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Original Article

Formulation and Evaluation of Pluronic F-127 Assisted Carboplatin Cubosomes

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ABSTRACT

Objectives: The objective of this study was to prepare carboplatin loaded cubosomes using high sheer homogenization technique. **Materials and Methods:** The cubosomes were prepared using Glyceryl Monooleate (GMO) as a lipophilic carrier along with pluronic F-127 (PF-127) and tween 80 as additive of the formulation. All the ingredients were subjected to chemical compatibility studies by Fourier Transform Infra-Red (FTIR) spectroscopy, thermal analysis using Differential Scanning Calorimetry (DSC), whereas X-ray Diffraction (XRD) studies were performed to evaluate the nature of drug in pure form as well as in formulation. The prepared cubosomes were characterized for their size and surface charge, surface morphology, drug release studies and drug permeation studies. **Results:** FTIR has confirmed the chemical compatibilities of the ingredients, while DSC has exhibited the thermal stabilities of the drug in alone as well as in cubosomes. The XRD has reviled that drug was crystalline, but upon incorporation in cubosmes, the crystallinity has reduced remarkably. The prepared cubosomes were of nanosized (diameter of 227 nm) and cubical in shape. The *in vitro* drug release and drug permeation studies have showed that concentration of both GMO and PF-127 has effected the release as well as permeation of the drug. However, in 3 hr studies the maximum amount of drug release was ~84% and that of permeation was ~74%. **Conclusion:** Conclusively, the selected composition of the formulation was suitable enough to prepare the nanosized cubosomes showing suitable entrapment efficiency of the drug.

Keywords: Anticancer, Cubosomes, *in vitro* drug release, *in vitro* permeation studies.

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INTRODUCTION

The anticancer drug carboplatin, also known as cis-diammine [1,1 cyclobutane dicarboxylato(2-)-0,0'], belongs to the second-generation and contains platinum.[1] Other cancers treated with carboplatin include head and neck, endometrial, esophageal, bladder, and cervical cancers, as well as tumors of the central nervous system and osteogenic sarcoma. It may be employed as well in high-dose therapy together with stem cell transplantation or transplanted bone marrow because it has no non-hematological effects.[2,3] It is helpful in numerous children's cancer treatment regimens due to the absence of long-term effects.[4]

In the presence of too much water, Glycerol Monooleate (GMO) has been shown to spontaneously transform into fluid crystalline cubic phases made up of bi-continuous bilayers of lipids that extend in three dimensions and divide into two sets of water channels.[5] Cubic phases can include and regulate the release of medicines with different molecular weights and polarity because of the special structure of GMOs.[6] There are three common macroscopic types of cubic phase: precursor, bulk, and particle (also known as cubosomes). Typically liquid, precursor materials only enter the cubic phase in reaction to external stimuli like dilution.[7] Bulk forms of the cubic phases are fluid-like crystalline substances that are often composed of hydrated monoolein and frequently contain a medication.[8] The bulk cubic gel is a superb option for use as a drug delivery matrix due to its high viscosity, biodegradability, capacity to integrate and distribute pharmaceuticals of various sizes and water solubilities, and capacity to improve the biochemical and/or physical properties of the included drugs. However, the cubic gel's substantial viscosity and stiffness restrict its ability to be used as a delivery system on its own.[9] Cubosomes are produced as a result of the cubic lipid phases being emulsified in water. These nanoparticulate dispersal systems have great bioadhesion and biocompatibility.[10] It has been established that the internal structure and properties of the bulk phase are retained by the dispersed particles. These adaptable systems of delivering drugs can be used for a variety of administration methods, including parenteral, intravenous, and percutaneous.[11] Cubosomal dispersions have some advantages

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over bulk gel, such as a higher surface area and great fluidity (low viscosity).[12] However, cubosomes are not anticipated to provide the same chances to control the release of drugs as compared to the bulk cubic phase because of their extremely small dimensions (and consequently short diffusion paths).[13] Additionally, the integration of water-soluble medicines is challenging due to the substantial quantity of liquid present during cubosome formation.[14]

This study aims at creating a cubic phasic gel matrix containing the hydrophilic medication (carboplatin), which may be dispersed in water to create a cubosomal nanoparticle dispersion. To investigate the cubosomes' capability as a specialized system for drug delivery that could safely deliver the highest possible concentration of carboplatin, the *in vitro* properties were assessed.

MATERIALS AND METHODS

Materials

Glycerol monooleate (GMO), Pluronic F-127, carboplatin, and tween 80 were purchased from Sigma-Aldrich (Milwaukee, USA). D. All the chemicals used were of analytical grade.

Method of Preparation

Cubosomes are prepared using a similar methodology as used in the previous study, following the composition of formulation depicted in Table 1.[15] Both Pluronic F-127 and GMO were melted at 70°C to create blank cubic gel. To produce a homogeneous state, the resultant molten solution was vortexed at high speed at room temperature while being added dropwise to distilled water (70°C). During this stage, the drug was introduced and thoroughly mixed to create a homogeneous solution. To create the cubosomes, the mixture was allowed to equilibrate at room temperature for 48 hr (Figure 1).

A ratio between the Pluronic F-127, GMO and Tween 80 has been used.

Characterization tests

Spectrophotometric analysis

The spectrophotometric assay adopted for carboplatin analysis by screening of carboplatin in the distilled water using UV spectrophotometer (Shimadzu, 2401/PC, Japan) through a scan range of 200–400 nm. Stock solution of 1 mg/mL was prepared, and then further dilutions were prepared, and their absorbance were recorded.

Fourier Transform Infrared Spectrophotometer (FTIR)

For FTIR analysis, a small quantity of all samples as well as of all the formulations were used. Data of infrared transmittance was screened over a wave number between 600 to 3800 cm^{-1}. Spectrums were recorded in FTIR instrument (Perkin Elmer Spectrum Two, USA), by means of PC based software-controlled instrument operation and processing of the data.

pH

Without dilution beforehand, the pH of the samples was measured at 25°C with a certified pH meter.

Viscosity

Utilizing the Brookfield DV III Ultra V6.0 (Brookfield Engineering Laboratories, Inc., Middleboro, MA) at 25°C, the viscosity of the formulations was assessed without dilution.

Zeta potential and Particle size analysis

By employing Zeta Sizer Nano-series (Nano ZS, Malvern, Worcestershire, UK) dynamic light scattering, particle size distribution (Z-average) and zeta analysis were carried out. Samples have been diluted (100-fold) in distilled water before being tested in triplicate at 2570.5 1C.[15]

Scanning Electron Microscopy (SEM)

The morphology and structure of the cubosomes were examined using the scanning electron microscopy technique (ZEISS EVO LS10 Germany) with direct point-resolution. To conduct the SEM observations, a drop of the produced formulation was immediately placed to the grid of the holey film, and the images were taken after drying.

X-ray Diffraction (XRD)

Using an X-ray diffractometer (JDX-3523, JEOL, Tokyo, Japan), an X-ray Diffraction investigation of pure drug and carboplatin loaded cubosomes were performed. The pure drug and cubosome formulation were packed securely into an aluminum cell and then were subjected to Cuka monochromatic radiation of wavelength 1.54056 A°. Samples were examined between 5° and 60° using 2θ at a rate of 3°/min.[16]

Drug entrapment efficiency (%)

Entrapment Efficiency (EE) is an important parameter to check the suitability of material used in formulation as well as the employed method. The prepared cubosomal dispersion was centrifuged at 10,000 rpm in centrifuge machine and the supernatant was taken from the mixture after centrifugation and analyzed spectrophotometrically to find the un-entrapped drug. The quantification was performed by using double beam UV-visible spectrophotometer at the wavelength of 254nm, and %EE was calculated by following mathematical expression.[17]

$$\%EE = (\text{Total drug added} - \text{Free drug} \div \text{Total drug added}) \times 100$$

In vitro drug release studies

Based on the USP XXIV technique, an *in vitro* release test was carried out in 500 mL of distilled water (Dissolution apparatus #

2, at 50 rpm and 37.5 degrees C).[18] The dialysis bag was filled with one milliliter of the formulation. At regular times (0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 20, 24 hr), samples (1 mL) were taken out and a small amount of distilled water was added in their place. After that, the samples were examined with a UV spectrophotometer at 254 nm.[19]

In vitro permeation studies

The Franz diffusion cell was used for *in vitro* permeation experiments. The donor compartment and recipient compartment each received 1 mL of sample and 7 mL of buffer. The drug might flow through because the membrane of cellophane was left exposed. To ascertain how much of the drug had permeated, the samples, each 1 mL in volume, were gathered at various periods and adequately diluted before being examined with UV light.

Stability studies

Centrifugation

The synthesized formulations were subjected to stability investigations, which involved centrifuging them for 30 min at 5000 rpm using a Refrigerated microcentrifuge, INNO MC 16R. After that, the generated cubosomes were evaluated.[20]

Freeze thaw method

The chemical compositions were transferred to NMR tubes for the freeze-thaw cycling after they had undergone centrifugation as part of the freeze-thaw technique investigations. The samples were then frozen for 2 hr each day in a -20°C freezer, melted at 40°C for 1 hr, and then kept at 25°C for analysis.[20]

Thermal stability analysis (DSC)

The optimized formulation was thermally analyzed using a Differential Scanning Calorimeter (DSC) and thermogravimetric analyzer (TG analyzer; PerkinElmer STA 6000, USA). For DSC analysis, the formulation sample was put in closed aluminum pans and heated at a flow rate of 10°C/min from 25 to 40°C. The samples' DSC thermogram were used to record the peak transition temperature.[21]

RESULTS AND DISCUSSION

The studies were designed to formulate the cubosomal formulation of carboplatin and its carious characterization. High share homogenization technique was turned fruitful, as the nanosized cubosomes had been prepared successfully. Various combinations and compositions have been tried but the combination of PF-127 and tween 80 with GMO was found useful. The formulations were evaluated for a variety of characteristics and the outcomes have reviled that the trials were successful.

Spectrophotometric analysis

At a wavelength of 254 nm, a calibration curve for carboplatin was built with concentration along the horizontal x-axis and absorption along the vertical y-axis.

Fourier Transform Infrared Spectrophotometer (FTIR)

The FTIR spectrum of formulation showed similar peaks to that of reported spectrum of pure drug and other excipients used.

PF-127 exhibited a stretching region of C-H in the ranges of 2810-2889 cm^{-1}. Prominent peaks of alcohols, carboxylic acids and ethers have also been observed at 1075 cm^{-1}, 1100 cm^{-1} and 1120 cm^{-1} respectively.[22] Similarly, the FTIR scan of GMO showed sharp and intense peek corresponding to C=O at about 1700 cm^{-1} and a broad band appeared at 3320-3400 cm^{-1}, showing the presence of –OH group. On the other hand, the FTIR spectrum of carboplatin has shown characteristic peaks, corresponding to the ester groups (C=O) at 1640 cm^{-1} and C-O at 1345 cm^{-1}. The peeks associated with the NH group was appeared at 3270 cm^{-1}, whereas, the bands appeared at 2955 and 2861 cm^{-1} were due to the presence of asymmetric and symmetric CH stretching

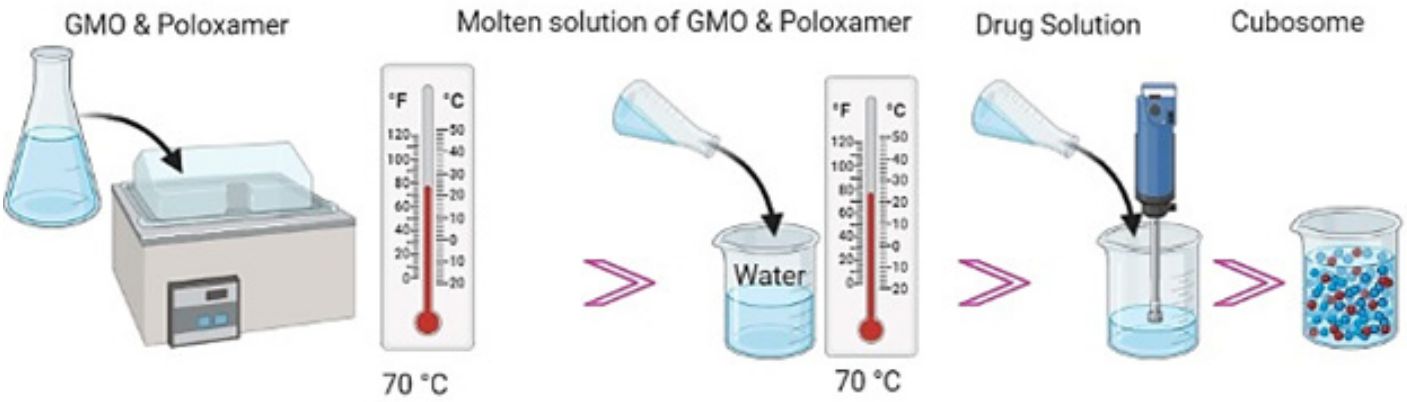

Figure 1: Illustration of method used for the preparation of cubosomes.

Table 1: Composition of Formulations, describing different ratios of the used ingredients.

Formulations	Pluronic F-127	GMO	Tween 80
F1	0.3	1	0.5
F2	0.35	1	0.3
F3	0.4	1	0.25
F4	0.5	1	0.2

Table 2: Describing the pH and viscosity outcomes of prepared formulations.

Formulations	pH	Viscosity (cP)
F1	6.8 ± 0.2	16.09 ± 0.89
F2	6.7 ± 0.3	22.98 ± 0.45
F3	6.4± 0.1	35.12 ± 0.95
F4	6.6 ± 0.2	41.44 ± 0.12

vibrations, respectively.[23] However, in the FTIR scan of prepared formulation, it has been noticed that all the characteristic peeks of drug and other excipients were present, confirming the chemical compatibilities of the ingredients (Figure 2).

pH of the formulation

The pH and viscosity of the formulations were studied, and it has been observed that both the parameters were quite satisfactory. The pH was neither strongly acidic nor the strong basic (Table 2).

Viscosity of the formulation

Viscosity was found effecting different parameters including drug release and drug permeation. The formulations with lesser viscosity have released greater amount of the drug and vice versa. The prepared formulation's viscosity spans from 16.09 to 41.44 cP. Faster release of drugs from the formulation is ensured by reduced viscosity, which encourages quick absorption and, as consequently, a speedy start of action.

Zeta potential and Particle size analysis

Figure 4 shows that the average zeta potential of cubosomes carrying carboplatin was 0.1 mV. The carboplatin-loaded cubosomes' mean particle size was calculated to be 227.7 nm, as illustrated in Figure 3. In comparison high poloxamer concentrations are advantageous for the development of smaller particles and also favor vesicular particle formation over the intended cubic structure particle formation.[24]

Scanning Electron Microscopy (SEM)

The cubosomes' surface morphology has been studied using scanning electron microscopy. The findings revealed that nanosized, somewhat cubic-shaped particles had been found. Additionally, it has been shown that the particles are well disseminated and segregated, which indicates an even formulation (Figure 4).

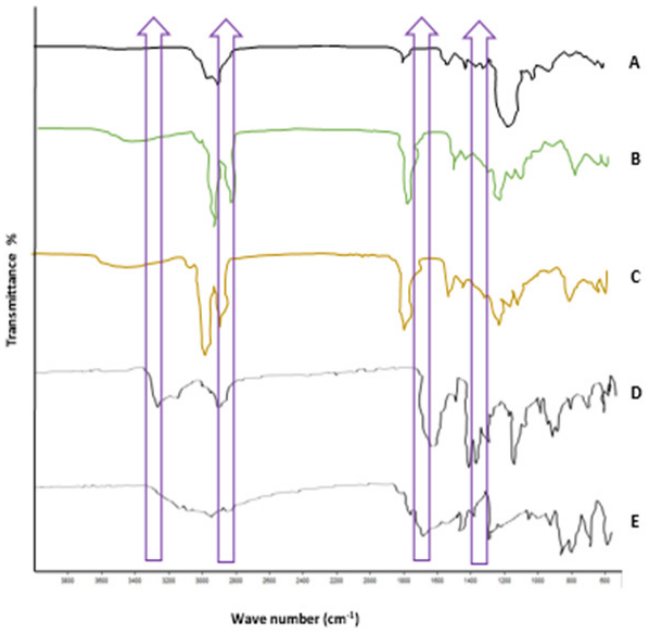

Figure 2: FTIR Spectrum of (A) Tween 80, (B) Pluronic F-127, (C) GMO, (D) Carboplatin, (E) Formulation.

X-ray Diffraction (XRD)

XRD studies have described that pure drug is crystalline in nature, exhibiting sharp and intense peeks at different angles. However, the drug in formulation has lost the crystallinity, as diffuse and undistinguishable peeks have been observed. This is the indication that the drug has been completely immersed and entrapped in the cubososmal structure (Figure 5).

Drug entrapment efficiency

The entrapped drug was ranging from 82-94%. F1 has entrapped 82%, F2, 85%, F3 89% and F4 entrapped maximum amount of the drug, i.e., 94%. It might be due to the fact that PF-127 along with tween 80 has great ability to improve the drug entrapment in cubosomes. Hence, it could be considered that there was gradual increase in the concentration of the PF-127, that lead to increase in the entrapped amount of the drug in prepared formulations.

In vitro drug release studies

The results of drug release *in vitro* experiments at 254 nm are depicted in Figure 2. In comparison to the other formulations, F4 had demonstrated a higher drug release. As the proportions of Pluronic F-127 and GMO were raised, a discernible increase

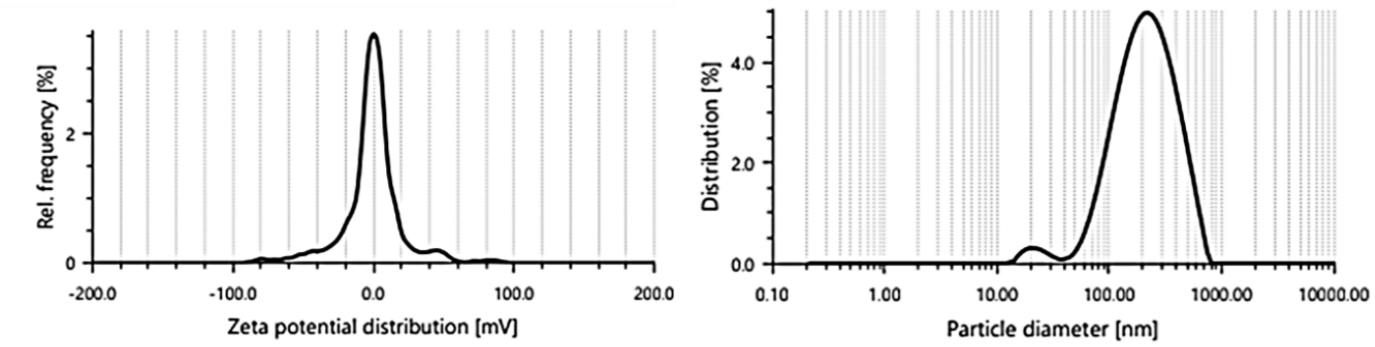

Figure 3: Representation of zeta potential and particle size analysis of prepared cubosomes.

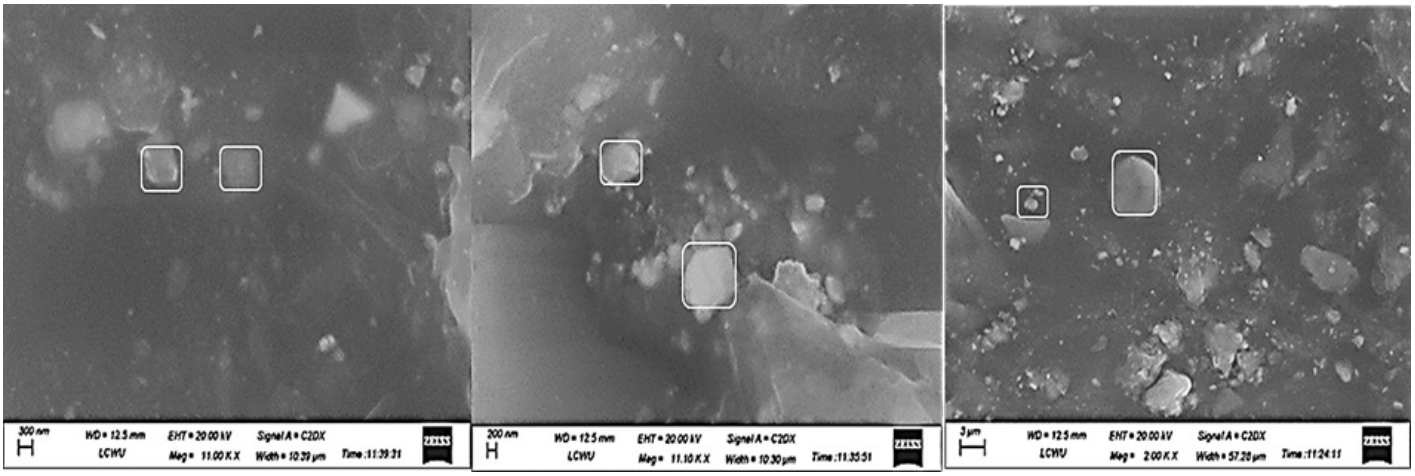

Figure 4: Scanning Electron Microscopy, indicating nano-sized particles with suitably cubic shaped structures.

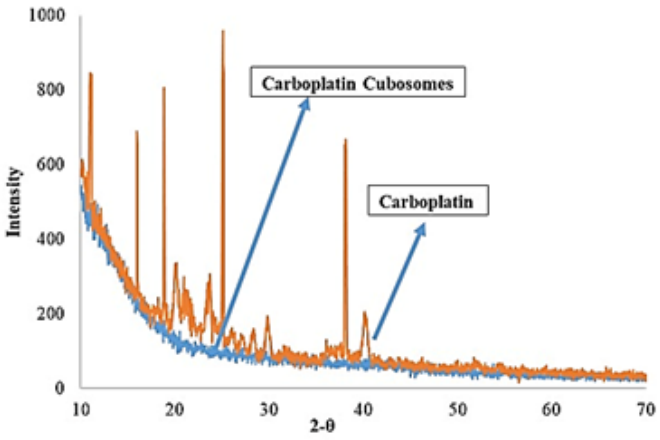

Figure 5: XRD patterns of carboplatin and cubosomes.

in drug release was noted. It has been observed that formulation with greater concentration of Pluronic F-127 had shown greater released concentration of the drug. it has been an established fact that the poloxamers have the ability to increase the release and dissolution profile of various drugs. Similar outcomes have been noticed in current studies.[25,26]

In vitro permeation studies

After being removed from the procedure at various intervals of time, samples were measured for absorbance at 254 nm wavelengths. The relationship between concentration and absorbance was shown as a graph. In Figure 6, the percentage of drug formulations that pass through the membrane is represented graphically. With the largest amounts of Pluronic F-127 and GMO compared to the other formulations, F4 had the highest drug permeability of all the formulations. The trend in outcomes is similar to that of release of the drug. The poloxamers have also been considered in the class of surfactants, and surfactants are considered to increase the drug permeability of the drugs as well. Hence, the combination of a lipid with surfactant turned useful in not only increasing the release of the drug as well as permeability from the prepared cubosomes.

Stability Studies

Centrifugation

The formulations were subjected to study using the freeze-thaw method after centrifugation because there were no indications of phase separation or of any kind of instability. Recent studies have revealed that the method of centrifugation involves utilizing

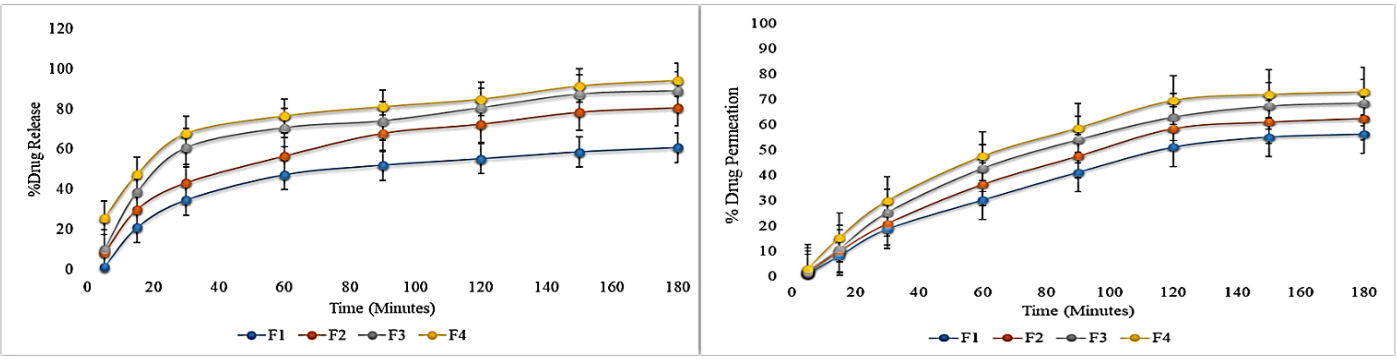

Figure 6: Describing the drug release and drug permeation studies of carboplatin from cubosmes.

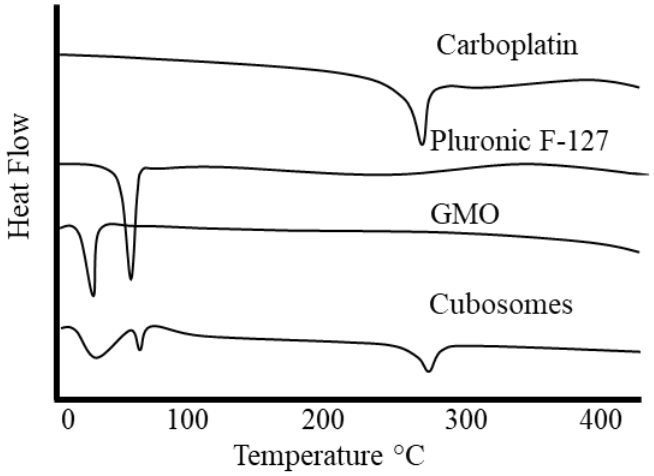

Figure 7: DSC analysis of Carboplatin, GMO, Pluronic F-127, and Carboplatin loaded Cubosomes.

a device known as a centrifuge that utilizes the centrifugal force as a tool to separate heterogeneous materials in both commercial and scientific environments. However, no layer or particle sedimentation has been seen following the test, suggesting a stable formulation.

Freeze Thaw Method

The formulations were highly stable because there was no evidence of particle sedimentation. The thawing process is more delicate and improves the dewatering outcomes. Temperature around 20°C in a water bath or in ambient air provide the ideal thawing conditions.[27,28]

Thermal stability analysis (DSC)

Figure 7 displays the DSC thermal imaging of cubosomes made from the carboplatin formulation. It is apparent that the DSC thermogram of carboplatin has a single distinct, an endothermic melt peak, which is consistent with earlier data.[29] The individual ingredients have shown their characteristics endotherms, representing their corresponding melting points, such as carboplatin showed a strong endotherm at 280-285°C, Pluronic F-127 and GMO at 55-60°C and 30-35°C respectively. Several studies have reported the similar behavior of these ingredients.[30-32] However, in the formulation these endotherms were broader with considerably less intense peaks. The drug, that has shown a very sharp endotherm alone, has exhibited a broader and less intense peak, confirming its entrapment in cubosomes.

CONCLUSION

The objectives of nanosized cubosomes of carboplatin have been achieved successfully. The application of homogenization in the formulation preparation was found to be useful. The use of GMO has once again proved to facilitate the preparation of cube like structure. The use of PF-127 and tween 80 was good additives and found supportive in preparing the particles with suitable amount of entrapped drug and capable of releasing and permeating more than 70% of the drug. In short, the selected method and composition of the formulation is suitable for the preparation of anticancer cubosomes that is hydrophilic in nature.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GMO: Glyceryl monooleate; **FTIR:** Fourier transform infra-red; **DSC:** Differential scanning calorimetry; **EE:** Entrapment efficiency.

SUMMARY

This study aimed to create carboplatin-loaded cubosomes using high sheer homogenization technique. The cubosomes were prepared using Glyceryl Monooleate (GMO), Pluronic F-127 (PF-127), and tween 80 as additives. Chemical compatibility studies were conducted using FTIR spectroscopy, DSC, and XRD. The cubosomes were characterized for size, surface charge, drug

release, and permeation. Results showed that the concentration of GMO and PF-127 affected drug release and permeation, with a maximum of 84% and 74% in 3 hr studies.

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