Advances in Bioresearch
Adv. Biores., Vol 15 (5) November 2024: 147-158

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.6.147158

Advances in Bioresearch

ORIGINAL ARTICLE

Development and Evaluation of formula for Solubility enhancement of Modafinil using Nanosponge technology: Optimisation by DOE approach

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ABSTRACT
The objective of the study was to develop β-cyclodextrin (β-CD)nanosponges (NS) loaded with Modafinil to enhance solubility as well as dissolution rate. A 2^2 full factorial design utilised for the formulation of Modafinil-loaded β-CD nanosponges, with β-CD (A, mg) and diphenyl carbonate (DPC) (B, mg) as independent variables at two levels (-1 and +1). The dependent variables were drug content (Y1) and solubility (Y2). The developed nanosponges were characterized through saturation solubility, drug content, SEM, particle size, polydispersity index (PDI), zeta potential, FTIR, DSC, and in vitro release studies in 0.1N HCl. Pure Modafinil exhibited a solubility of 0.45 mg/mL in distilled water, while the optimized NS formulation showed a significant increase in solubility to 3.43 mg/mL. SEM analysis confirmed the spherical surface morphology of the Modafinil-loaded nanosponges. The average particle size of 290.11 ± 15.50 nm with PDI of 0.215 ± 0.011 was observed. The zeta potential was found to be -3.4 ± 0.5 mV. FTIR and DSC analyses confirmed good compatibility. In vitro release studies showed significantly faster release in 0.1N HCl compared to pure Modafinil. These findings highlight the effectiveness of nanosponge technology in improving the solubility and dissolution rate of poorly water-soluble drugs like Modafinil.
Keywords: *Modafinil, Nanosponge, Solubility, Cyclodextrin, Dissolution.*

Received 16.09.2024 Revised 15.10.2024 Accepted 26.11.2024

How to cite this article:
Mohammed A K, Rana Z, Ramraja U, Jaiprakash N. S. Development and Evaluation of formula for Solubility enhancement of Modafinil using Nanosponge technology: Optimisation by DOE approach. Adv. Biores. Vol 15 [6] November 2024. 147-158

INTRODUCTION

Solubility is a crucial factor in the pharmaceutical industry when evaluating the efficacy of any therapeutic agent or drug molecule. In recent years, most of the newly synthesised drug molecules have faced significant challenges related to poor solubility and bioavailability [3]. These limitations often hinder their therapeutic potential, as insufficient solubility leads to inadequate absorption in the body, reducing clinical efficacy. This issue has prompted a great deal of research into innovative formulation techniques and drug delivery systems with the goal of enhancing solubility, dissolution, and eventually bioavailability [2, 5].

Among these drugs with poor water solubility is Modafinil, a central nervous system stimulant that is mostly prescribed to treat narcolepsy and sleep disorder. A popular drug for treating excessive drowsiness is Modafinil, a wakefulness-promoting substance. Different structurally from amphetamines and other conventional stimulants, Modafinil acts on the dopamine, norepinephrine, and histamine neurotransmitter systems [24, 20]. Modafinil is an effective drug molecule used in various conditions, however when taken orally, its low water solubility (around 0.49 mg/mL) severely reduces its absorption and bioavailability [4, 22]. The drug is categorized as BCS Class II drug with lower solubility and high

permeability [21]. As a result, pharmaceutical researchers aiming to improve the therapeutic potential of Modafinil have been interested in the formulation issues around it.
Traditionally, methods such solid dispersions, particle size reduction, surfactant usage, and co-solvent systems have been employed to improve the solubility of pharmaceuticals that are poorly soluble in water [25]. Although these approaches have yielded differing levels of success, they are not without restrictions. For example, stability and manufacturing scalability are common problems for solid dispersions, while compatibility and toxicity can arise in surfactant-based systems. Although micronization or nanonization can reduce particle size and increase dissolving rates, it frequently falls short of improving bioavailability as intended [3, 8]. Modafinil's solubility problems are complicated, thus a more creative strategy is required, one that can get around the drawbacks of current methods without sacrificing effectiveness or patient safety. An innovative substitute that is both effective and flexible for the administration of poorly soluble drug is a nanosponges platform [10-12].
A relatively new family of drug carriers called nanosponges is intended to improve the solubility, stability, and bioavailability of drugs that are poorly water soluble [16]. They are produced by cross-linking polymers to build a three-dimensional, porous structure with a morphology like a sponge. The drug molecule can be encapsulated by these porous nanoparticles in both hydrophilic and hydrophobic drug molecules, preventing degradation and enabling regulated and prolonged drug release. Enhancing the solubility and dissolving rate of drugs such as Modafinil is a particularly good use for nanosponges because of their large surface area and adjustable pore size [14]. Nanosponge technology has emerged as a possible approach for the development of improved formulations aimed at improving the solubility of Modafinil. The many benefits that nanosponges provide over traditional solubility enhancement methods have attracted attention. Because of their special structure, drugs can load more readily, degrade less, and have better control over their release patterns. Furthermore, nanosponges may form stable complexes with a wide range of drugs and are biocompatible. They are therefore perfect for drug delivery systems that are oral, topical, or even intravenous [17].
Modafinil's low solubility and issues with bioavailability especially as a BCS Class II drugs are the reason behind the development of a nanosponges-based formulation. Because of their porous shape, nanosponges are perfect for administering Modafinil, a drug used to treat chronic diseases like narcolepsy. They can also increase absorption and provide controlled release. Additionally, this formulation prevents the drug from being degrade down in the gastrointestinal system, increasing bioavailability, lowering dosage requirements, and boosting patient compliance [15]. Numerous investigations have exhibited the capability of nanosponges to augment the solubility and bioavailability of medicines with low water solubility [7]. One effective application of nanosponges has been to increase the solubility of medications such as itraconazole, curcumin, and resveratrol. These investigations have demonstrated that, in comparison to traditional formulations, nanosponge-based formulations can achieve considerable increases in solubility and dissolution rates [1]. Furthermore, several studies have demonstrated the sustained and regulated release capabilities of nanosponges, highlighting their potential for long-term therapeutic applications.
Developing a nanosponge formulation for Modafinil requires optimizing various parameters like polymer type, cross-linking agents, and drug-to-polymer ratio. A design of experiments (DOE) approach is crucial for efficiently exploring these variables, identifying optimal conditions, and achieving desired solubility, drug loading, and release profiles [13]. DOE accelerates formulation development, ensuring a robust, reproducible, and scalable product for industrial production [17]. The development of a Modafinil formulation based on nanosponges shows great potential in addressing the drug's solubility and bioavailability issues. The aim of the research study was to formulate a reliable and efficient system that can enhance the therapeutic effects of Modafinil by optimizing the formulation using a DOE approach. This study will potentiate wider use of nanosponge technology in the formulation of additional drugs that are poorly soluble, improving patient care and the field of drug delivery.

MATERIAL AND METHODS

Materials:

Modafinil was obtained as a gift sample from Tooba pharmaceutical. β- CD was purchased from S. D. Fine Chemicals Ltd., Mumbai [India]. Diphenyl carbonate (DPC), DMF, and ethanol were purchased from Spectrochem Pvt. Ltd. Mumbai [India].

Methods:

Statistical Design of experiments (DOE):

A 2^2 full factorial design approach was utilised in manufacturing of Modafinil loaded β-CD nanosponges.β-CD (A, mg) and DPC (B, mg) were considered as independent variables which were varied at -1 and +1

level. Drug content (Y1) and solubility (Y2) were considered as dependent variables. The specific variables and their corresponding levels are provided in **Table 1.** The statistical analysis of the experimental data was conducted using the Design-Expert® Software.

"Table 1: variables and levels"

"Variable"	"(-1) Low level"	"(+1) High level"
"Independent variables"		
A=β-CD	100 (mg)	200 (mg)
B= DPC	200 (mg)	300 (mg)
Dependent variables		
Y1= Drug content		
Y2 = Solubility		

Formulation of Modafinil loaded β-CD nanosponges:

β-CD-based nanosponges (NS) were produced utilising DPC with varying concentrations as shown in **Table 1.** Anhydrous β-CD and DPC were homogenized and transferred to a conical flask, where the mixture was magnetically stirred and gradually heated to 100°C. It was allowed to react for 5 hours, during which phenol crystals formed at the neck of the flask. After cooling, the product was coarsely broken up and thoroughly washed several times with distilled water to remove any unreacted β-CD. It was then washed with acetone to eliminate unreacted DPC and phenol by-products. The purified nanosponges were stored at 25°C for future experimentation [11].

The details of the batches are presented in **Table 2.**

Table 2: Formulation batches of nanosponges of Modafinil

Batch	Factor	
	A (β-CD) (mg)	B (DPC) (mg)
F1	-1 (100)	1(300)
F2	-1(100)	1(300)
F3	-1(100)	-1(200)
F4	-1(100)	-1(200)
F5	1(200)	-1(200)
F6	1(200)	1(300)
F7	1(200)	-1(200)
F8	1(200)	1(300)

Characterization of Modafinil nanosponges:

Saturation solubility study:

Experiments were conducted by adding an excess amount of the drug to a 20 mL aqueous solution. The same procedure was followed for the nanosponges formulations. The solution was stirred for 48 hours at a temperature of 25 ± 0.5°C until equilibrium was reached. Following this, the samples were filtered, and the absorbance was measured at 260 nm using a Jasco UV/Vis spectrophotometer [11].

Percentage drug content:

The dried Modafinil-loaded nanosponges were accurately weighed and dissolved in sufficient volume of DMF. The drug content was measured using a UV spectrophotometer, and the percentage of drug content was determined [11].

Scanning electron microscopy (SEM):

The surface morphology of the NS was examined using a scanning electron microscope under high vacuum conditions. The samples were coated with a thin layer of gold using a sputter coater, and digital images were captured with an accelerating voltage of 20 kV.

Fourier transform infrared (FT-IR) spectroscopy:

FT-IR spectroscopy was performed to assess potential interactions between Modafinil and the excipients used in the nanosponge loading process, as well as the drug's stability throughout the procedure. The analysis utilized the potassium bromide disc method, in which samples of approximately 2-3 mg were mixed with KBr, pelletized under vacuum, and analyzed using an FT-IR spectrophotometer over a wavelength range of 4000-400 cm^{-1}.

Differential scanning calorimetry (DSC):

The analysis was performed using a Shimadzu DSC-50 instrument with a computerized data station. Samples weighing five milligrams were heated at a rate of 100^0C/min in flat-bottomed aluminum pans in the presence of nitrogen with a flow rate of 30 ml/min over a temperature range of 33-300^0C. Empty aluminum pans were used as a reference.

Particle size, Polydispersity index (PDI), and zeta potential (ZP):
Particle size, PDI, and ZP were measured using a Malvern Zetasizer. Initially the samples were suitably diluted with distilled water. Analysis was performed in triplicate at a temperature of 25 ± 0.5^{0}C, and the results were presented as the mean value and standard deviation (±SD).

***In vitro* release study:**
Using the USP dissolution test apparatus II, the release properties of the pure drug and NS loaded with Modafinil were examined. The temperature was maintained at 37^{0}C ± 0.5^{0}C while the paddles were turned at 50 rpm. In dialysis bags with a molecular weight cutoff of 12,000–14,000 Da, equivalent quantities of pure drug and NS loaded with Modafinil, each weighing 10 mg, were attached to the paddle and submerged in the release medium. The first release tests were carried out in 900 milliliters of 0.1N HCl buffer. At specified intervals, three-milliliter samples were taken out and swapped out for an equivalent volume of brand-new media. After filtering, the samples were subjected to spectrophotometric analysis at 260 nm. Three separate release trials were carried out, and the total percentage of drugs released over time was computed.

RESULTS AND DISCUSSION
Beta-cyclodextrin (β-CD) mediated nanosponges offer a promising approach for improving the solubility and bioavailability of poorly soluble drugs like Modafinil [2]. Cyclodextrins, due to their unique molecular structure, form inclusion complexes with hydrophobic drugs, enhancing their solubility in aqueous media [18]. In β-CD nanosponges, the cross-linked polymeric network creates a porous structure capable of trapping Modafinil within its cavities, stabilizing the drug and preventing its crystallization, a common cause of low solubility. This encapsulation also helps in controlling the release rate, improving the drug's dissolution profile and bioavailability [9]. Furthermore, the nanoscale size of these systems increases the surface area, allowing for faster drug release and enhanced absorption. Overall, β-CD nanosponges significantly enhance Modafinil's solubility, stability, and therapeutic efficacy.
The current method used in this research work found to be suitable for the development of Modafinil nanosponges.

Effect of independent variables on drug content (Y1) and statistical analysis:
Modafinil nanosponges were developed by combination of β-CD and DPC and optimised using A 2^2 full factorial design approach. The formulation batches suggested by design expert software were manufactured and evaluated for drug content which was considered as independent variable. The results of the drug content and of all the formulations are presented in Table 3 along with the coded levels of the dependent variables.

Table 3: Formulation batches of nanosponges of Modafinil

Batch	Factor		Y1
	A (β-CD)	B (DPC)	Drug content (%)
F1	-1	1	94.6
F2	-1	1	94.8
F3	-1	-1	92.5
F4	-1	-1	92.8
F5	1	-1	95.4
F6	1	1	99.4
F7	1	-1	95.6
F8	1	1	99.5

The drug content of the nanosponges ranged between 92.5% (F3) to 99.5% (F8). F8nanosponges showed highest drug content than other formulations. The diagnostic case statistics of drug content with actual and predicted value is presented in **Table 4.**

Table 4: Diagnostic case statistics of drug content of nanosponges

Run Order	Actual Value	Predicted Value	Residual	Leverage	Internally Studentized Residuals	Externally Studentized Residuals	Cook's Distance	Influence on Fitted Value DFFITS
1	94.60	94.70	-0.1000	0.500	-0.943	-0.926	0.222	-0.926
2	94.80	94.70	0.1000	0.500	0.943	0.926	0.222	0.926
3	92.50	92.65	-0.1500	0.500	-1.414	-1.732	0.500	-1.732
4	92.80	92.65	0.1500	0.500	1.414	1.732	0.500	1.732
5	95.40	95.50	-0.1000	0.500	-0.943	-0.926	0.222	-0.926
6	99.40	99.45	-0.0500	0.500	-0.471	-0.420	0.056	-0.420
7	95.60	95.50	0.1000	0.500	0.943	0.926	0.222	0.926
8	99.50	99.45	0.0500	0.500	0.471	0.420	0.056	0.420

The data in **Table 3** demonstrates the influence of β-CD and DPC on the drug content of Modafinil-loaded nanosponges. When β-CD is present at a high level (+1), the drug content tends to be higher, reaching up to 99.5% in formulations F6 and F8. This suggests that increasing β-CD enhances the drug content, likely due to its ability to form inclusion complexes with Modafinil, thereby improving its encapsulation efficiency. On the other hand, DPC seems to have a less pronounced effect. When DPC is at its high level (+1), there is a slight increase in drug content compared to the low level (-1), as seen in F6 and F8, but the effect is not as substantial as that of β-CD. This indicates that while DPC plays a role in the polymerization process of nanosponge formation, β-CD is the primary factor influencing drug encapsulation in this system. This relationship and the impact of the independent variables on drug content are graphically represented in **Figure 1.**

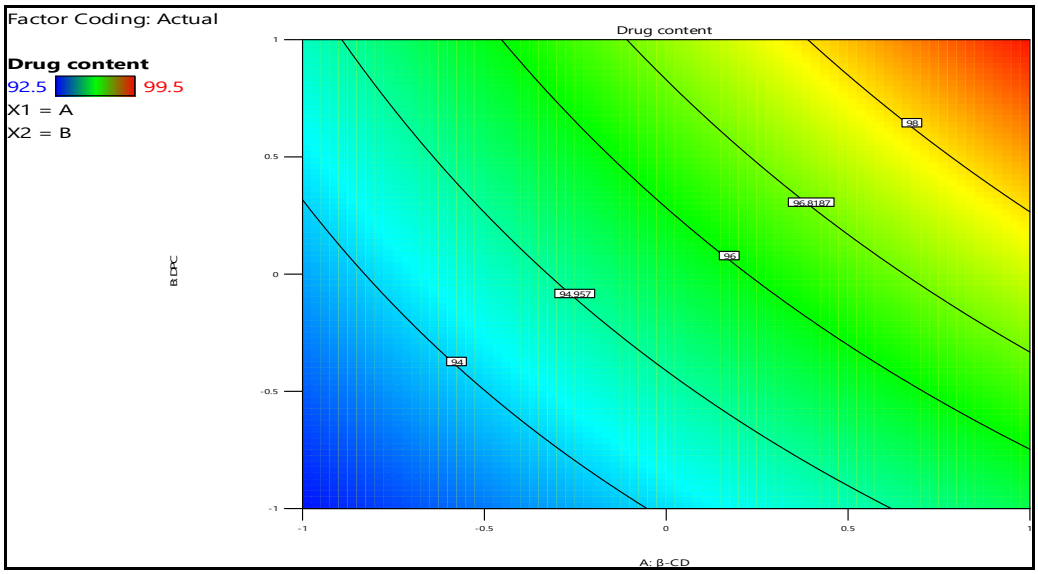

Figure 1: Contour plot showing the responses of β-CD and DPC on the drug content

The final polynomial equation for drug content (Y1) in coded factors can be presented below

$$\mathbf{(Y1) = +95.57 + 1.90A+1.50B+0.4750AB}$$

In the equation above, Y_1 represents the drug content, A denotes the β-CD concentration, and B refers to the DPC concentration. The equation, expressed in terms of coded factors, allows predictions of the response at specific levels of each factor. By default, the high levels of the factors are coded as +1, while the low levels are coded as -1. This coded equation is useful for assessing the relative influence of each factor by comparing their respective coefficients.

P-values below 0.0500 indicate that the model terms are significant. The Model F-value of 721.26 suggests that the model is highly significant, with only a 0.01% chance that such a large F-value could result from random noise. In this case, A, B, and AB are significant model terms, as shown in Table 5. P-values above 0.1000 suggest that the model terms are not significant.

Table 5: ANOVA for selected factorial model of drug content

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	48.69	3	16.23	721.26	< 0.0001	significant
A-β-CD	28.88	1	28.88	1283.56	< 0.0001	
B-DPC	18.00	1	18.00	800.00	< 0.0001	
AB	1.81	1	1.81	80.22	0.0009	
Pure Error	0.0900	4	0.0225			
Cor Total	48.78	7				
Fit statistics						
Std. Dev.	0.1500		R^2	0.9982		
Mean	95.58		Adjusted R^2	0.9968		
C.V. %	0.1569		Predicted R^2	0.9926		
			Adeq Precision	64.1110		

The Predicted R^2 of 0.9926 is in good agreement with the Adjusted R^2 of 0.9968, as the difference is less than 0.2. Adeq Precision, which measures the signal-to-noise ratio, indicates a ratio above 4 is desirable.

In this model, a ratio of 64.111 demonstrates an adequate signal, making the model suitable for navigating the design space.

Effect of independent variables on solubility (Y2) and statistical analysis:

The results of the solubility and of all the formulations are presented in Table 6 along with the coded levels of the dependent variables.

Table 6: Formulation batches of nanosponges of Modafinil with solubility

Batch	Factor		Y2
	A (β-CD)	B (DPC)	Solubility (mg/ml)
F1	-1	1	2.6
F2	-1	1	2.7
F3	-1	-1	1.8
F4	-1	-1	1.9
F5	1	-1	3
F6	1	1	3.39
F7	1	-1	3.1
F8	1	1	3.43
Pure Modafinil			**0.45**

The solubility of the nanosponges ranged between 1.8 (F3) to 3.43 (F8)mg/ml. F8nanosponges showed highest solubility than other formulations. The pure Modafinil showed solubility of 0.45 mg/ml.The diagnostic case statistics of drug content with actual and predicted value is presented in **Table 7.**

Table 7: Diagnostic case statistics of drug content of nanosponges

Run Order	Actual Value	Predicted Value	Residual	Leverage	Internally Studentized Residuals	Externally Studentized Residuals	Cook's Distance	Influence on Fitted Value DFFITS
1	94.60	94.70	-0.1000	0.500	-0.943	-0.926	0.222	-0.926
2	94.80	94.70	0.1000	0.500	0.943	0.926	0.222	0.926
3	92.50	92.65	-0.1500	0.500	-1.414	-1.732	0.500	-1.732
4	92.80	92.65	0.1500	0.500	1.414	1.732	0.500	1.732
5	95.40	95.50	-0.1000	0.500	-0.943	-0.926	0.222	-0.926
6	99.40	99.45	-0.0500	0.500	-0.471	-0.420	0.056	-0.420
7	95.60	95.50	0.1000	0.500	0.943	0.926	0.222	0.926
8	99.50	99.45	0.0500	0.500	0.471	0.420	0.056	0.420

The data in **Table 6** highlights the effect of β-CD and DPC on the solubility of Modafinil-loaded nanosponges compared to pure Modafinil. Pure Modafinil has a solubility of 0.45 mg/ml, while all nanosponge formulations significantly enhance solubility, ranging from 1.8 mg/ml (F3) to 3.43 mg/ml (F8). Formulations with a higher level of β-CD (+1) show a substantial increase in solubility, with the highest solubility observed in F8 (3.43 mg/ml), suggesting that β-CD plays a major role in improving solubility by forming inclusion complexes with Modafinil [6].

DPC also influences solubility, as formulations containing a higher level of DPC (+1) generally show better solubility than those without (e.g., F6: 3.39 mg/ml vs. F7: 3.1 mg/ml). However, the impact of DPC is secondary to β-CD, as the formulations with high β-CD levels show the most pronounced solubility improvements. Overall, the nanosponges demonstrate a significant enhancement in solubility, with the highest formulation (F8) showing a 7.62-fold increase compared to pure Modafinil. This relationship and the impact of the independent variables on solubility are graphically represented in **Figure 2.**

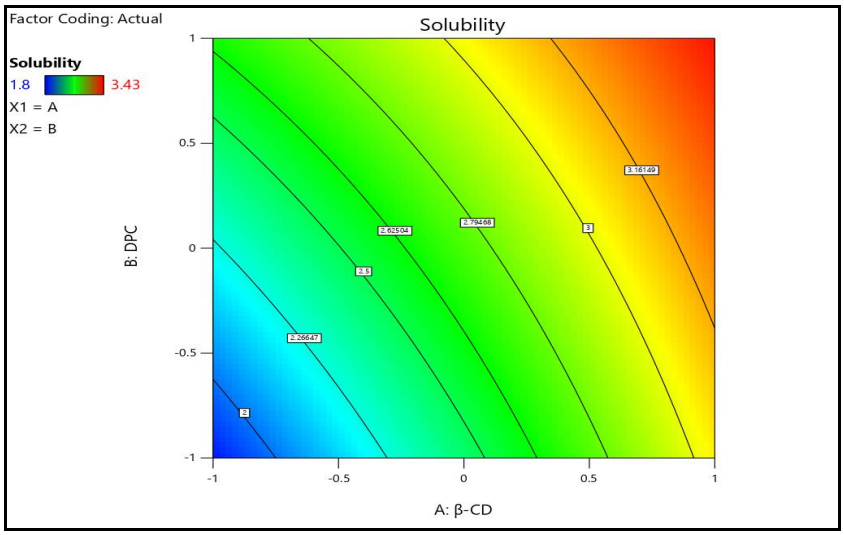

Figure 2: Contour plot showing the responses of β-CD and DPC on the solubility

The final polynomial equation for drug content (Y2) in coded factors can be presented below

(Y2) = +2.74 + 0.4900A+0.2900B-0.1100AB

The equation expressed in coded factors can predict the response at specific factor levels, with high levels coded as +1 and low levels as -1. This coded equation helps compare the factor coefficients to determine their relative impact. P-values below 0.0500 indicate significant model terms. A Model F-value of 227.04 suggests the model is significant, with only a 0.01% chance of such a large F-value occurring due to noise. In this case, A, B, and AB are significant model terms, as shown in Table 8. P-values above 0.1000 suggest the model terms are not significant. If many model terms are insignificant (except those required for hierarchy), model reduction may enhance the model.

Table 8: ANOVA for selected factorial model for solubility

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.69	3	0.8968	227.04	< 0.0001	significant
A-β-CD	1.92	1	1.92	486.28	< 0.0001	
B-DPC	0.6728	1	0.6728	170.33	0.0002	
AB	0.0968	1	0.0968	24.51	0.0078	
Pure Error	0.0158	4	0.0040			
Cor Total	2.71	7				
Fit statistics						
Std. Dev.	0.0628		R^2	0.9942		
Mean	2.74		Adjusted R^2	0.9898		
C.V. %	2.29		Predicted R^2	0.9766		
			Adeq Precision	35.1027		

The Predicted R^2 of 0.9766 aligns well with the Adjusted R^2 of 0.9898, as the difference is less than 0.2. Adeq Precision assesses the signal-to-noise ratio, with a desirable ratio exceeding 4. The ratio of 35.103 indicates an adequate signal, suggesting that this model is suitable for navigating the design space.

FTIR study:

The FTIR spectra of pure Modafinil and Modafinil-loaded nanosponges reveal distinct differences that can be attributed to the interaction of Modafinil with the nanosponge matrix.

In the pure Modafinil spectrum**(Figure 3)**, the characteristic peaks are observed around 3300 cm^{-1}, corresponding to the N-H stretching vibrations, indicating the presence of amine groups. The peak around 1650 cm^{-1} corresponds to the C=O stretching vibrations, characteristic of the carbonyl group in the Modafinil structure. Additional peaks in the region of 1400-1600 cm^{-1} are indicative of aromatic C=C stretching, and the peaks around 1200-1000 cm^{-1} correspond to C-N and S=O vibrations, reflecting the sulfoxide functional group.

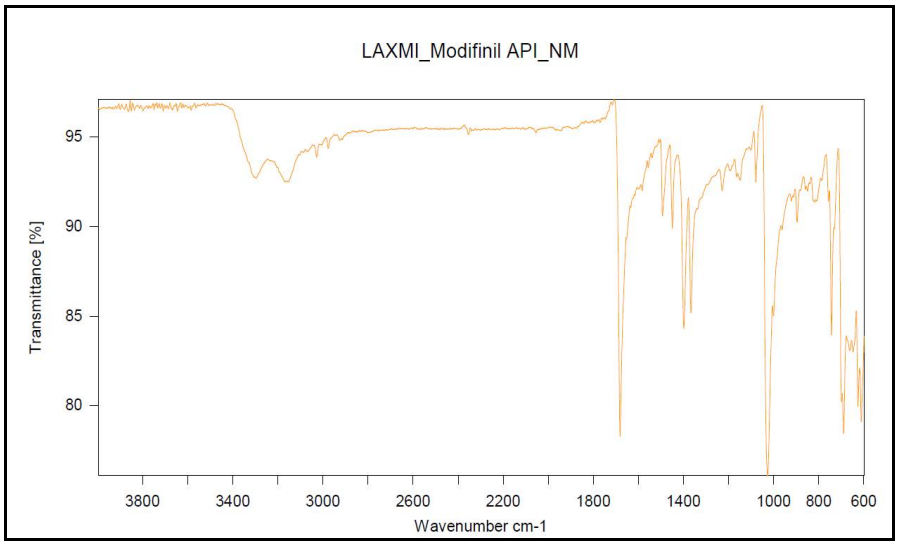

Figure 3: FTIR spectra of pure Modafinil

In comparison, the FTIR spectrum of Modafinil-loaded nanosponges**(Figure 4)** shows broadening and shifting of some key peaks. The N-H stretching peak is broader and slightly shifted, indicating possible hydrogen bonding interactions between Modafinil and the nanosponge matrix. The carbonyl (C=O) stretching peak at 1650 cm^{-1} also appears to be slightly altered, reflecting interactions between the drug and the nanosponge. Moreover, the intensity of peaks related to the sulfoxide group is reduced, suggesting the encapsulation of Modafinil within the nanosponge, which may have altered the free functional group availability.

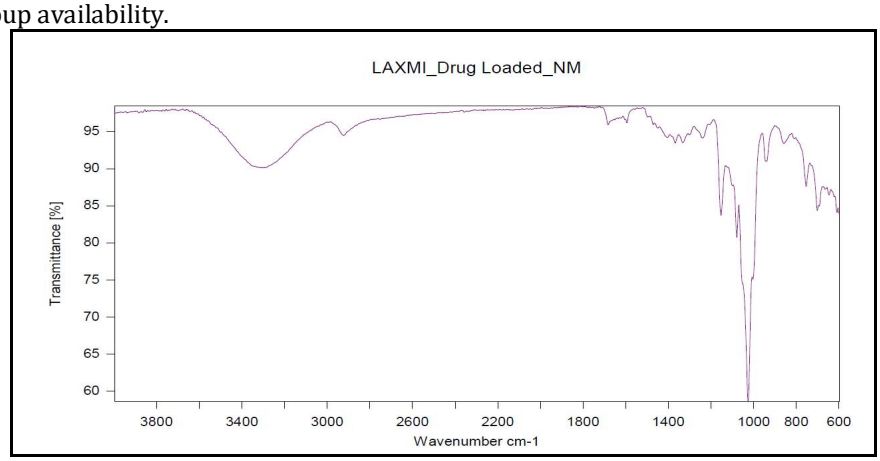

Figure 4: FTIR spectra of Modafinil-loaded nanosponges

These spectral differences confirm that Modafinil has been successfully encapsulated into the nanosponge system, with potential interactions between the drug and the matrix material contributing to these observed changes in the FTIR spectra.

DSC study:

The DSC thermogram of pure Modafinil**(Figure 5)** reveals several important thermal events that help characterize its thermal stability and crystalline nature. The first significant endothermic peak occurs at 168.44°C, with an enthalpy of 163.7 J/g, which corresponds to the melting point of Modafinil (Jigar, et al., 2012). This sharp endothermic peak indicates that the drug is in a crystalline form, as crystalline materials typically exhibit well-defined melting points. Following the melting event, a broad endothermic transition occurs around 226.23°C to 253.26°C, with an associated enthalpy of 155.0 J/g. In summary, the DSC thermogram provides a clear indication of Modafinil's melting point at 168.44°C, along with additional thermal events at higher temperatures, likely indicating decomposition. This data confirms the crystalline nature of the pure drug.

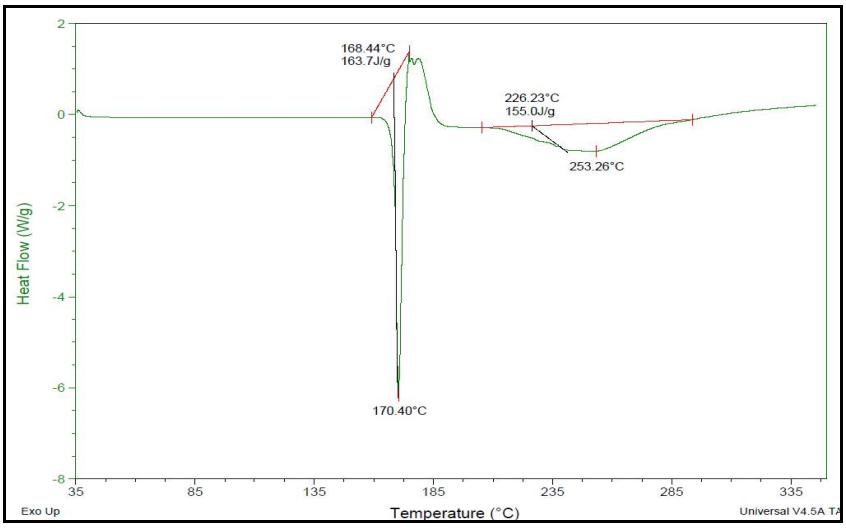

Figure 5: DSC thermogram of pure Modafinil

In contrast, the DSC thermogram of Modafinil loaded into nanosponges (β-CD and DPC) shows significant alterations **(Figure 6)**. A broad peak at 104.76°C is observed, which could indicate the dehydration of the nanosponge system or an interaction between Modafinil and the carrier matrix. The disappearance of Modafinil's sharp melting peak (168.44°C) and the appearance of a small peak at 158.88°C suggest a change in the crystalline structure of the drug, possibly due to encapsulation in the nanosponge. The shift in the melting peak to a lower temperature indicates a reduced crystallinity, as the drug is now in an amorphous or molecularly dispersed state within the nanosponge.

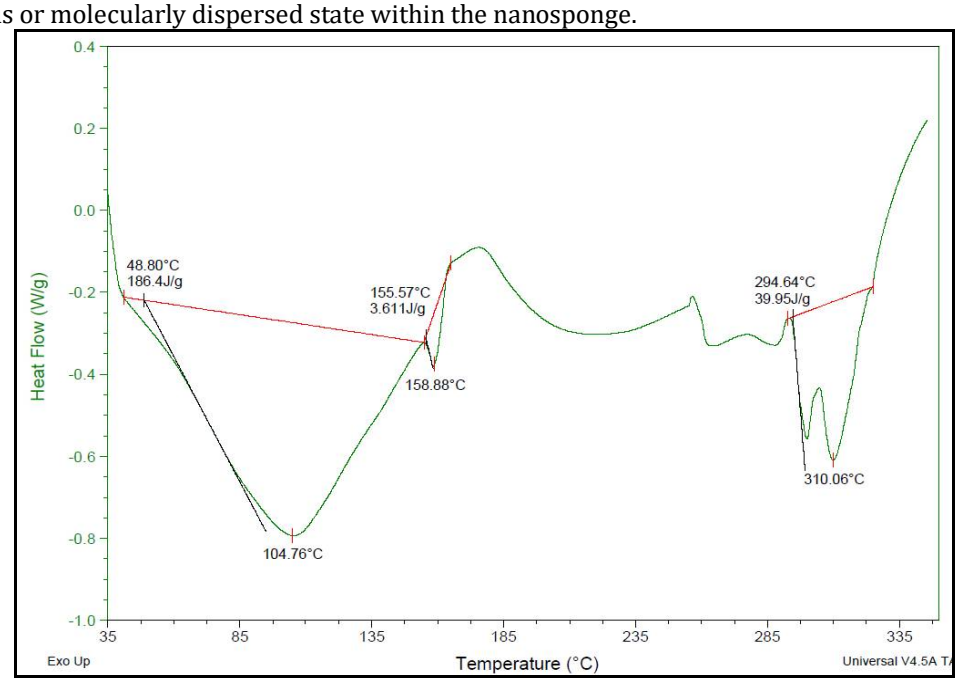

Figure 6: DSC thermogram of Modafinil loaded nanosponges

Furthermore, a peak at 310.06°C was observed in the loaded system, which likely corresponds to the decomposition of the nanosponge matrix or drug-matrix complex at higher temperatures. This peak was not present in the pure Modafinil thermogram, further supporting the interaction between Modafinil and the nanosponge materials.

Overall, these changes in thermal behaviour indicate that encapsulation of Modafinil in nanosponges significantly alters its thermal profile, reducing its crystallinity and improving its solubility and stability.

Scanning electron microscopy:

The SEM analysis of Modafinil-loaded nanosponges, as depicted in Figure 7, revealed a highly spherical surface morphology. The nanosponge formulation displayed nano-scale dimensions with a sponge-like structure. This porous architecture allows for efficient drug entrapment within its interwoven network, facilitating improved drug loading and release efficiency.

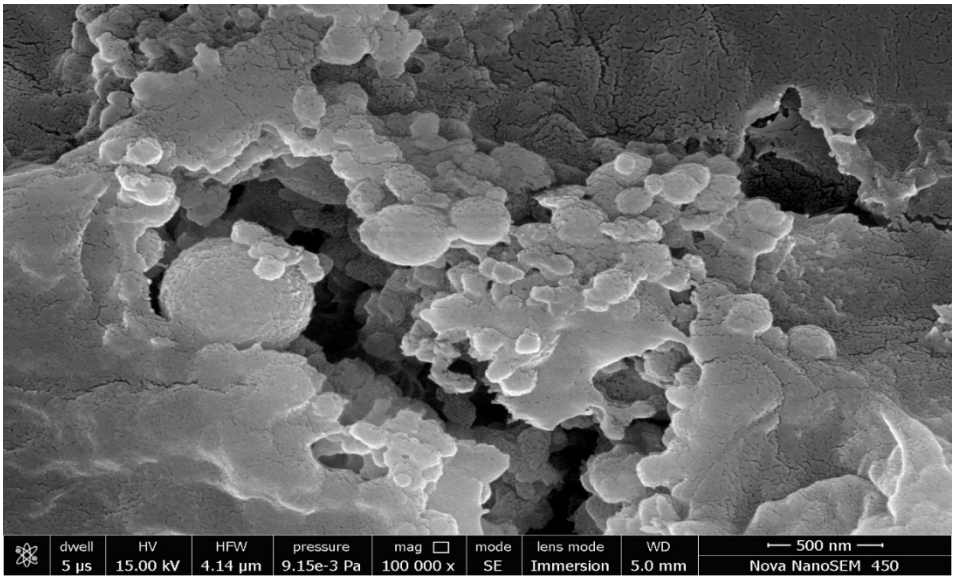

Figure 7: Surface morphology of Modafinil loaded nanosponge

Particle size, Polydispersity index, and zeta potential:

For formulation containing higher levels of β-CD and DPC, the average particle size was measured at 290.11 ± 15.50 nm, with a low polydispersity index of 0.215 ± 0.011. The zeta potential was found to be -3.4 ± 0.5 mV, indicating sufficient electrostatic repulsion to maintain particle dispersion. The zeta potential distribution is presented in **Figure 8**

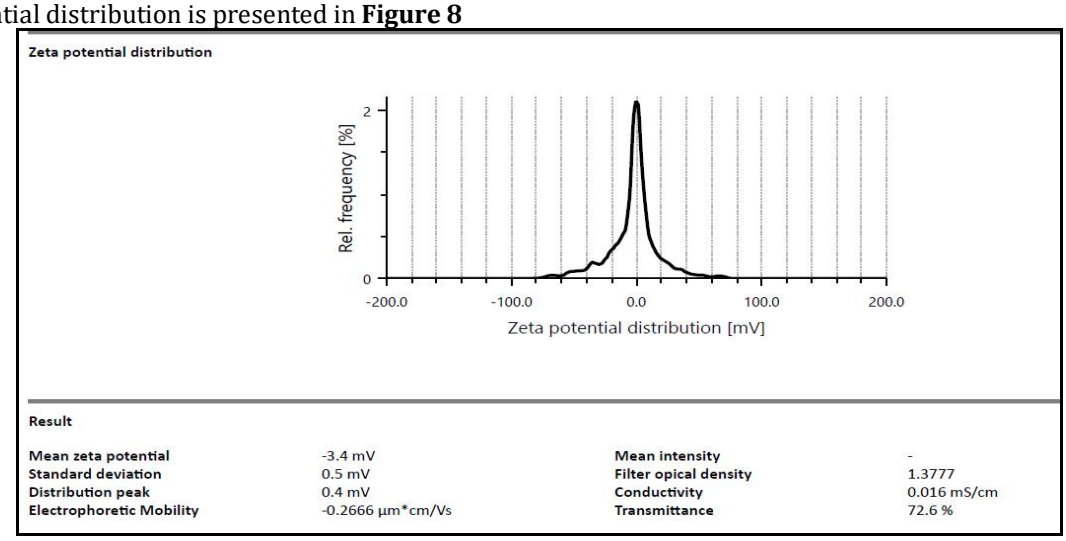

Figure 8: Zeta potential distribution of

***In vitro* release study:**

Compared to pure Modafinil, Modafinil-loaded nanosponges (NS) demonstrated significantly faster release in 0.1 N HCl, indicating enhanced dissolution properties. The in vitro release studies showed a slow dissolution of pure Modafinil over a 2-hour period. However, the ternary complexes formed with β-cyclodextrin (β-CD), diphenyl carbonate (DPC), and Modafinil at various ratios markedly improved the dissolution rate, as shown in Figure 9. Among these, the complex with a higher ratio of β-CD (200 mg) to DPC (300 mg) exhibited the most rapid release profile. This improvement is attributed to the presence of surface-bound Modafinil that was not completely encapsulated within the nanosponges or the ternary complex, leading to an initial burst release of approximately 45%.

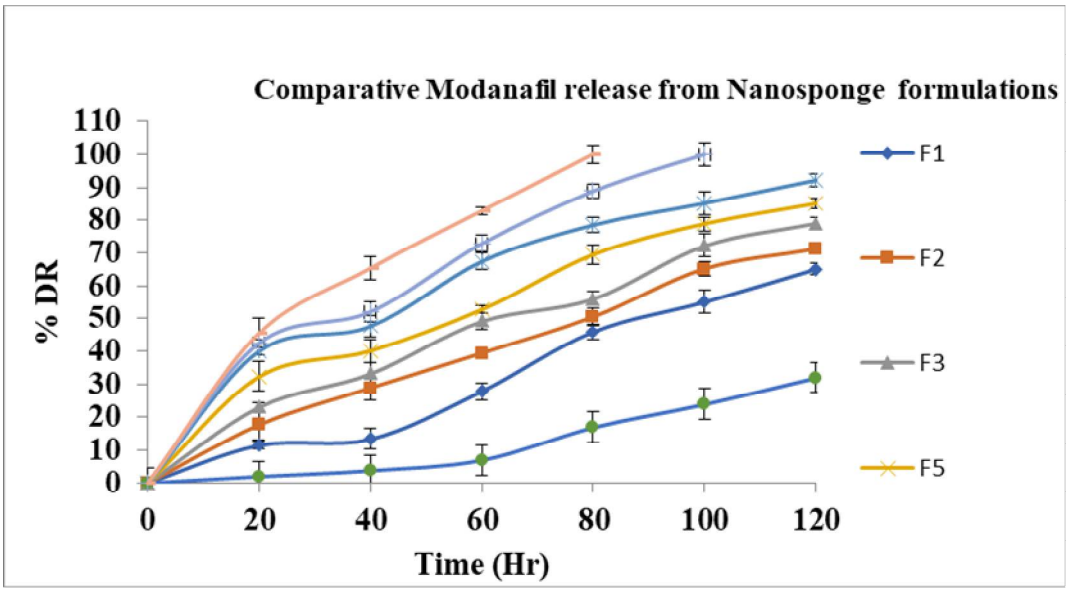

Figure 9: Comparative dissolution profile

Nanosponges enhance the dissolution of poorly water-soluble drugs by trapping them within their porous nanostructure, which helps to mask the hydrophobic regions of the drug [24]. This process increases the apparent solubility by creating a more hydrophilic environment around the drug molecules. Encapsulation within nanosponges also reduces the crystallinity of Modafinil, improving its wettability, thereby allowing a higher proportion of the drug to remain in a molecularly dispersed state [19]. The observed faster release in Modafinil-loaded NS at higher β-CD and DPC levels supports the potential for these nanosponges to improve Modafinil's bioavailability by overcoming its limited solubility and poor dissolution rate.

CONCLUSION

The research successfully demonstrated the development of β-cyclodextrin (β-CD) based nanosponges (NS) as an effective approach for enhancing the solubility and dissolution rate of poorly water-soluble drugs like Modafinil. The application of a 2^2 full factorial design enabled the optimization of β-CD and diphenyl carbonate (DPC) concentrations, resulting in a 7.62-fold increase in Modafinil solubility. The nanosponges exhibited desirable characteristics, including spherical morphology, a uniform particle size of 290.11 ± 15.50 nm, a low polydispersity index (PDI), and good electrostatic stability, as indicated by the zeta potential. FTIR and DSC studies confirmed the compatibility of Modafinil with the excipients, while in vitro release studies demonstrated significantly faster drug release from the nanosponges compared to pure Modafinil. These findings confirm the potential of nanosponges as a promising strategy for improving the bioavailability of hydrophobic drugs through enhanced solubility and dissolution.

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