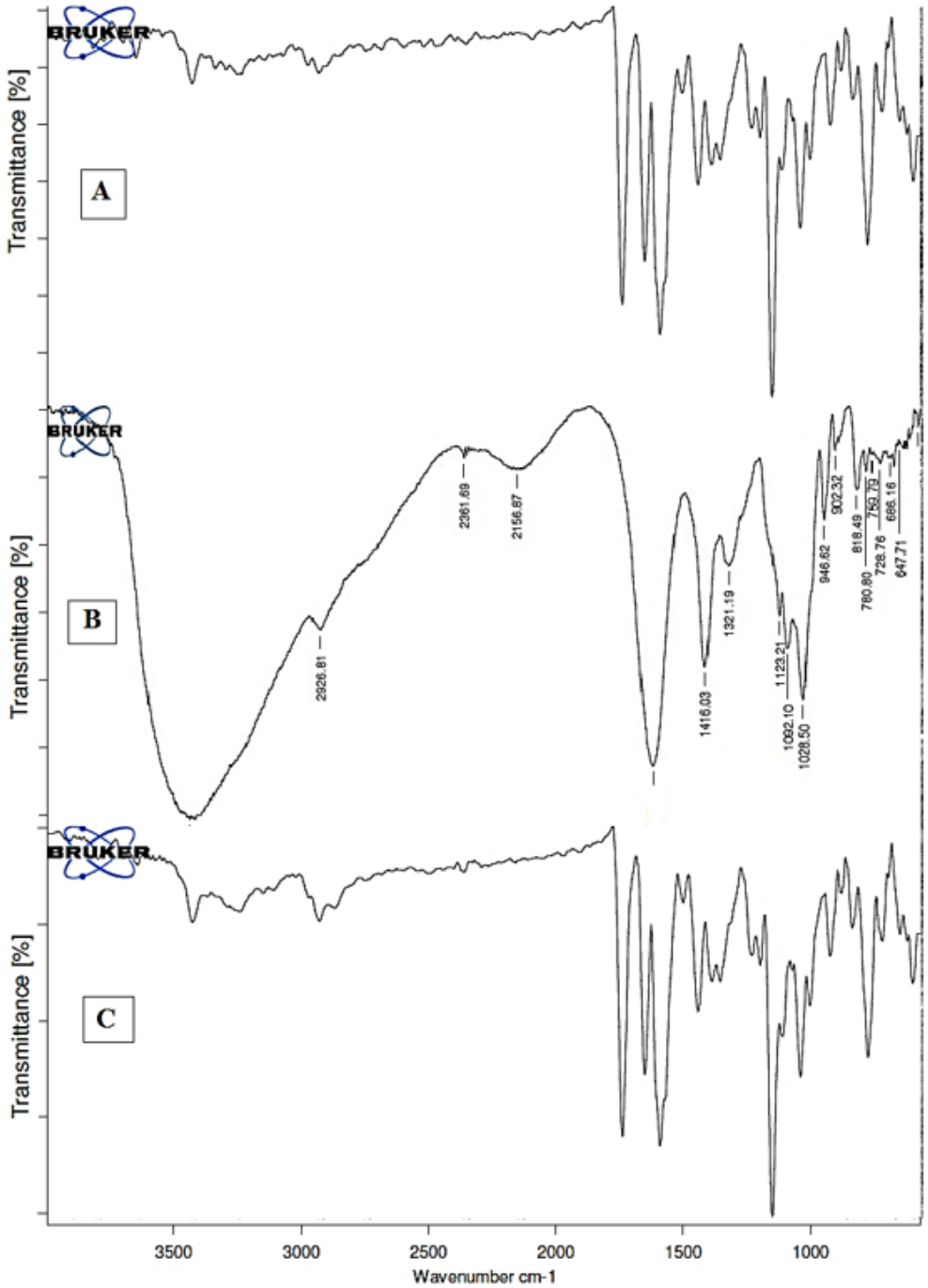

Figure 1: FTIR of A) CPT B) Sodium Alginate C) CPT Colloidosomes.

Optimization of CPT- loaded colloidosomes

Effect of formulation variables on particle size (Response 1; Y1)

Contour plot (Figure 3A) and 3D surface response plot (Figure 3B) were used to divulge the consequence of calcium carbonate concentration (A) and volume of water (B) on the particle size of colloidosomes. Both variables established positive effects on particle size. The augment in A and B displayed diminish in the particle size. Besides, the negative influence (increased) was observed on the particle size with 2 variable interactions. The ANOVA analysis of results yielded F-value 7337.6 and *p*-value 0.0001, (*p>0.05*) which indicates the implication of the quadratic model. The formulation and optimization of 11 batches of colloidosomes is depicted in Table 1.

The relevant model for drug content (R^2=0.999) was observed to be a quadratic model. The final equation in terms of coded factors for particle size is,

Particle size=+424.3- 131.527A -124.407 B+27.26 AB+207.18 A2-25.82B2

Effect of formulation variables on entrapment efficiency (Response 2; Y2)

Contour plot (Figure 3C) and 3D surface response plot (Figure 3D) were used to divulge the consequence of calcium carbonate concentration (A) and water volume (B) on the entrapment efficiency of colloidosomes. Both variables demonstrated positive effects on entrapment efficiency. The augment in A and B caused an augment in the entrapment efficiency. Besides, a decrease in the entrapment efficiency was observed with the interaction amid two variables. The ANOVA analysis of results yielded F-value 255.61 and *p*-value 0.0001, (*p>0.05*) which indicates the implication of the quadratic model. The relevant model for drug content (R^2=0.996) was observed to be a quadratic model. The final equation in terms of coded factors for entrapment efficiency is,

Entrapment efficiency=+84.1274+4.675A+10.2433B-1.17AB-1.23342A2-1.21842B2

Among the 11 batches prepared batch F9 displayed minimum particle size (327±9 nm) (Figure 4A) and PDI of (0.267±0.019) and substantially higher entrapment efficiency (95.64±1.49) when compared to other batches. Therefore, batch F9 was considered

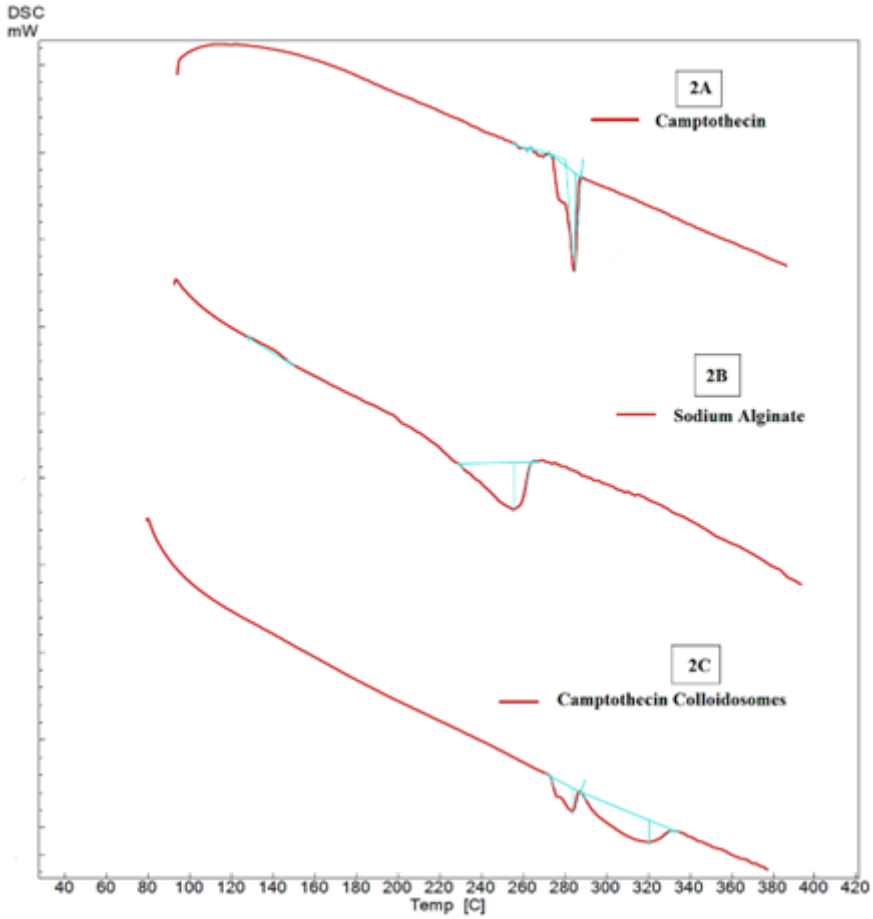

Figure 2: DSC of A) CPT B) Sodium Alginate C) CPT Colloidosomes.

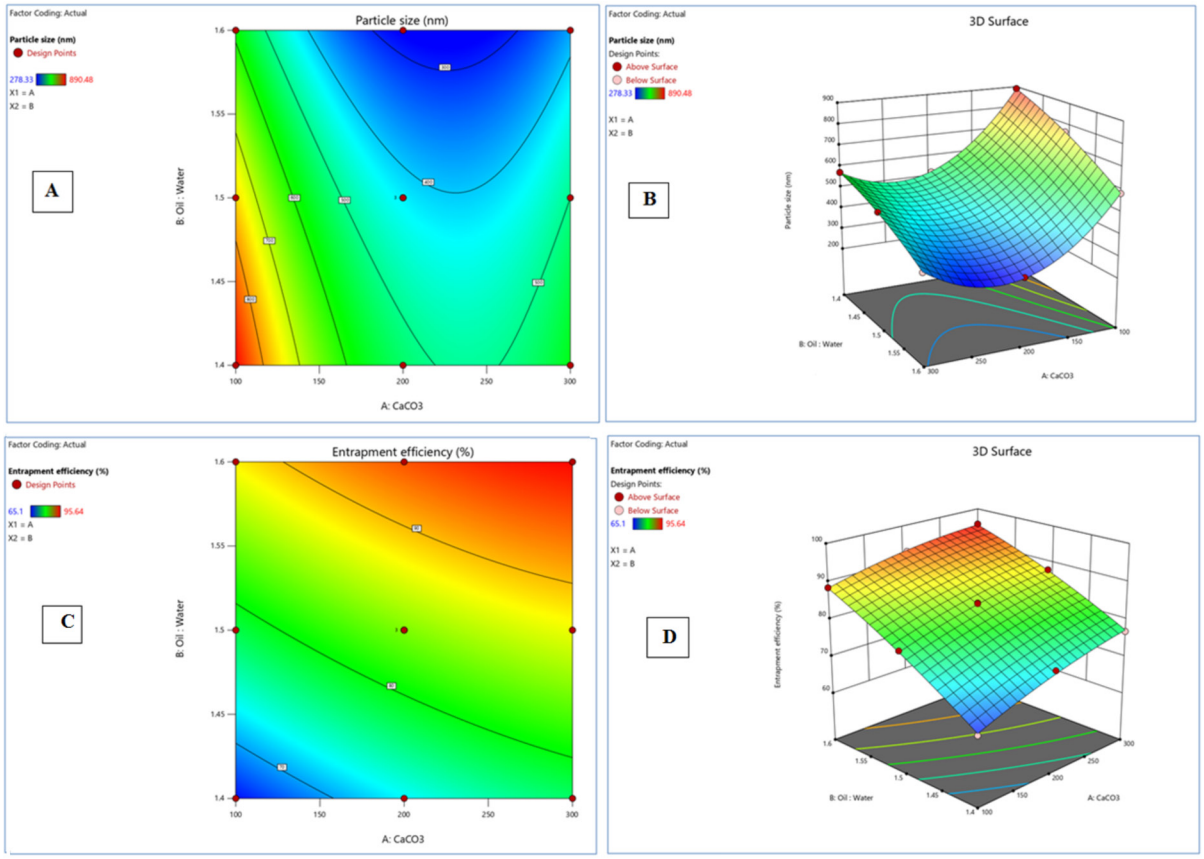

Figure 3: Particle Size 3A) Contour 3B) 3D surface response plot; Entrapment Efficiency C) Contour plot D) 3D surface response plot.

as optimized batch and used for further characterization. Furthermore, the optimized batch showed zeta potential of -24.5±3.2 mV (Figure 4B). The formulation and optimization of 11 batches of colloidosomes is depicted in Table 1.

Lyophilization of optimized CPT-loaded Colloidosomes and process yield determination

The optimized colloidosomes (batch 9) was lyophilized using a cryoprotectant trehalose to keep formulation physically and chemically stable till further characterization. F9 batch displayed % process yield of 91.26±2.49% at optimized parameters (Primary and Final drying for 6 hr at -50°C and 0.05 mbar) of lyophilize.

Surface morphology by Transmission Electron Microscopy (TEM)

To check surface morphology and presence of colloidosomes in lyophilized powder the lyophilized powder samples were subjected to transmission electron microscopy. The TEM confirmed the presence of self-assembled and spherical CPT-loaded colloidosomes in the reconstituted solution of lyophilized powder (Figure 4C).

P-XRD Studies

The influence of process parameter's colloidosomes preparation on physiochemical nature of CPT was determined by p-XRD. The p-XRD motif of plain CPT and optimized lyophilized colloidosomes is delineated in Figure 5. The p-XRD motif of CPT (Figure 5A) manifested distinctive intensity reflections counts of 4470, 2613, 1638 and 4749 at diffraction angles of 13.217, 17.549, 26.460 and 25.653 (2θ), respectively, indicating its crystalline nature. However, these distinctive peaks were vanished in CPT lyophilized colloidosomes p-XRD pattern (Figure 5D) which conforms that change crystalline nature of CPT during processing of colloidosmes.[46]

In vitro drug release study from Colloidosomes

The *in vitro* release of CPT from lyophilized optimized CPT Colloidosomes and plain CPT solution was studied by USP Type-I (Basket type) dissolution test apparatus using 0.1 N HCL and PBS of pH 7.4 as dissolution medium. The release of CPT (98.2±4.5%) from colloidosomes was found to be significantly ($p<0.01$) higher than its release from plain CPT solution (39.5±2.4%) at end of 8 hr.

Cytotoxicity Study

The *in vitro* cytotoxicity of lyophilized colloidosomes was studied against A549 cells using MTT assay and compared with plain CPT. % viability A549 cells with respect formulation concentration after 48 hr incubation is depicted in (Figure 5E). The lyophilized colloidosomes exhibited significant ($p<0.01$) cytotoxicity (low IC_{50}: 2.9±0.46 µg/mL) than plain CPT (5.25±0.87 µg/mL) against A549 cells after 48 hr of incubation.

Apoptosis by Flow Cytometer

The cytometric evaluation of A-549 cells treated with plain CPT and CPT Colloidosomes is shown in Figure 6. In control sample the untreated cells are predominantly healthy (99.70% live cells) with only 0.15%, 0.12% and 0.020% of the cells were in early, late apoptotic and necrotic states (Figure 6A). About 7.96% of the cells were found in early apoptotic state and 16.2% of the cells were observed in late apoptotic stage treated with CPT. Thus, the % of live cells rapidly decreased from 99.70% to 55.3% when treated with CPT (Figure 6B). On the other hand 15.8% and 54.9% of the cells were found in early and late apoptotic state respectively once treated with optimized lyophilized colloidosomes. Thus, the % of live cells drastically reduced from 99.70% to 22.4% when treated with optimized lyophilized colloidosomes (Figure 6C).

Apoptosis by DAPI

DAPI staining technique was utilized to check programmed cell death for 48 hr in A549 lung cancer cells after treatment with CPT and CPT Colloidosomes. Nuclear morphological changes in negative control cells along with treated with CPT and lyophilized CPT colloidosomes are shown in Figure 7. The untreated (negative control) cells (Figure 7A) showed weak homogenous blue staining along with intact normal nuclei whereas, in the cells treated with CPT (Figure 7B) and lyophilized CPT colloidosomes (Figure 7C) Circle represents chromatin condensation and nuclear shrinkage, square represents nuclear blebbing, nuclear fragmentation and arrow represents apoptotic bodies. The percentage apoptosis for control, plain CPT and lyophilized CPT Colloidosomes was found to be 3.36±1.45%, 47.38±3.46 and 65.28±5.27% respectively.

Stability study

We observe no significant changes in the drug content and drug release of optimized CPT colloidosomes after storage of 3 months at 40°C±2°C and 75%±5% RH. The Drug content and drug release of optimized CPT colloidosomes after 1, 2 and 3 months

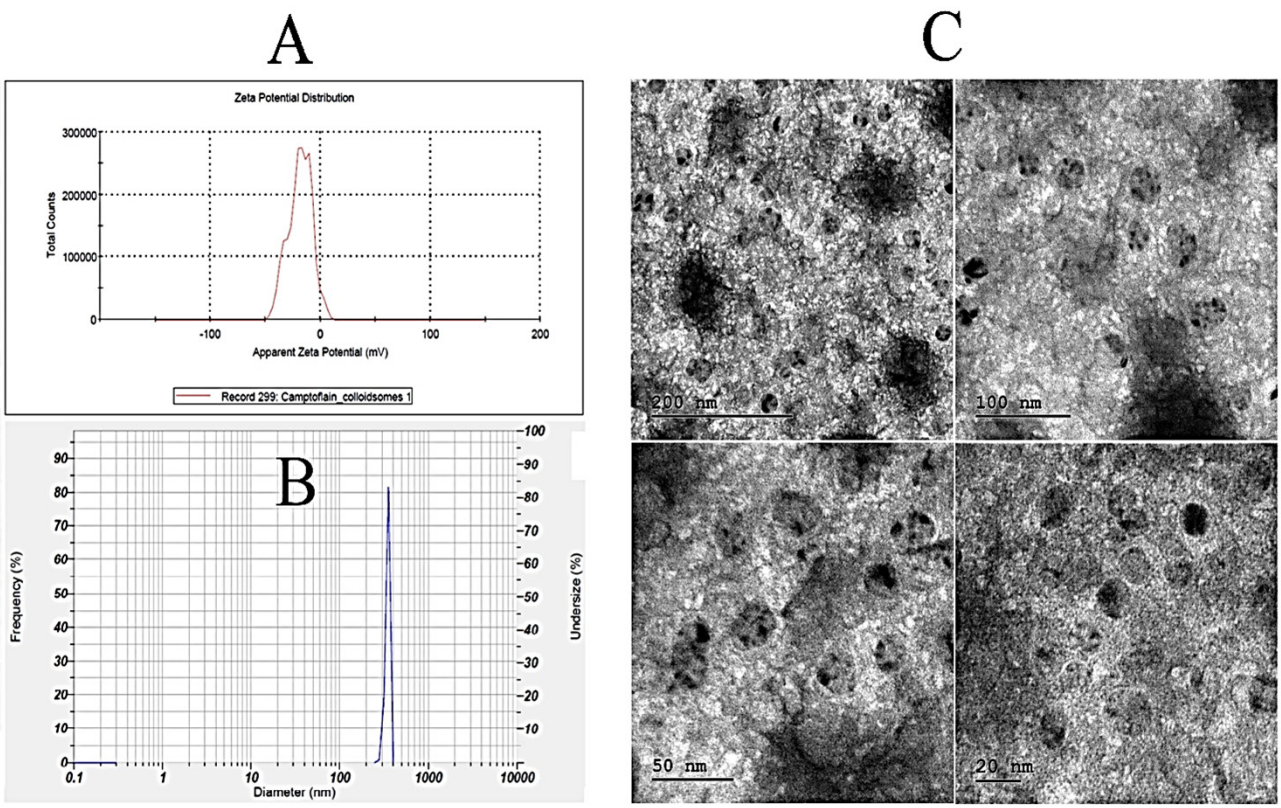

Figure 4: A) Particle size B) Zeta Potential C) Surface Morphology by TEM of optimized CPT Colloidosomes.

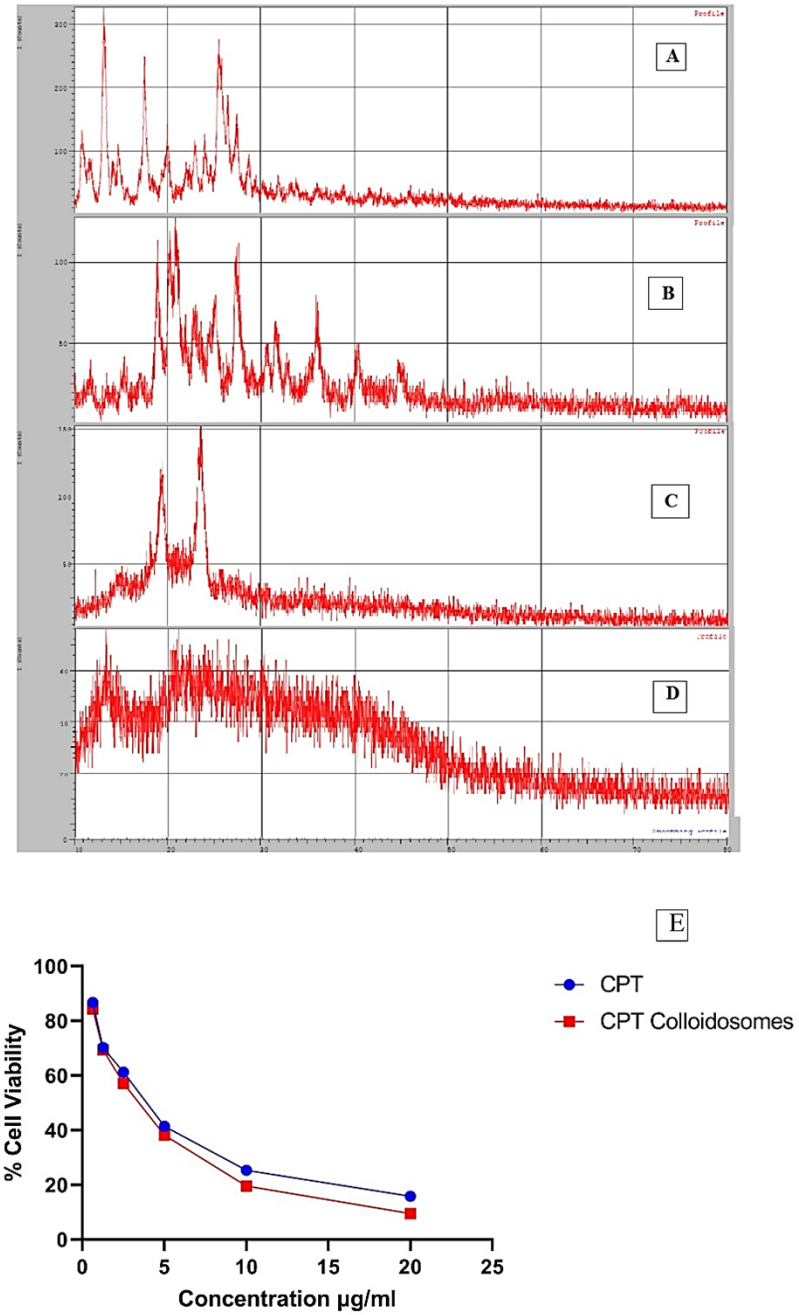

Figure 5: XRD of A) CPT B) Sodium Alginate C) $CaCO_3$ D) CPT Colloidosomes; E) % Cell Viability of Plain CPT and Optimized CPT Colloidosomes.

of storage are depicted in Table 2. Thus, the obtained results clearly revealed high stability of colloidosomes.

DISCUSSION

The FTIR and DSC analysis conformed compatibility of CPT with colloidosomal excipients. The fundamental peaks of the CPT are retained in the formulation indicating no chemical interaction between CPT and excipients used.[47] Besides DSC studies revealed that CPT incorporated in the colloidosomes is existed in amorphous state indicating that CPT might be molecularly dispersed in colloidosomal nanoparticles.[48,49] In the colloidosomes, sunflower oil containing porous $CaCO_3$ emulsified by aqueous solution of sodium alginate to produce the o/w emulsion. Porous $CaCO_3$ micro particles act as stabilizer for the o/w emulsion and cross-linker for the alginate. The increased %EE at 1:6 ratio of oil to water is due to availability of high concentration of $CaCO_3$ which act as a cross-linking agent and decrease in % EE at 1:4 ratio of oil to water due to shrinkage of colloidosomes during cross linking which expel drug outside. The size of colloidosomes was primarily determined by the water fraction employed in the formulation. When the volume of water

fraction changed, certain colloidosomes underwent deformation, resulting in a non-spherical shape and even breakage. Furthermore, the particle size of all formulations was shown to be significantly influenced by the stirring speed.[50,51] An increase in stirring speed leads to a drop in the average size of colloidosomes. This could be attributed to the high stress generated at the interface, which promotes the formation of new surfaces. These surfaces are effectively stabilized by amphiphiles, resulting in a smaller distribution of particle sizes.[50,51] Negative value of zeta potential of optimized formulation of CPT Colloidosomes indicating better stability of colloidosomes.[38] XRD pattern of lyophilized CPT Colloidosomes confirmed that the CPT might be molecularly dispersed in non-crystalline state.[52] The *in vitro* release of CPT from lyophilized CPT Colloidosomes was found to be substantially higher than plain CPT solution. This higher release of CPT from the lyophilized CPT Colloidosomes could be due to the decrease in the particle size. Moreover, the colloidosomes exhibited concentration dependent cytotoxicity towards A549 cells.[53,54] The lyophilized CPT Colloidosomes showed higher cytotoxicity than that of plain CPT. Thus, remarkably increased cytotoxicity of colloidosomes against lung cancer might be due to enhanced intracellular uptake of CPT by colloidosomes and endocytosis. Moreover, the nanovesicle size range and sustained release of CPT from colloidosomes also responsible for higher cytotoxicity.[55] In tumor apoptosis is the key mechanism by which anticancer agents can induce cell death. The cells treated with CPT Colloidosomes showed reduction in live cells and increased % of early and late apoptotic cells revealing high efficacy and quick uptake of CPT loaded colloidosomes by cancerous cells.[43] Moreover, the potential of CPT colloidosomes was investigated against A459 cells using the Annexin V-FITC/PI staining technique.[56,57] Apoptotic potential always accompanied with movement of phosphatidyl serine from cytosol to cell membrane. Results of flow-cytometry displayed a great extent of cells in the early and late apoptotic stage in the case of CPT Colloidosomes treated when compared to control.[58,59] Evaluation of nuclear morphology by fluorescence microscopy using a DAPI stain is commonly used for apoptosis analysis. Apoptosis by DAPI indicate that CPT Colloidosomes induce apoptosis in A549 cells crumbling of nuclei and irregular edges close to the nuclei which

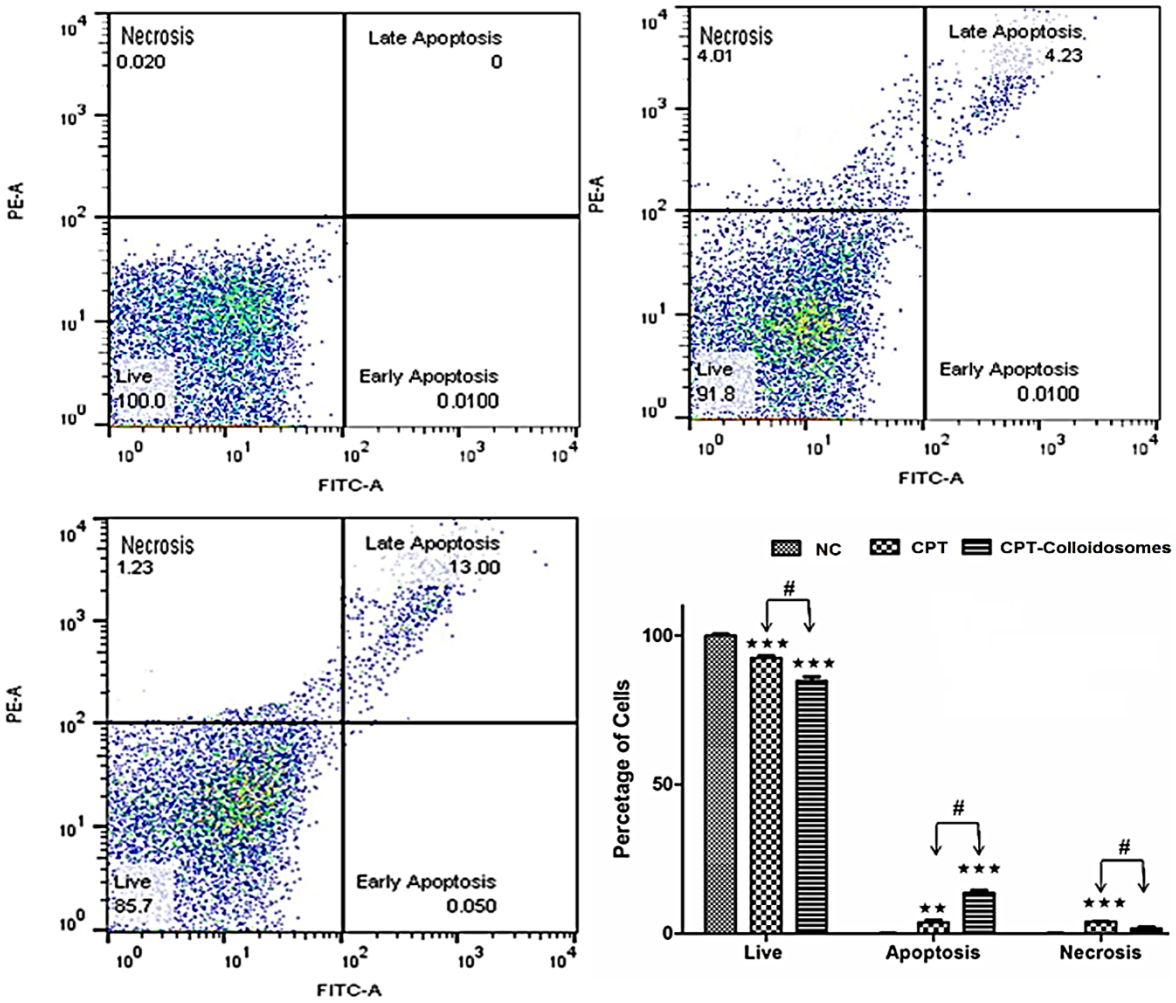

Figure 6: Flow Cytometry A) Normal Control B) CPT C) CPT Colloidosomes D) Percentage of cells undergoing apoptosis and necrosis compared to control on treatment with CPT and CPT colloidosomes for 12 h.

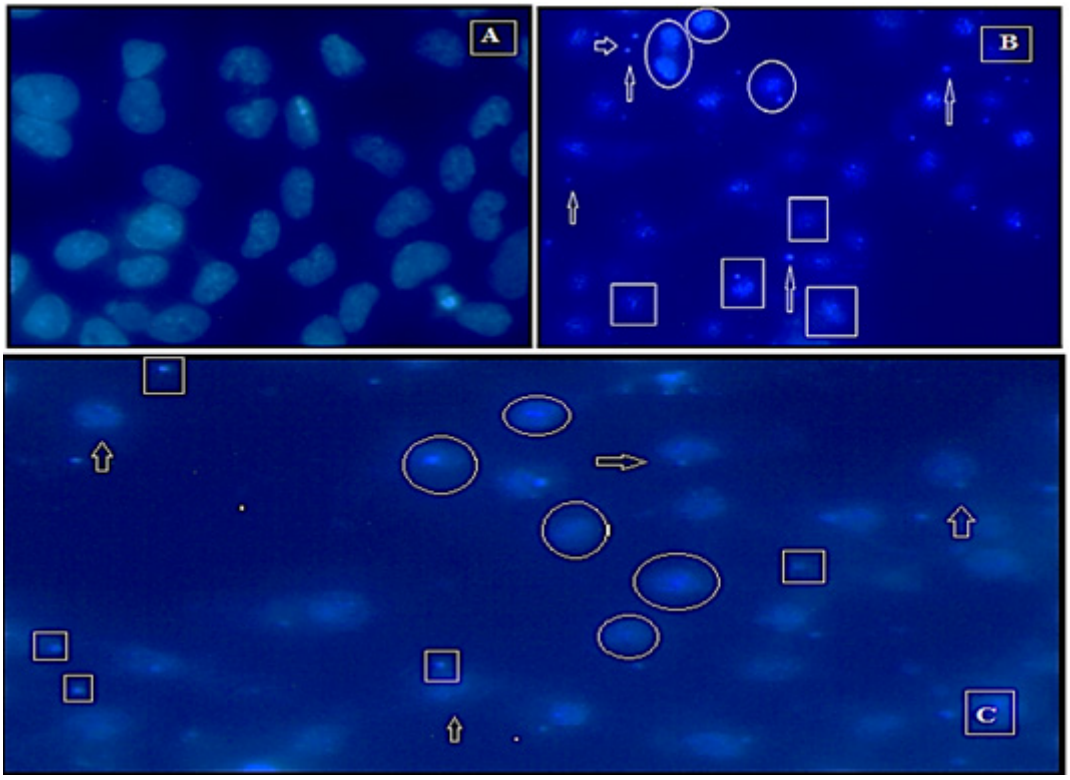

Figure 7: DAPI Apoptosis A) Normal Control B) CPT C) Optimized CPT Colloidosomes.

Table 2: Stability study data of evaluation of optimized CPT colloidosomes.

	Initial	1 Month	2Month	3 Month
%Drug Release	98.67±4.5	98.54±2.3	98.54±2.3	98.02±2.8
%Drug Content	94.06±0.04	94.82±0.08	94.08±0.35	94.11±0.15

are a sign of cell undergoing apoptosis.[60] In normal control cells, unharmed nucleus was observed where as in CPT Colloidosomes treated cells nuclear condensation and nuclear breakup of cells was observed.[61,62] This type of morphological alterations reveals cell apoptosis subsequent the treatment with CPT Colloidosomes indicating their powerful cytotoxic activity.[63,64] Furthermore, no significant difference in the drug content and cumulative % CPT release was observed for optimized colloidosomes at 40±2°C/75±5% RH after 3 months storage indicating its better stability.

CONCLUSION

In the present study, camptothecin-loaded colloidosomes were prepared and optimized based on vesicle size and % entrapment efficiency. Outcome form drug release, particle size, zeta potential and *in vitro* anticancer potential strongly recommends developed CPT loaded colloidosomes overcomes drawbacks associated with CPT and improves its half-life which is prime requirement of cancer treatment. Thus, the colloidosomes could be a potential approach for the efficient delivery of CPT in lung cancer treatment. Furthermore, establishing appropriate dosage guidelines and conducting comprehensive *in vivo* studies will be essential to evaluate the safety and efficacy of CPT Colloidosomes for potential clinical applications, paving the way for their integration into modern therapeutic strategies.

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ABBREVIATIONS

ADDS: Advanced drug delivery systems; **CPT:** Camptothecin; **SA:** Sodium Alginate; **FTIR:** Fourier Transforms Infrared Analysis; **DSC:** Differential Scanning Calorimetry; **XRD:** Powder X-ray Diffraction; **µg:** Microgram; **M.P:** Melting Point; **PDI:** Polydispersity index; **SD:** Standard Deviation; **nm:** Nanometer;

S1 to S11: Camptothecin Colloidosomes Batch no 1 to 11; **mV:** Milivolts; **ICH:** International Conference on Harmonization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

SG and KM: Investigation, Methodology, Writing-original draft, review and editing Visualization, Validation, Conceptualization, Resources, Supervision, Project administration. **AM and SH:** Methodology, Writing-review and editing, Supervision and Visualization. **MP and DB:** Writing: review and editing, Software, Visualization, Investigation, Methodology. **RT,LP,KB and AP:** Investigation, Methodology Software GK,PK,RK and KS: Writing-review, editing, Conceptualization, Resources, Supervision.

SUMMARY

Among the various cancers, lung cancer is the second leading cause of mortality after the breast carcinoma. Camptothecin (CPT) has broad spectrum anticancer potential used in the effective management of cancer including lung cancer. Outcome form drug release, particle size, zeta potential and *in vitro* anticancer potential strongly recommends developed CPT loaded colloidosomes overcomes drawbacks associated with CPT and improves its half-life which is prime requirement of cancer treatment. Thus, the colloidosomes could be a potential approach for the efficient delivery of CPT in lung cancer treatment.

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