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ORIGINAL ARTICLE

Preparation, Characterization, and Optimization of Abimaciclib-Loaded Mesoporous Silica Nanoparticles for Tumor Targeting Cytotoxicity and *In Vitro* Cell Line Studies

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Abstract

Background: The current investigation involves preparation and characterization Abimaciclib (ABE) loaded mesoporous silica nanoparticles. A tremendous amount of research and development has gone into using mesoporous silica nanoparticles as drug delivery system carriers in the past ten years. This study primarily aims to synthesise silica carriers using sol-gel technology. **Methods:** The materials employed include tetraethyl orthosilicate (TEOS) as the silica precursor and cetyltrimethylammonium bromide (CTAB) as the pore manufacturing agent. To tweak the synthesis conditions, we played around with the TEOS molar ratio, stirrer speed, and CTAB quantity. The zita-potential and field emission scanning electron microscopy (FESEM) methods were used to identify the silica particles. **Results:** According to the findings, the specific surface area and porosity of silica particles were significantly impacted by the introduction of CTAB and the quantity of water. Mesoporous silica particles are able to disperse and remain stable despite their very reactive surfaces. The formulations were optimized using a Box- Behnken design, and their physicochemical properties were assessed. In terms of particle size, zeta potential, and entrapment efficacy, the improved ABE-MSNP formulation performed admirably. A FE-SEM examination confirmed the shape of the ABE-MSNP. Research conducted outside of living organisms confirmed that ABE-MSNPs-OPT have a permeability of. **Conclusion:** These results show that ABE-loaded mesoporous nanoparticles, when taken orally, could be a new way to deliver anti-cancer medication. Abemaciclib-loaded MSNs may warrant further investigation as a drug-delivery approach. The reported findings should be interpreted in view of the in vitro and ex vivo study design.

Key words: Abimaciclib, Cetyltrimethylammonium bromide, Silica, Tetraethyl orthosilicate

INTRODUCTION

To meet the demands of applications in the many domains of information technology, consumer items, medicine, and environmental health, research and design of nanomaterials have significantly increased. Their biocompatibility with medicinal drugs is exciting, which allows them to interact well with single cells. Long circulation periods in biological and blood media, limited non-specific interactions, and consequently excellent specificity for intended target cells and tissues are typical benefits of these nanosystems.[1] Mesoporous silica nanoparticles (MSNs) are including high surface area. The surface hydroxyl groups of MSNs (both the outside and inside of the pores) are readily functionalized, rendering MSNs intriguing multifunctional nanocarriers for use in biomedical applications. The majority of MSNs can be produced with simple, low-cost procedures. Some authors argue that parameters, such as particle dosage, surface and shape, mesoporous structure, pore size, and particle size, are less important than the biological media

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response of MSNs when it comes to their biomedical applications. Despite multiple *in vitro* and *in vivo* studies showing the good biocompatibility of both there has been a dearth of clinical trials reporting on the effect of MSNs administered through diverse routes on 100% clearance from human organisms.[2]

MATERIALS AND METHODS

Materials

Abimaciclib (ABE) was obtained from Eli Lilly Pvt. Ltd, Tetra-Ethyl-Ortho-Silicate (TEOS), Cetyl-Trimethyl Ammonium Bromide (CTAB), and 3-amino-propyl trimethoxy silane were procured from Loba Chemie Pvt. Ltd., Mumbai. Other chemicals and the reagents used were of analytical grade.

Methodology

Fourier transform-infrared (FTIR) spectrum interpretation

The FTIR spectra (Shimadzu®, Tokyo, Japan) were captured using an IR prestige-21 instrument. In the solid state, FTIR may assess the relationship among Mesoporous silica nanoparticles and therapeutic molecules. The main element of MSNs is silica, and unique peak shapes corresponding to Si-O-Si vibrations of stretching frequently appear in the FTIR spectrum. The existence of mesopores in silica could influence the FTIR spectra. A wide peak suggests the presence of surface hydroxyls. The Changes in peak locations or intensities during chemical adsorption on MSNs may indicate specific bonds involving the surface groups that are functional.[3,4]

Differential scanning calorimetry (DSC)

The ABE, CTAB, blank, and ABE-MSNNP DSC thermograms were obtained with a DSC Q2000 instrument. Each sample was weighed into T zero aluminum pans and covered with T zero lids. The samples were then scanned at a rate of 10°C/min, covering a temperature range of 30–350°C. The samples were collected using an empty reference pan and a nitrogen stream at a rate of 50 mL/min.[5]

Powder X-ray diffraction (PXRD)

The PXRD patterns were captured utilizing an X-ray diffractometer (X-ray generator, model 1729; Philips, Eindhoven, Netherlands). The specimens were investigated during irradiation with monochromatized CuKa radiation at temperatures ranging from 2°C to 80°C. For pattern collection, a voltage of 30 kilovolts and a current of 30 mA were utilized. The scanning velocity was established at 10°C/min (2 cycles/min).[6]

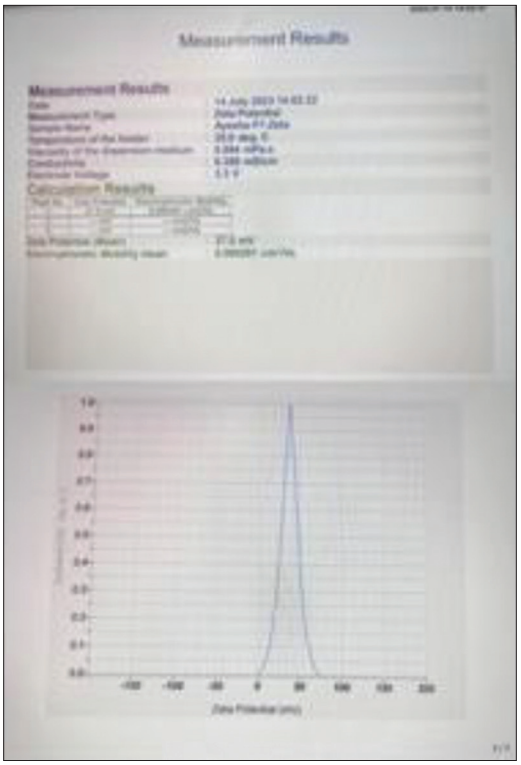


Figure 1: Particle size and zeta potential determination

Formulation development

Preparation of drug-loaded mesoporous silica nanoparticles

A magnetic stirrer was used to constantly swirl a mixture of 200 mL of distilled water, 60 mL of anhydrous ethanol, and a precisely weighed quantity of 1.6 g of CTAB and 0.075 g of ABE at room temperature when the mixture was formed. Then, 40 mL of di-ethyl ether and 1.6 mL of ammonia solution were added to the clear solution. The product was finally subjected to 6-h air calcination at 550°C to remove any remaining organic components unrestricted drying.[7]

Drug loading procedure

By using the solvent evaporation technique, ABE-loaded mesoporous silica nanoparticles (ABE MSNs) have been developed. MSNs were added to the drug solution after a drug had been well dissolved in chloroform, stirring continuously for 24 h and the solvent has been evaporated. The solvent was subsequently evaporated, while being stirred at room temperature, and it was allowed to dry overnight. The dried ABE MSNs were kept in an airtight container until further investigation.[8]

Factorial design for formulation of ABE-NGs

We started by conducting trial experiments to determine which variables were most crucial and to get a sense of

approximately where the optimal values should be placed. The entrapment efficiency (EE), zeta potential, and size of the vesicles were investigated in relation to the three variables: Surfactant speed, polymer concentration, and agitation speed. Crosslinker, Dimethylformamide, and cyclodextrin concentrations ranging from 25 to 150 mg, 50 to 125 mg, and 5 to 20 mL. The following equation illustrates this equation.

$$Y = b0 + b1x1 + b2x2 + b3x3 + b4x4 + b12x1x2 + b13x1x3 + b23x2x3 + b11x21 + b22x22 + b33x23 \quad (1)$$

Table 1: Design and optimization of mesoporous silica nanoparticles

Factors (X)	Response (Y)
CTAB (X1)	Particle Size (Y1)
TEOS (X2)	Entrapment efficiency (Y2)
Stirring speed (X3)	Zeta Potential (Y3)

TEOS: Tetraethyl orthosilicate, CTAB: Cetyltrime thylammonium bromide

Table 2: Factors and responses used in Box-Behnken design

Factors	−1	0	+1
X1: CTAB (g)	0.3	0.6	0.9
X2: TEOS (mL)	5	7.5	10
X3: Stirring speed (rpm)	500	600	700

TEOS: Tetraethyl orthosilicate, CTAB: Cetyltrime thylammonium bromide

Evaluation and characterization of MSN

Physical appearance

Particle size

Using ELS-Z2 (Osaka, Japan), the particle size and zeta potential of MSNs were determined. After 5 min of sonication, 5 mg of MSNs were suspended in 10 mL of phosphate-buffered saline buffer (10 mM, pH 7.4). At 25°C, a 90° angle was used to measure the prepared suspension. Furthermore, all samples were appropriately diluted with distilled water before to testing. The parameters were measured 50 times.[9-12]

Zeta potential

The zeta potential, a measure of surface charge, can be calculated using particle size equipment with an additional electrode. Electrostatically stable particles have zeta potentials that are

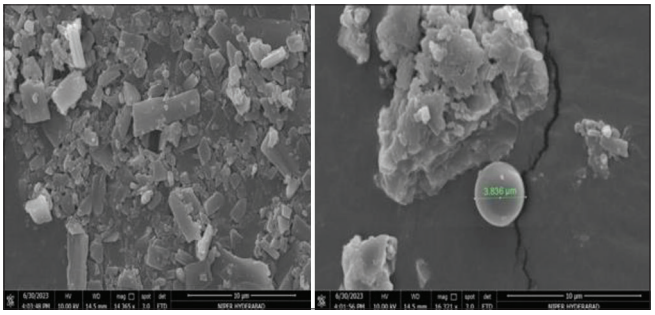


Figure 2: Scanning electron microscopy of drug-loaded nanoparticles *in vitro* drug release study

Table 3: Independent variables and dependent variables in BBD

Runs	Factors			Response		
	X1: CTAB (g)	X2: TEOS (mL)	X3: Stirring speed (rpm)	Y1: Particle size (nm)	Y2: EE(%)	Y3: Zeta potential (mv)
ABE1	0.6	7.5	600	179	74.3	38.2
ABE2	0.6	5	700	175.3	74.9	37.9
ABE3	0.3	7.5	700	153	68.5	36.6
ABE4	0.3	7.5	500	151.6	66.9	36.8
ABE5	0.6	7.5	600	179.2	73.9	38.3
ABE6	0.6	10	500	181	74	38.5
ABE7	0.6	10	700	183	75	38.1
ABE8	0.6	7.5	600	179.5	73.9	38.7
ABE9	0.9	7.5	500	182.1	78.8	39.3
ABE10	0.9	10	600	186.2	78.6	39.5
ABE11	0.6	7.5	600	179.9	73.9	38.8
ABE12	0.6	5	500	177.9	73.5	37.5
ABE13	0.3	10	600	155	68.1	36.9
ABE14	0.9	5	600	180.1	79.9	39.4
ABE15	0.6	7.5	600	180	73.6	38.9
ABE16	0.9	7.5	700	184	78	39.2
ABE17	0.3	5	600	149	67.9	36.7

TEOS: Tetraethyl orthosilicate, CTAB: Cetyltrime thylammonium bromide, BBD: Box-Behnken design

more than or less than these limitations. Mesoporous silica nanoparticles were used in this study [Figure 1]. The saturated containing substances and diluted having 0.1 mol/1 KCL prior inserting them in an electrophoretic cell with an electricfield strength of 15 V/cm all around. We calculated the overall hydrodynamic diameter through taking the mean of all values.[13]

EE

Using an ultraviolet spectrophotometer, the amount of drug encapsulated within the MSNPs was ascertained. To dissolve the medication, 10 mg of precisely weighed MSNNPs were mixed with 10 mL of methanol and extracted in a phosphate buffer solution (pH 6.8). The percentage EE in the filtrate was ascertained at 236 nm following the proper dilution with phosphate buffer solution.[14] The following equations were used to compute the encapsulation efficiency (%EE):

%EE = Weight of drug in MSNPs/Theoretical weight of drug × 100

Zeta potential analysis

As an indicator of the physical stability of a colloidal system, its zeta potential is computed from the surface charges of its particles. It is possible to measure the particulate size by supplementing the instrument with an additional electrode. The nanoparticles were diluted with 0.1 mol/L KCl. At a temperature of 25°C, an electric field of approximately 15 V/cm was introduced, and the zeta potential of the dispersion of ABE-MNPs by Laser Doppler Micro electrophoresis was determined utilizing a Zeta sizer produced by Malvern Instruments of Malvern, United Kingdom.[15]

Table 4: Response 1: Particle size

Source	Sum of squares	Degree of freedom	Mean square	F-value	*P*-value	
Model	2581.74	9	286.86	657.83	<0.0001	Significant
A-CTAB	1915.81	1	1915.81	4393.33	<0.0001	
B-TEOS	65.55	1	65.55	150.32	<0.0001	
C-Stirring speed	0.9113	1	0.9113	2.09	0.1915	
AB	0.0025	1	0.0025	0.0057	0.9418	
AC	0.0625	1	0.0625	0.1433	0.7162	
BC	5.29	1	5.29	12.13	0.0102	
A^2	588.76	1	588.76	1350.15	<0.0001	
B^2	0.1684	1	0.1684	0.3862	0.5540	
C^2	0.0421	1	0.0421	0.0966	0.7651	
Residual	3.05	7	0.4361			
Lack of Fit	2.19	3	0.7308	3.40	0.1340	Not significant
Pure error	0.8600	4	0.2150			
Cor total	2584.79	16				

TEOS: Tetraethyl orthosilicate, CTAB: Cetyltrime thylammonium bromide

Table 5: Response 2: Entrapment efficiency

Source	Sum of squares	Degree of freedom	Mean square	F-value	*P*-value	
Model	247.86	9	27.54	178.42	<0.0001	Significant
A-CTAB	240.90	1	240.90	1560.67	<0.0001	
B-TEOS	0.0313	1	0.0313	0.2025	0.6664	
C-Stirring Speed	1.28	1	1.28	8.29	0.0237	
AB	0.5625	1	0.5625	3.64	0.0979	
AC	1.44	1	1.44	9.33	0.0185	
BC	0.0400	1	0.0400	0.2591	0.6264	
A^2	2.68	1	2.68	17.35	0.0042	
B^2	1.06	1	1.06	6.89	0.0342	
C^2	0.0221	1	0.0221	0.1434	0.7162	
Residual	1.08	7	0.1544			

TEOS: Tetraethyl orthosilicate, CTAB: Cetyltrime thylammonium bromide

Table 6: Response 3: Zeta potential

Source	Sum of squares	Degree of freedom	Mean square	F-value	*P*-value	
Model	13.97	9	1.55	32.98	<0.0001	significant
A-CTAB	12.25	1	12.25	260.27	<0.0001	
B-TEOS	0.4513	1	0.4513	9.59	0.0174	
C-Stirring Speed	0.0050	1	0.0050	0.1062	0.7540	
AB	0.0225	1	0.0225	0.4780	0.5116	
AC	0.0100	1	0.0100	0.2124	0.6588	
BC	0.1600	1	0.1600	3.40	0.1078	
A^2	0.3360	1	0.3360	7.14	0.0319	
B^2	0.2276	1	0.2276	4.84	0.0638	
C^2	0.3981	1	0.3981	8.46	0.0227	
Residual	0.3295	7	0.0471			
Lack of Fit	0.0375	3	0.0125	0.1712	0.9106	Not significant
Pure Error	0.2920	4	0.0730			
Cor Total	14.30	16				

TEOS: Tetraethyl orthosilicate, CTAB: Cetyltrime thylammonium bromide

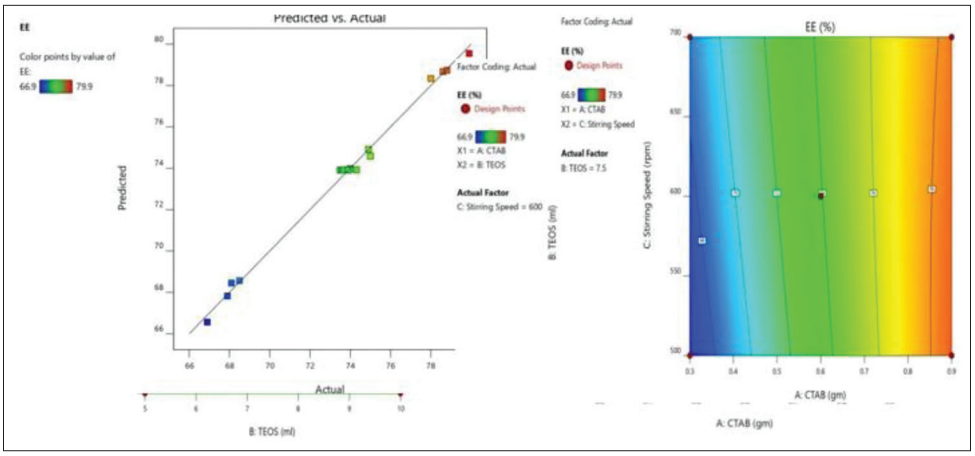


Figure 3: Effect of independent variables on % entrapment efficiency

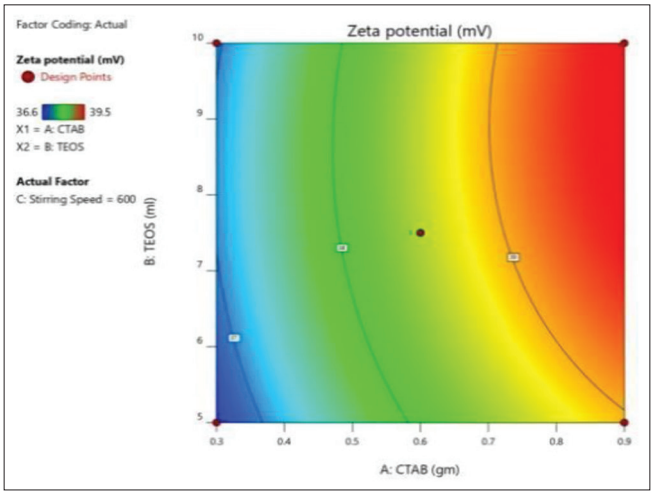


Figure 4: Effect of independent variables on zeta potential

Scanning electron microscopy (SEM) analysis

We independently analyzed the surface morphology of the freeze-dried and reconstituted nanoparticles using SEM. Before imaging, samples of mounted freeze-dried nanoparticles were sputtered with platinum was adsorbed using carbon membranes. After that, the cassettes were allowed to cure for 24 h at room temperature (25°C). Before the freeze-drying process, an analysis was conducted on the surface morphological characteristics of the nanoparticles [Figure 2].[16]

These samples were filtered through Whatman filter papers before being analyzed at a designated μ max of ABE.[17]

Table 7: The point prediction

Factor	Name	Level	Low level	High level	Standard deviation coding	
A	CTAB	0.6000	0.3000	0.9000	0.0000	Actual
B	TEOS	7.50	5.00	10.00	0.0000	Actual
C	SrirringSpeed 600.00		500.00	700.00	0.0000	Actual

TEOS: Tetraethyl orthosilicate, CTAB: Cetyltrime thylammonium bromide

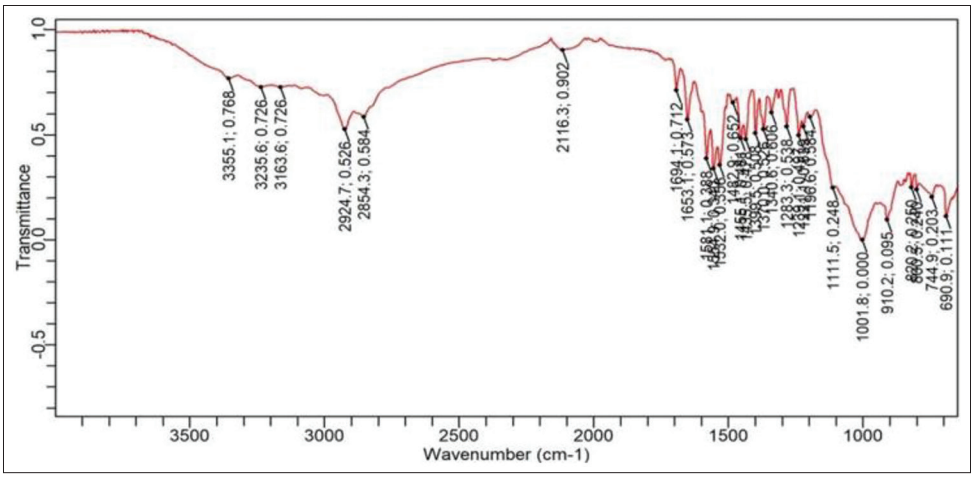


Figure 5: The spectra of drug loaded silica particles

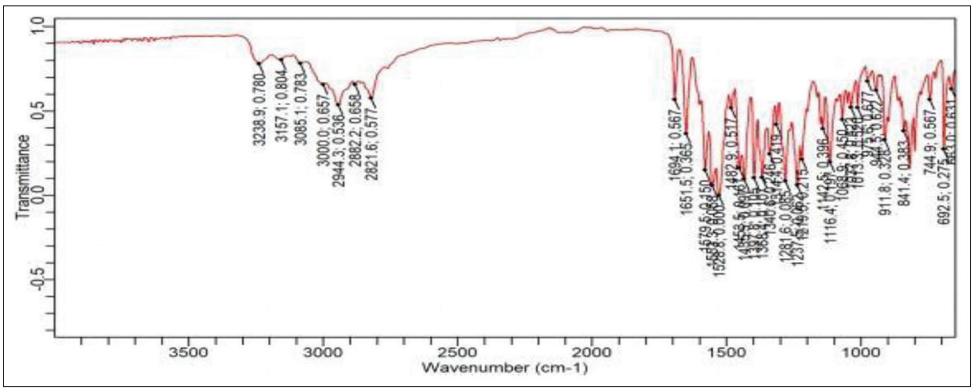


Figure 6: Physical mixture of compound

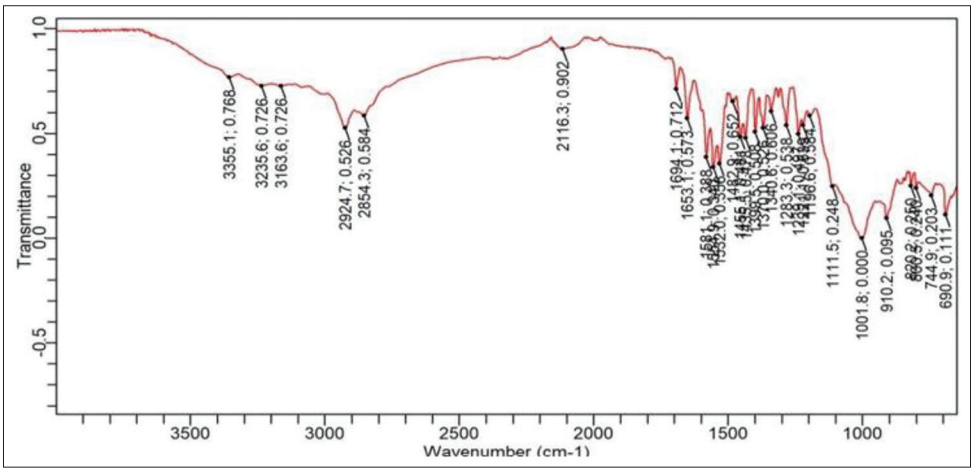


Figure 7: Pure drug form

RESULTS AND DISCUSSION

Box-Behnken design (BBD) is a good tool for response surface design analysis and parameter level optimization. Factor selection and ranges were based on screening [Tables 1-3] with the CTAB amount (X1, g), TEOS volume (X2, mL), and stirring speed (X3, rpm) set in the ranges presented in, each response's stated model was examined using analysis of variance (ANOVA).[18,19]

Effect of independent variables on particle size: ANOVA for quadratic model

Response 1: Particle size

The CTAB amount (X1, g), TEOS volume (X2, mL), and stirring speed (X3, rpm) were estimated [Table 4] to determine the ranges for factor selection and screening. Particle size

Table 8: Observed values of particle size, entrapment efficiency, zeta potential

Response	Predicted mean	Predicted median
Particle size	179.6	179.6
Entrapment efficiency %	73.92	73.92
Zeta Potential	38.54	38.54

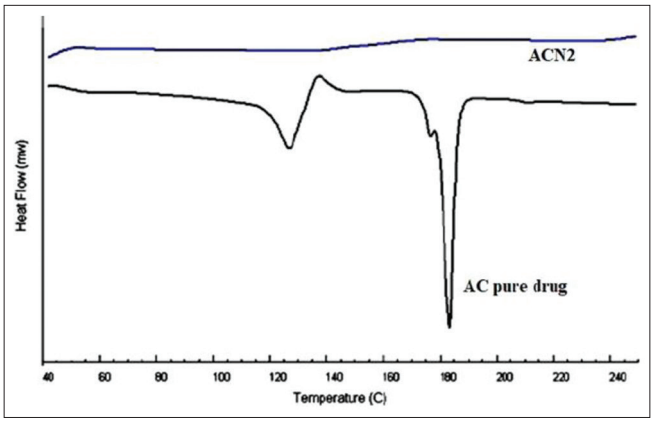


Figure 8: Differential scanning calorimetry of pure drug and formulation

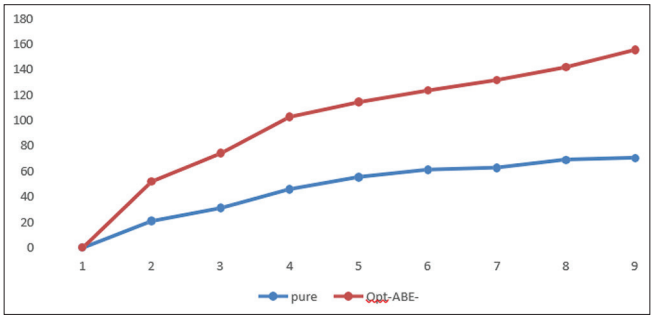


Figure 9: The % drug release *in vitro* studies

Table 9: Test compounds treated (ABE-Suspension [standard]) with MCF-7 cells showing the IC_{50} values

Concentration (µg): Opt-MSN ABE	Absorbance at 570 nm (1)	Absorbance at 570 nm (2)	Absorbance at 570 nm (3)	Mean	% inhibition	% Viability	IC_{50} (µg)
100	0.119	0.125	0.106	0.1166667	81.93	18.06±0.01	41.63 (µg)
75	0.21	0.243	0.203	0.2186667	66.04	33.95±0.02	
50	0.303	0.321	0.3012	0.3084	52.02	47.97±0.01	
25	0.357	0.335	0.321	0.3376667	47.5	52.49±0.02	
15	0.403	0.398	0.4012	0.4007333	37.69	62.3±0.00	
5	0.467	0.485	0.483	0.4783333	25.54	74.45±0.01	
Untreated	0.642	0.642	0.642	0.642	0	100	

IC_{50}: Half-maximal inhibitory concentration. ABE: Abimaciclib, MCF-7: Michigan Cancer Foundation-7

Table 10: Test compounds treated (Opt-MSN-ABE+NP)

Concentration (µg)	Absorbance at 570 nm (1)	Absorbance at 570 nm (2)	Absorbance at 570 nm (3)	Mean	% Inhibition	% Viability	IC_{50} (µg)
100	0.094	0.102	0.089	0.095	85.2	14.79±0.01	22.94 µg
75	0.143	0.141	0.132	0.138667	78.5	21.49±0.01	
50	0.201	0.199	0.204	0.201333	68.69	31.3±0.00	
25	0.283	0.243	0.265	0.263667	59.03	40.96±0.02	
15	0.321	0.312	0.332	0.321667	50	50±0.01	
5	0.354	0.387	0.65	0.463667	27.88	72.11±0.16	
Untreated	0.642	0.642	0.642	0.642	0	100	

IC_{50}: Half-maximal inhibitory concentration. ABE: Abimaciclib

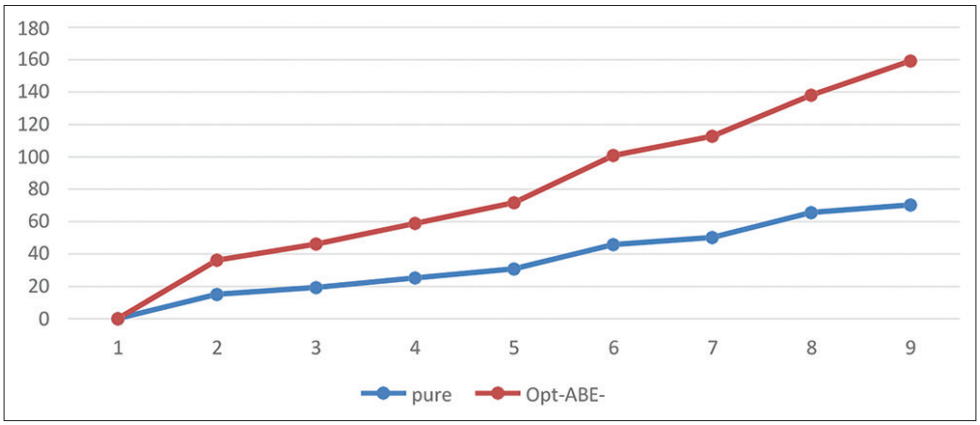


Figure 10: *Ex vivo* intestinal permeation



Figure 11: *Ex vivo* intestinal permeation studies

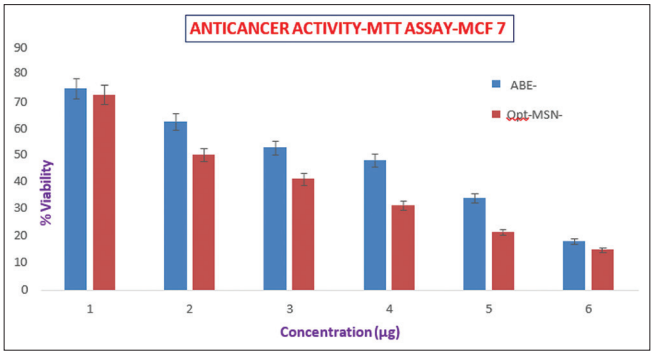


Figure 12: Graphical representation of optimized mesoporous silica nanoparticles-abimaciclib (ABE) + nanoparticle and ABE sample with Michigan Cancer Foundation-7 cells showing the % viability

(Y1, nm), EE (Y2%), and Zeta potential (Y3, mv) If the $P < 0.05$, the model is statistically significant; if the $P > 0.1000$ it is not significant.[20]

$$\text{Particle Size (Y1)} = +179.60 + 15.48A + 2.86B + 0.3375C + 0.0250AB + 0.1250AC + 1.15BC\ 11.83A2 - 0.2000B2 - 0.1000C2$$

Mesoporous silica nanoparticle particle size was found to increase when X1 [CTAB (g)] was enormous, as evidenced by a positive coefficient of the term X1 ($P = 0.0001$). However, an increase in the X2 [TEOS (mL)] concentration was observed to have significant effects on the particle size of Mesoporous silica nanoparticles. Specifically, increasing the stirring speed (X3) produced a significant effect on particle size Effect of independent variables on EE: [21]

Shows the results, [Table 5] which reveal that the entrapment effectiveness of ABE Mesoporous silica nanoparticles ranged from. The data were analyzed using polynomial analysis fitted using a quadratic model ($P = 0.0001$). The corrected R2 (0.9573) and predicted R2 (0.9205).

Entrapment efficiency = +73.92 + 5.49A − 0.0625B + 0.4000C − 0.3750AB − 0.6000AC 0.1000BC − 0.7975A2 + 0.5025B2 − 0.0725

The receiving medium's percentage of EE [Figure 3] is assumed to be unentrapped. The results show that raising the concentration of surfactant (CTAB) improves the entrapment effectiveness of ABE MSNs.[22]

Effect of independent variables on zeta potential

ANOVA for quadratic model:
The data were analyzed using polynomial analysis fitted using a quadratic model (P = 0.0001). The corrected R2 (0.9573) and predicted R2 (0.9205) were in reasonable agreement, [Table 6 and Figure 4] indicating strong correlation. A response surface plot depicts particle size as a function of CTAB (X1), TEOS (X2), and Stirring speed (X3). We present the linear equation in terms of coded values that relate the Zeta potential (Y3) to CTAB (X1), TEOS (X2), and Stir ring speed (X3):

Zeta potential = +38.54 + 1.24A + 0.2375B − 0.0250C + 0.0750AB + 0.0500AC − 0.2000BC 0.2825A2 − 0.2325B2 − 0.3075C2

The Box-Behnken design (BBD) produces an optimal formulation that describes the optimal combination of dependent variables. We were able to develop the Optimized drug loaded Mesoporous silica nanoparticles formulation (Opt-EMSNs) [Tables 7 and 8] which has a particle size of 145.6 nm, a polydispersity index of 0.371, and a maximum EE of 81%. Three of them are very close to the BBD prediction's projected value.[23]

FTIR and DSC: There is no chemical interaction between chemical and formulation.

In vitro studies

A dialysis bag was used for the *in vitro* dissolution of formulation [Figures 5-9]. The *in vitro* drug release studies are carried out between Pure-ABE and Opt-ABE-MSNP. The drug release from the Opt-ABE-MSNP is 85% at 12 h [Table 9].

Ex vivo studies

The *ex vivo* intestinal permeation was carried out between Pure-ABE and Opt-ABE - MSNP. The drug release from Opt-ABE -MSNP is 89% at 12 h [Figures 10 and 11].

Cell line studies

Test compounds treated (Opt-MSN-ABE+NP) with Michigan Cancer Foundation-7 cells showing the IC_{50} values [Table 10 and Figure 12].

CONCLUSION

Mesoporous silica nanoparticles were prepared successfully by the co-precipitation method. The formulated nanoparticles were characterized by particle size, EE, zeta potential. The MSNPs were optimized by using Box-Benkhen design by using BBD, factors are chosen as CTAB, TEOS and Stirring speed and the responses are particle size, EE, and Zeta potential. The particle size range lies in between (170nm-180nm), entrapment efficiency lies in between (70%-80%), zeta potential lies in between (35mv-40mv). The optimized formulation has the particle size, EE, and zeta potential. *In vitro* drug release was performed ABE-MSNPs showed the higher drug release at 85% in 12 h, *ex vivo* intestinal permeation was performed Opt-ABE-MSNPs a show higher intestinal permeation at 89% in 12 h. The ABE Cell line studies and MTT Assay were performed by the studies the results suggest the test drug decreased the anti-cancer activity.

ETHICAL APPROVAL

Reference No.: I/IAEC/AU/015/2023WR.

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