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Original Article

PREPARATION AND EVALUATION OF NANOSPONGES BASED TRAMADOL HCL C/R TABLETS USING DESIGN OF EXPERIMENT

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ABSTRACT

Objective: The goal was to develop a controlled release formulation of tramadol utilizing the cyclodextrin-based nanosponges as a nanocarrier.

Methods: Based on the preliminary trials a 3-factor, 3-level Box-Behnken design was employed. Five types of nanosponges from β-cyclodextrin (NS1-NS5) were purposely designed. Tramadol was loaded into nanosponges by the freeze-drying method. The prepared nanosponges were characterized and formulated into tablets and evaluated.

Results: The particle sizes of tramadol-loaded nanosponges are in between 34.38 to 134.26 nm, encapsulation efficiency of 41.13-86.72% and drug release% at 6h of 52.34-81.12%. *In vitro* release studies showed that more than 90 % of the drug were released from nanosponge formulations as compared to only around 20% from free drug suspension after 24 h. The FTIR, DSC and XRPD studies confirmed the interaction of Tramadol with nanosponges. TEM image revealed the spherical structure of drug-loaded nanosponges. The drug-loaded in the nanosponge structure can be retained and released slowly over time. The nanosponges were formulated into tablets and evaluated for weight variation, hardness, friability and disintegration studies and obtained satisfactory results. *In vitro* release of drug from tablet showed controlled release behavior for a period of 12 h. The percentage of tramadol released from nanosponges tablets after was 87.48 percent and stability studies indicated no significant changes within 6 months.

Conclusion: Cyclodextrin-based nanosponges showed superior complexing ability with increased solubility of poorly soluble Tramadol tablets made for controlled drug delivery, which can reduce dosing frequency.

Keywords: Tramadol, Opioid analgesic, Nanosponges, Tablets, Experimental design

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INTRODUCTION

Tramadol is a centrally acting synthetic opioid analgesic and SNRI (serotonin/norepinephrine reuptake-inhibitor) that is structurally related to codeine and morphine. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water, log partition coefficient (logP) is 1.35 at pH 7.

Tramadol is available in several commercial products in immediate-release and extended-release formulations [1]. Several different technologies are used to achieve the prolonged release of the drug [2]. Most of these formulations are available in doses of 100, 200, 300 and 400 mg. In general, controlled-release delivery attempts to; sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with minimization of undesirable side effects [3].

The use of cyclodextrin-based nanosponges represents another emerging technological approach to increasing drug solubility and stability. Cyclodextrin-based nanosponges showed superior complexing ability than natural cyclodextrins towards many molecules [4]. Over the years, nanosponges have been extensively explored for solubilization, chemical stabilization, enhancement of permeability, ocular delivery, potentiating of cytotoxicity, modulation of drug release, reduction of toxicity, protein delivery and others [5]. Nanosponges have proven capable of keeping up with the advances in nanomedicine, responding positively to the need for targeted treatments aimed at improving the efficacy and reducing the adverse effects of the drugs. Cyclodextrin-based nanosponges have been extensively investigated for the effective and targeted delivery of several anticancer drugs such as camptothecin, resveratrol, paclitaxel, tamoxifen, curcumin, dexamethasone etc., to enhance bioavailability and therapeutic effects of these drugs [6].

In the present study, we intended to develop a controlled release formulation of tramadol using cyclodextrin nanosponges as novel nanocarriers [7]. Cyclodextrin-based nanosponges were prepared in our laboratory using β-Cyclodextrin and diphenyl carbonate as cross-linking agent.

MATERIALS AND METHODS

Materials

Tramadol was obtained as a gift sample from MSN laboratories Pvt. Ltd, β-Cyclodextrin was obtained from Gangwal Chemicals Pvt. Ltd. (Mumbai, India)., Diphenyl carbonate purchased from Euclid Pharmaceuticals Limited, Mumbai, Dimethyl sulfoxide and Ethanol was purchased from Qualigens, Thermo Fisher Scientific India Ltd, Mumbai.

Preparation of β-cyclodextrin nanosponges (NS)

Cyclodextrin-based nanosponges were prepared in our laboratory using diphenyl carbonate for the crosslinking as reported elsewhere [8]. Five types (NS1-NS5) of nanosponges were prepared using different molar ratios of reactants. The molar ratios and concentrations of both the reactants were used as shown in table 1.

Table 1: Molar ratios and concentrations of β-cyclodextrin and diphenyl carbonate

S. No.	Type of NS	Molar ratio (β-CD: DPC)	Concentration of β-cyclodextrin (gm)	Concentration of diphenyl carbonate (gm)
1	NS1	1:2	4.548	1.712
2	NS2	1:4	4.548	3.424
3	NS3	1:6	4.548	5.136
4	NS4	1:8	4.548	6.848
5	NS5	1:10	4.548	8.560

Characterization of β-cyclodextrin nanosponges

Characterization of the prepared β-cyclodextrin nanosponges for Particle size, polydispersity index and zeta potential were analysed using a Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, UK) [9].

Fabrication of tramadol-loaded β-cyclodextrin nanosponges

Tramadol-loaded nanosponges were prepared by lyophilisation technique as reported elsewhere [10, 11]. To the above mixture 100 mg of tramadol was added and the mixture was sonicated for 20 min to prevent aggregation. After lyophilisation the collected dry powder was stored in a desiccator.

Design of experiments

Based on the Box-Behnken design model provided by Stat-Ease Design Expert® software V8.0.1, 17 model experiments were randomly arranged (table 2 and 3) [12].

Data analysis

The obtained results were subject to statistical analysis, the lack of a fit test for checking the fitness of the model. A model with a significant lack-of-fit (Prob>F value 0.05 or smaller) lacks prediction efficiency, so a non-significant lack of fit value in the model is highly desirable [13].

Table 2: BBD with list of dependent and independent variables with their respective levels and goals

Independent variables			Levels		
Variable		Units	Low	Intermediate	High
A	Molar ratio of polymer to cross linker		0.2	0.5	0.8
B	Stirring speed	Rpm	2000	3500	5000
C	Stirring time	Min	360	450	540
Dependent variables			Goal		
Y1	Mean particle size	Nm	Minimize		
Y2	Encapsulation efficiecny	%	Maximize		
Y3	Percent drug release at 6h	%	Minimize		

Table 3: Trial experiments as per BBD

Expt	Molar ratio of polymer to crosslinker	Stirring speed (rpm)	Stirring time (min)
1	0.5	2000	540
2	0.8	3500	540
3	0.8	2000	450
4	0.5	2000	360
5	0.5	3500	450
6	0.5	3500	450
7	0.5	5000	540
8	0.2	5000	450
9	0.5	5000	360
10	0.8	3500	360
11	0.2	3500	540
12	0.5	3500	450
13	0.8	5000	450
14	0.5	3500	450
15	0.2	2000	450
16	0.2	3500	360
17	0.5	3500	450

Optimization

The nanoformulation was prepared in triplicate under optimal conditions to verify the validity optimization technique.

Physico-chemical characterization of IBNS

Particle size, polydispersity index and zeta potential were determined as per the procedure adopted for β-Cyclodextrin nanosponges. The formulations analysed for FTIR, DSC, PXRD, TEM as per the procedure adopted in reference [14].

Characterisation of prepared tramadol nanosponges

The ‘‘percent drug payload” and “percent drug encapsulation efficiency’’ were calculated using the following equation 1 and 2:

$$\% \text{ Drug pay load} = \frac{\text{Weight of drug encapsulated in NS formulation}}{\text{Weight of the NS formulation taken for analysis}} \times 100 \quad (1)$$

$$\% \text{ Drug encapsulation efficiency} = \frac{\text{Weight of drug encapsulated in NSformulation}}{\text{Initial weight of the drug fed for loading}} \times 100 \quad (2)$$

Preparation of tramadol loaded nanosponges tablets

An accurately weighed quantities of tramadol loaded nanosponges equivalent to 100 mg tramadol and the calculated Avicel pH-102, which was added to attain 300 mg tablet, were mixed for 10 min using mortar and pestle, after which the magnesium stearate (6 mg) was added and blended for another 2 min. The final mixtures were compressed using a single punch tablet machine with 8 mm, round, flat-faced single punch.

Evaluation of tablet formulation

Uniformity of weight, Hardness test, Friability test, Drug content, *In vitro* disintegration test [15].

***In vitro* release study of tramadol**

In vitro release of drug from tramadol-loaded tablets and marketed tramadol tablet (Tramazac 100 mg) was performed using the type II USP dissolution apparatus [16]. The dissolution medium was 900 ml 0.1 N HCl for the first 2 h then replaced with phosphate buffer pH 6.8 at a speed of 50 rpm and a temperature of 37±0.5 °C. The samples were withdrawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h. Equal amount of the fresh dissolution medium, retained at the same temperature, was immediately replaced. The samples were suitably diluted and analysed using UC-spectrophotometer at 271.32 nm. The dissolution experiments were conducted in triplicate.

Stability studies

Stability studies of the optimized formulation was carried out for 6 mo according to ICH guidelines. These were stored at three different

temperatures and relative humidity (i.e., 25±2 ℃, 60%±5; 30±2 ℃, 65%±5; and 40±2 ℃, 65%±5) and were inspected visually and the samples were withdrawn at specified time points and were examined for appearance, hardness, disintegration time, dissolution, and drug content.

Statistical analysis

All the parameters were expressed as mean±standard deviation (SD). The parameters were further subjected to statistical analysis using Graph Pad Prism software (Graph Pad Software Inc., San Diego, CA). The p-value is calculated using the sampling distribution of the test statistic under the null hypothesis, the sample data, and the two-sided test. If p-value is 0.05, that means 5% of the time, would see a test statistic at least as extreme as the one found if the null hypothesis was true.

RESULTS AND DISCUSSION

Fabrication of nanosponges by BBD trials and their observations given in table 4.

Table 4: Observed responses of trial experiments as per BBD

Expt	Mean particle size±SD (nm)	Encapsulation efficiecny±SD (%)	Percent drug release at 6h±SD (%)
1	104.56±0.21	83.74±0.27	69.16±0.14
2	49.34±0.59	86.72±0.53	54.34±0.19
3	94.46±0.15	82.67±0.45	53.12±0.54
4	128.74±0.66	70.56±0.49	68.76±0.88
5	58.34±0.79	76.78±0.71	68.12±0.61
6	59.16±0.26	77.22±0.22	67.89±0.34
7	34.38±0.39	81.22±0.63	68.96±0.84
8	49.12±0.42	46.68±0.41	80.86±0.21
9	58.34±0.25	80.32±0.76	69.22±0.67
10	78.12±0.57	86.56±0.81	54.45±0.92
11	73.12±0.20	55.88±0.24	79.12±0.41
12	61.62±0.48	75.34±0.44	69.76±0.87
13	41.46±0.73	85.12±0.58	52.34±0.23
14	60.78±0.26	76.18±0.17	68.92±0.63
15	134.26±0.16	43.12±0.34	80.34±0.18
16	101.78±0.28	41.13±0.57	81.12±0.59
17	61.26±0.46	75.82±0.69	69.28±0.97

(n = 3)

Five types of nanosponges were prepared using different molar ratios of reactants [17]. The percent practical yield, particle size, polydispersity index and zeta potential were measured and are as presented in table 5.

Table 5: The percent practical yield, Particle size, polydispersity index and zeta potential of different nanosponges

S. No.	Type of NS	Molar ratio (β-CD: DPC)	Practical yield±SD (%)	Mean particle size±SD (nm)	Polydispersity index±SD	Zeta potential±SD
1	NS1	1:2	76.34±2.76	112.56±9.52	0.256±0.005	-23.56±2.12
2	NS2	1:4	81.72±1.98	108.34±6.88	0.312±0.005	-26.56±1.13
3	NS3	1:6	84.58±3.12	116.58±10.42	0.268±0.005	-27.58±3.24
4	NS4	1:8	89.16±2.44	121.42±8.26	0.422±0.005	-24.72±1.74
5	NS5	1:10	91.66±1.89	98.48±5.48	0.272±0.005	-23.98±1.46

(n = 3).

From the trials, the range of polymer to the cross-linker ratio (0.2-0.8), stirring speed (2000-5000 rpm) and stirring time (360-540 min) were identified. Based on the initial results, a Box-Behnken design was employed to optimize the influencing variables.

Mean particle size

Particle size of the nanoformulation ranges from 34.38–134.26 nm. The model terms A, B, C, AB, A^2, B^2 and C^2 were found to be significant with a p-value less than 0.0500. (fig. 1). (fig. 2a and 2b).

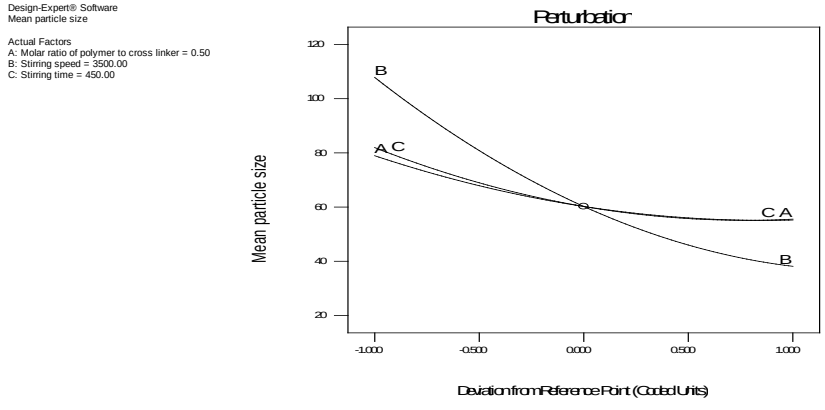
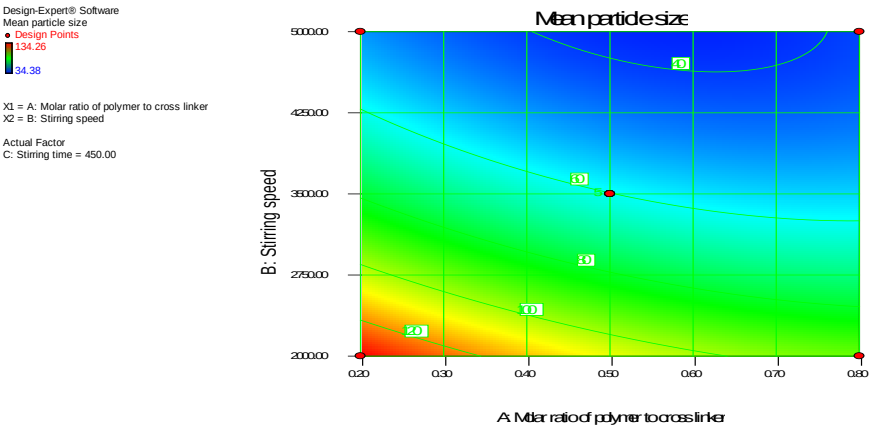
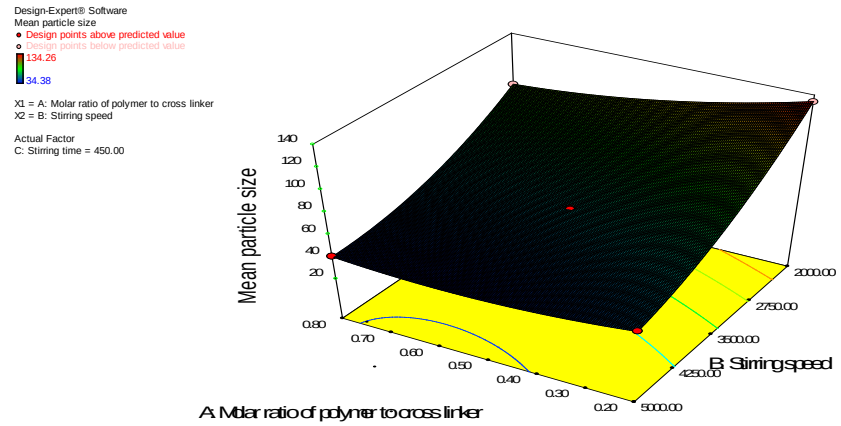


Fig. 1: Two-dimensional perturbation plot-effect of A, B and C on mean particle size



(a)



(b)

Fig. 2: (a). 3D-Contour plot showing the interactive effect of A and B (b). 3D-response surface plot showing the interactive effect of A and B on mean particle size at a constant level of C, respectively

Encapsulation efficiency

The encapsulation efficiency of nanosponges was found to be in the range of 41.13 % to 86.72 %. The polynomial model shown that factors A, B and C have a significant effect on encapsulation efficiency.

The model terms A, B, C, AC, BC, A^2 and C^2 were found to be significant with a p-value less than 0.0500. (fig. 3) (fig. 4a and 4b). (fig. 5a and 5b).

Percent drug release at 6h

Percent drug release at 6h is an important measure to assess the ability of nanosponges to control the release of the drug for a desired period. Percent drug release from the nanoformulation ranges from 52.34-81.12 %.

The mathematical model of percent drug release at 6h (Y3) was found to be significant, with model F-value 896.93. The model term A was found to be significant with a p-value less than 0.0500 (fig. 6).

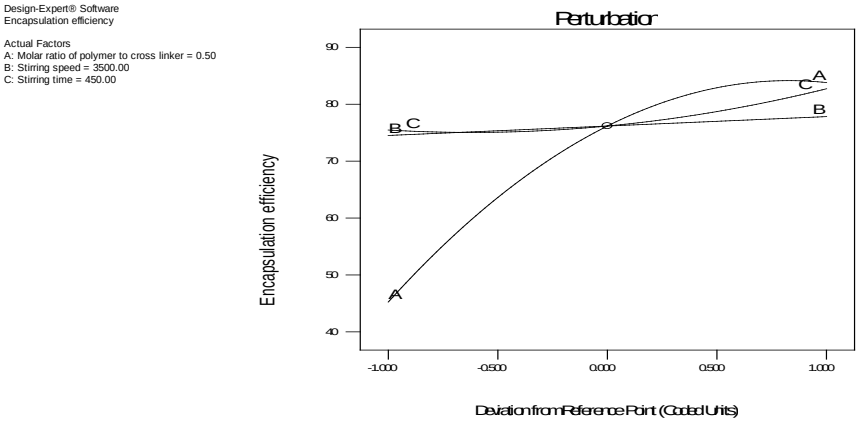
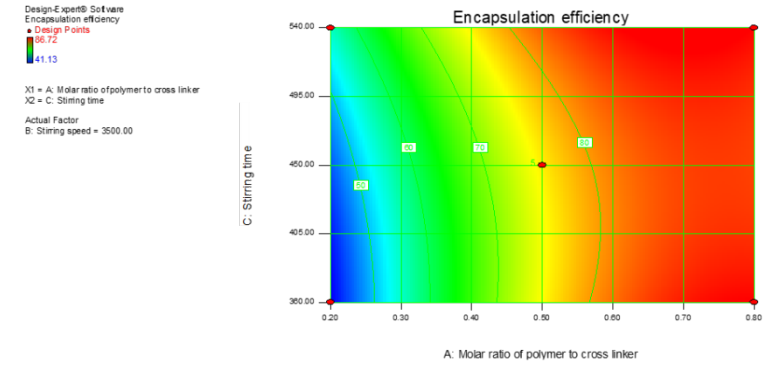
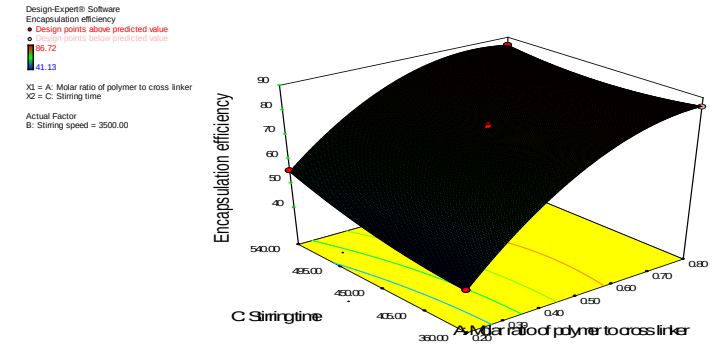


Fig. 3: Two-dimensional perturbation plot-effect of A, B and C on encapsulation efficiency

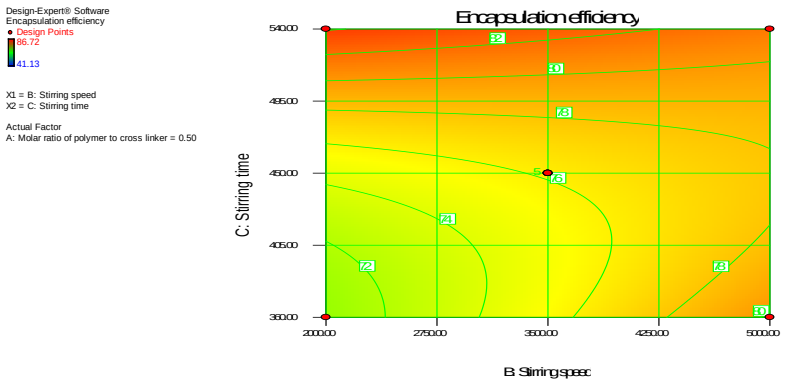


(a)

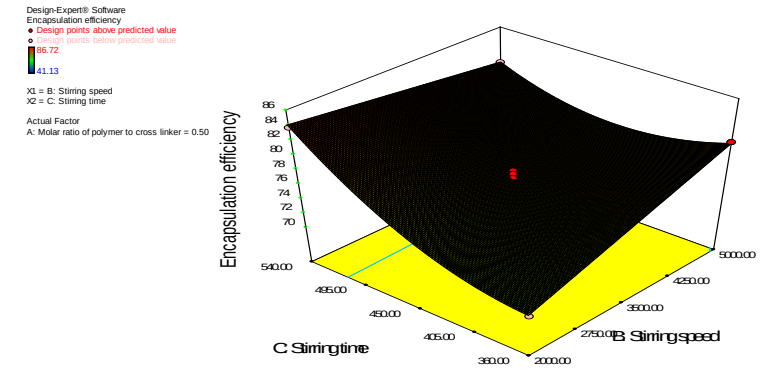


(b)

Fig. 4: (a). 3D-Contour plot showing the interactive effect of A and C (b). 3D-response surface plot showing the interactive effect of A and C on encapsulation efficiency at a constant level of B, respectively



(a)



(b)

Fig. 5: (a). 3D-Contour plot showing the interactive effect of B and C (b). 3D-response surface plot showing the interactive effect of B and C on encapsulation efficiency at a constant level of A, respectively

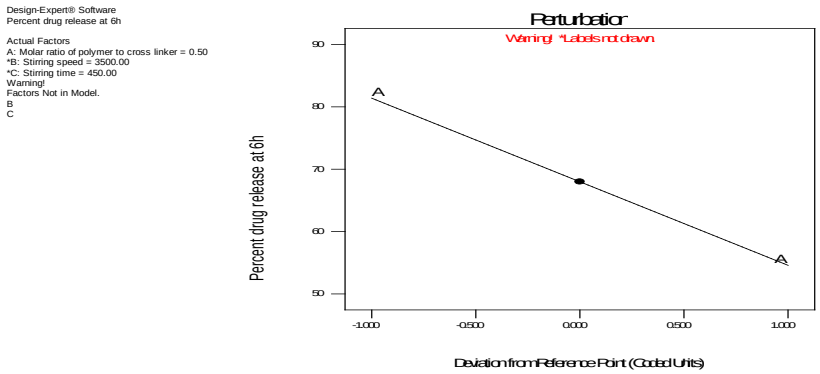


Fig. 6: Two-dimensional perturbation plot-effect of A on percent drug release at 6h

Table 6: Optimum conditions attained by applying restrictions on response parameters

Independent variables	Optimized values	Predicted values			Actual values			
		Mean particle size (Y_1) nm	Encapsulation efficiency (Y_2) %	Percent drug release at 6h (Y_3)	Batch	Mean particle size±SD (Y_1) nm	Encapsulation efficiency±SD (Y_2) %	Percent drug release at 6h±SD (Y_3)
Molar ratio of polymer to cross linker	0.73	38.03	87.04	57.84	F1	41.6±10.52	86.82±1.34	56.98±2.12
Stirring speed	4377				F2	47.23±4.56	85.92±1.22	57.24±3.12
Stirring time	540 min				F3	49.02±3.56	86.68±2.12	57.86±1.92

(n = 3).

Table 7: Particle size, polydispersity index and zeta potential of plain nanosponges and drug-loaded nanosponge formulation

Sample	Mean particle size±SD (nm)	Polydispersity index±SD	Zeta potential±SD (mV)	Drug payload	Encapsulation efficiency±SD
Plain NS	113.14±5.6	0.32±0.005	-21.76±1.2	-	-
F1	41.6±10.52	0.46±0.005	-20.6±2.1	47.89	86.82±1.34
F2	47.23±4.56	0.11±0.005	-22.3±1.6	48.34	85.92±1.22
F3	49.02±3.56	0.31±0.005	-23.7±1.1	47.12	86.68±2.12

(n = 3).

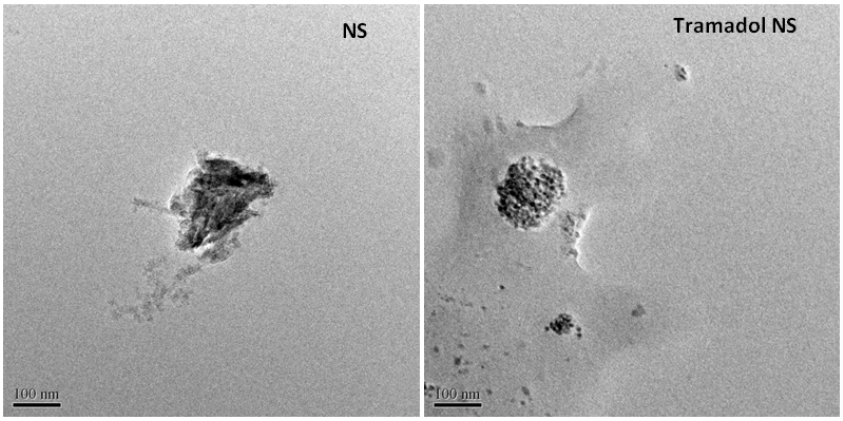


Fig. 7: A. TEM image of plain nanosponges B. Tramadol loaded nanosponge complexes

Optimization

Derringer's desirability function (D) was used to optimize the selected variables, which influences the response parameters [18] table 6.

Morphology and sizes of the tramadol loaded nanosponges

The average particle size of tramadol-loaded nanosponges was revealed around 40-50 nm with low polydispersity index (table 7).

Transmission electron microscopy (TEM) studies showed the regular spherical shape and size of plain nanosponges that are unaffected even after drug encapsulation, as shown in fig. 7.

The percent drug loading and encapsulation efficiency of tramadol nanosponges are presented in table 7.

FTIR spectra of free drug tramadol had characteristic peaks at 3421.83, 3308.03, 2929.97, 2860.53, 2602.06, 2513.33, 2482.47,

1606.76, 1579.75, 1481.38, 1288.49, 1244.13, 1161.19, 981.8, 970.23, 866.07, 774.34, 621.1 and 462.93 cm^{-1}. Plain nanosponge showed a characteristic peak of carbonate bond at around 1740–1750 $cm^{-1,}$ which confirms the formation of cyclodextrin-based nanosponges. Other characteristics peaks of nanosponges were found at 2918 cm^{-1} due to the C–H stretching vibration, 1418 cm^{-1} due to C–H bending vibration and 1026 cm^{-1} due to C–O stretching vibration of primary alcohol. The FTIR spectra of physical mixtures indicated all the peaks of the drug along with some additional peaks of polymers. The Comparison of FTIR spectra of tramadol and tramadol complex showed that there is a major change in the fingerprint region i.e., 900 to 1,400 cm^{-1} as shown in fig. 8. The main characteristic peaks of tramadol were disappeared in the formulations suggesting definite interactions between tramadol and nanosponges [19].

The DSC thermogram of the free drug shows a sharp melting point at approximately 181.75 °C indicating the crystalline nature of the drug. The DSC thermogram of plain nanosponges (NS2) showed exothermic peaks at around 350 °C. Tramadol nanosponge complex also exhibited a broad exothermic peak at around at 350 °C. The complete disappearance of tramadol endothermic peak was observed, indicating drug amorphization and/or inclusion complex formation (fig. 9) [20].

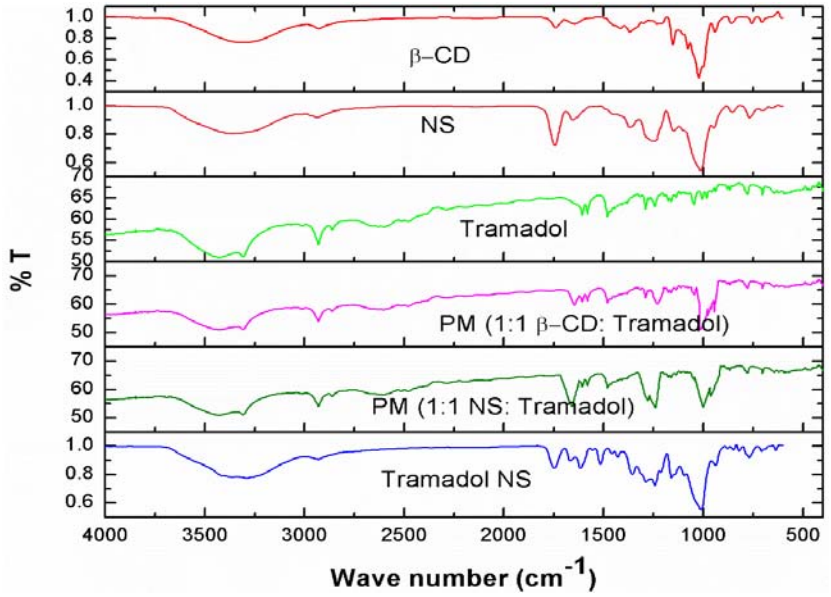


Fig. 8: FTIR spectra of β-Cyclodextrin, plain nanosponges, Tramadol, Physical mixture and tramadol loaded nanosponges

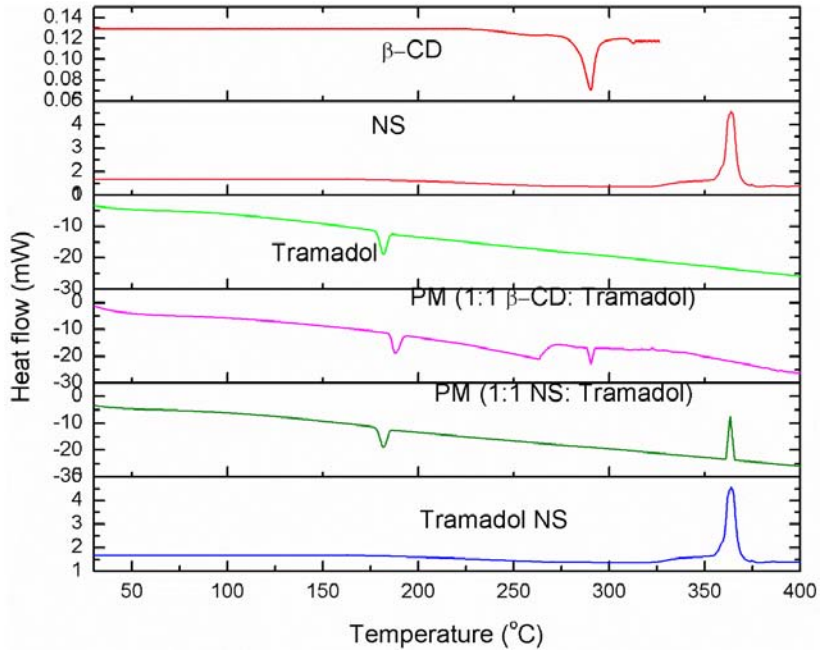


Fig. 9: DSC thermograms of β-Cyclodextrin, plain nanosponges, Tramadol, Physical mixture and tramadol loaded nanosponges

The X-ray diffractograms of plain tramadol exhibited sharp intense peaks at 2θ values of 10.40, 13.00, 15.35, 16.71, 18.49, 20.89, 24.43 and 30.80, confirming the drug's crystal form as shown in fig. 10. The absence of such crystalline peaks of tramadol in the nanosponge complex clearly indicates that the drug is encapsulated in nanosponges [21].

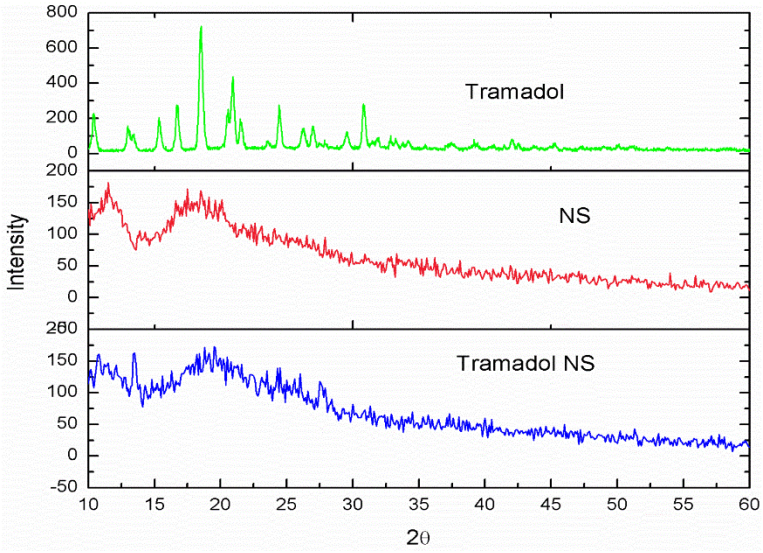


Fig. 10: XRPD pattern of tramadol, plain nanosponges (NS2) and tramadol loaded nanosponge complexes (IBNS)

Preparation of tramadol loaded nanosponges tablets

The prepared tablets were evaluated for different quality control parameters and the results were satisfactory as reported in references [22, 23].

The mean weight ranged from 299.34 to 301.78 mg, the mean thickness from 4.89 to 5.23 mm, the mean hardness from 5.28 to 5.48 kg/cm², the mean friability from 0.53 to 0.82 % and the average percentage drug content from 98.76 to 99.54%, and finally tablets completely disintegrated within 5 min (table 8).

Table 8: Evaluation parameters of tramadol tablets

Formulation	Weight±SD (mg)	Thickness±SD (mm)	Hardness±SD (kg/cm²)	Friability±SD (%)	Drug content±SD (%)
T1	299.34±2.32	4.89±0.76	5.28±0.42	0.53±0.18	98.76±1.22
T2	301.78±0.54	5.15±0.28	5.48±0.52	0.66±0.56	99.54±1.42
T3	301.78±1.32	5.23±0.36	5.36±0.91	0.82±0.29	99.17±0.18

(n = 3).

***In vitro* release study**

Maximum amount of the drug was released within 2 h from the marketed tablet of tramadol as shown in fig. 11. A biphasic release pattern of tramadol from the prepared nanosponges tablets was observed. The initial burst release was ranged from 15.45 % of the drug within 1 h, followed by sustained release of the drug for 12 h.

The percent of tramadol released from nanosponges tablets after 12 h was 87.48 %.

Short term stability studies

Stability study's results indicated that there was no significant change in the visual appearance, hardness, disintegration time, dissolution and drug content, as shown in table 8.

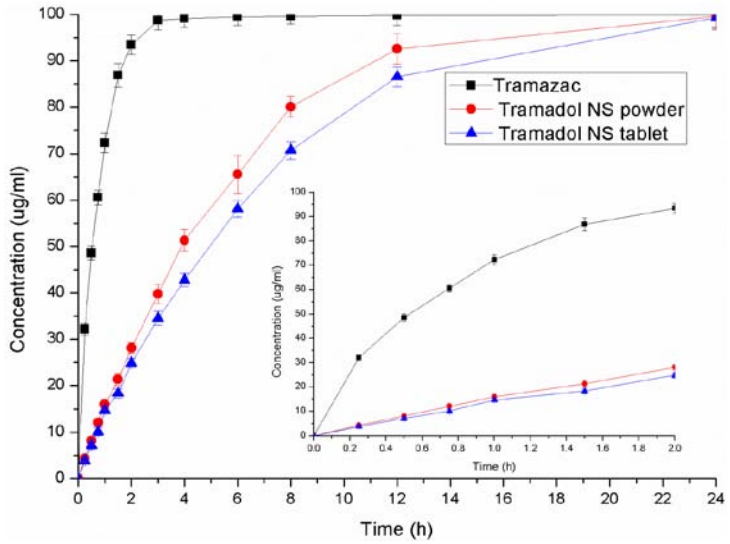


Fig. 11: *In vitro* release of tramadol nanosponges tablets and marketed tablets; results are represented by mean±SD, (n = 3)

Table 8: Results of stability studies of the tramadol tablets (T3)

Condition	Days	Appearance	Hardness±SD	Disintegration time±SD (min)	Percent dissolution±SD at 6 h	Drug content±SD
25±2 °C, 60%±5	0	White	5.23±0.36	2.15±0.22 min	58.12±1.78	99.17±0.18
% RH	90	White	5.38±0.42	2.56±0.31 min	59.33±2.28	98.96±0.39
	180	White	5.42±0.24	2.36±0.52 min	57.76±2.52	98.72±0.44
30±2 °C, 65%±5	0	White	5.23±0.36	2.15±0.22 min	58.12±1.78	99.17±0.18
	90	White	5.42±0.12	2.32±0.31 min	57.78±2.12	98.52±0.22
	80	White	5.48±0.48	2.10±0.26 min	59.14±1.44	99.04±0.34
40±2 °C, 75%±5	0	White	5.23±0.36	2.15±0.22 min	58.12±1.78	99.17±0.18
	90	White	5.33±0.18	2.42±0.16 min	57.34±2.04	99.12±0.28
	180	White	5.46±0.28	2.35±0.12 min	57.62±0.98	98.92±0.20

(n = 3).

CONCLUSION

The freeze-drying process was used in this investigation to prepare tramadol-loaded nanosponges. Because of the reduced drug particle size, the creation of a high-energy amorphous state, and intermolecular hydrogen bonding, the dissolution of the tramadol nanosponges was much higher than that of the pure drug. TEM image revealed the spherical structure of drug-loaded nanosponges. FTIR, DSC and XRD studies confirmed the formation of the inclusion complex of tramadol with nanosponges showing a highly porous structure losing all its crystallinity. The nanosponges were formulated in to tablets and evaluated for weight variation, hardness, friability and disintegration studies and obtained satisfactory results. The maximum quantity of the drug was released within 2 h from the marketed tablet, while the percentage of tramadol released from nanosponges tablets after 12 h was 87.48 percent and finally, stability studies indicated no significant changes within 6months. Overall, this study showed that cyclodextrin nanosponges can be a promising approach for controlled drug delivery of the opioid analgesic tramadol.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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