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Development And Evaluation Of Nanosponges Based Controlled Release Tapentadol Tablets By Box-Behnken Design

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ABSTRACT

Objective: The goal of this work was to create a tapentadol-controlled release formulation using cyclodextrin-based nanosponges as a carrier system.

Methods: Based on the early trials, a three-factor, three-level Box-Behnken design was used to investigate the influence of each independent variable on the dependent variables. Five different forms of cyclodextrin nanosponges (NS1-NS5) were created. The freeze-drying process was used to load tapentadol into nanosponges. The nanosponges were analysed, made into tablets, and tested.

Results: The particle diameters of tapentadol-loaded nanosponges range from 51.38 to 154.56 nm, with encapsulation efficiency ranging from 51.12 to 92.56 percent and drug release percentage at 6 hours ranging from 51.62 to 82.34 percent. Tapentadol interaction with nanosponges was validated by FTIR, DSC, and XRPD investigations. The spherical shape of drug-loaded nanosponges was revealed by TEM imaging**.** The drug may be maintained and released gradually over time by the nanosponge structure.The nanosponges were formulated in to 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 maximum quantity of the drug was released within 2 hours from the marketed tablet, while the percentage of tapentadol released from nanosponges tablets after 12 hours was 86.58 percent and finally stability studies indicated no significant changes within 6months.

Conclusion: Cyclodextrin-based nanosponges tablet formulation demonstrated enhanced complexing ability, stability as well as higher solubility of poorly soluble Tapentadol for regulated drug administration, potentially reducing dose frequency.

Keywords: Tapentadol, Opioid analgesic, Nanosponges, Tablets, Box-Behnken design

INTRODUCTION

Tapentadol is an orally available, synthetic benzenoid that acts as an agonist for the μ-opioid receptor and inhibits the reuptake of noradrenaline, with potential anti-nociceptive activity [1].

Tapentadol is available in the dose of 50 mg, 75 mg, and 100 mg in the form of oral tablets. Tapentadol has an oral bioavailability of 31.9 ± 6.8%, protein binding of 20% and half-life of 4 hrs. It also suffers from extensive first pass metabolism, about 97% of the parent compound is metabolized. None of the metabolites contribute to the analgesic activity [2].

The use of cyclodextrin based nanosponges represents another emerging technological approach to increase drug solubility and stability. Cyclodextrin based nanosponges have attracted great attention from researchers for solving major bioavailability problems such as inadequate solubility, poor dissolution rate and the limited stability of some agents, as well as increasing their effectiveness and decreasing undesirable side effects. These are novel class of hyperbranched polymers extensively studied in the last few years and are easily obtained by reacting cyclodextrin with a suitable cross-linking agent such as carbonyldimidazole or diphenyl carbonate [3]. 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 [6]. 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 [7].

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

MATERIALS AND METHODS

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

Preparation of β-Cyclodextrin Nanosponges (NS)

Cyclodextrin based nanosponges were prepared in our laboratory using diphenylcarbonate for the crosslinking as reported elsewhere [8]. Five types of nanosponges (NS1-NS5) were prepared using different molar ratios of reactants. The molar ratios and concentrations of both the reactants were used as shown in table1.

Table1: 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-cyclodextrinnanosponges for Particle size, polydispersity index and zeta potential were analysed using a Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, UK). [9]

Fabrication of tapentadol -loaded β-Cyclodextrin Nanosponges

Tapentadolloaded nanosponges were prepared by lyophilisation technique. 500 mg of nanosponges were suspended in 100 ml of Milli Q water using a mechanical stirrer. To the above mixture 500 mg of tapentadol was added and the mixture was sonicated for 20 min to prevent aggregation. After lyophilisation the collected dry powder was stored in a desiccator [10, 11].

Design of experiments

Based onBox-Behnken design model provided by Stat-Ease Design Expert® software V8.0.1, 17 model experiments were randomly arranged. (Table2 and 3) [12]

Data analysis

The obtained results were subject to statistical analysis. [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		

Optimization

The optimal points for the independent variables were attained using numerical optimization technique by setting restrictions on the response parameters and influencing factors.

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]

Drug pay load and encapsulation efficiency

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

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

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

Table 3. Observed responses of trial experiments as per BBD

Expt	Molar ratio of polymer to cross linker	Stirring speed (rpm)	Stirring time (min)	Mean particle size (nm)	Encapsulation efficiecny (%)	Percent drug release at 6h (%)
1	0.5	2000	540	146.46	89.74	65.69
2	0.8	3500	540	81.82	79.82	51.62
3	0.8	2000	450	154.56	76.54	55.18
4	0.5	2000	360	152.12	84.23	68.23
5	0.5	3500	450	72.74	91.34	59.86
6	0.5	3500	450	69.96	91.86	60.34
7	0.5	5000	540	51.38	92.56	60.54
8	0.2	5000	450	59.12	57.12	79.82
9	0.5	5000	360	67.34	86.32	62.22
10	0.8	3500	360	78.12	76.56	54.45
11	0.2	3500	540	62.12	57.88	79.12
12	0.5	3500	450	68.84	90.88	59.76
13	0.8	5000	450	61.46	75.12	52.34
14	0.5	3500	450	68.78	90.18	60.92
15	0.2	2000	450	152.26	51.12	82.34
16	0.2	3500	360	88.78	54.13	80.12
17	0.5	3500	450	67.26	90.82	60.28

Preparation of Tapentadol loaded nanosponges tablets

An accurately weighed quantities of tapentadol loaded nanosponges equivalent to 100 mg tapentadol 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 Tapentadol

In vitro release of drug from tapentadol loaded tablets and marketed tapentadol tablet (Tapcynta 100 mg) was performed using the type II USP dissolution apparatus [16]. The dissolution medium was 900 ml 0.1 N HCl for 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 272.4 nm. The dissolution experiments were conducted in triplicate.

Stability Studies

Stability studies of the optimized formulation was carried out for 6months according to ICH guidelines. The stability of tapentadol tablets was estimated after filling and sealing in light protective amber colored bottles with rubber caps and aluminum covering. These were stored at three different temperatures and relative humidity (i.e., 25 ± 2 °C, 60% ± 5; 30 ± 2 °C, 65% ± 5; and 40 ± 2 °C, 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.

RESULTS AND DISCUSSION

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 4.

Table 4: 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 (%)	Mean particle size (nm)	Polydispersity index	Zeta potential
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

(All determinations are expressed as mean±S.D., n=3)

From the trials, the range of polymer to 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 nano formulation ranges from 51.38 – 154.56 nm. The mathematical model of particle size was found to be significant with model F-value 897.03. The model terms A, B, C, AC, BC, A^2, B^2 and C^2 were found to be significant with p value less than 0.0500. (Figure 1). The interactive effect of AC on particle size at constant level of Bis as shown in figure 2a and 2b. The interactive effect of BC on particle size at constant level of A is as shown in figure 3a and 3b.

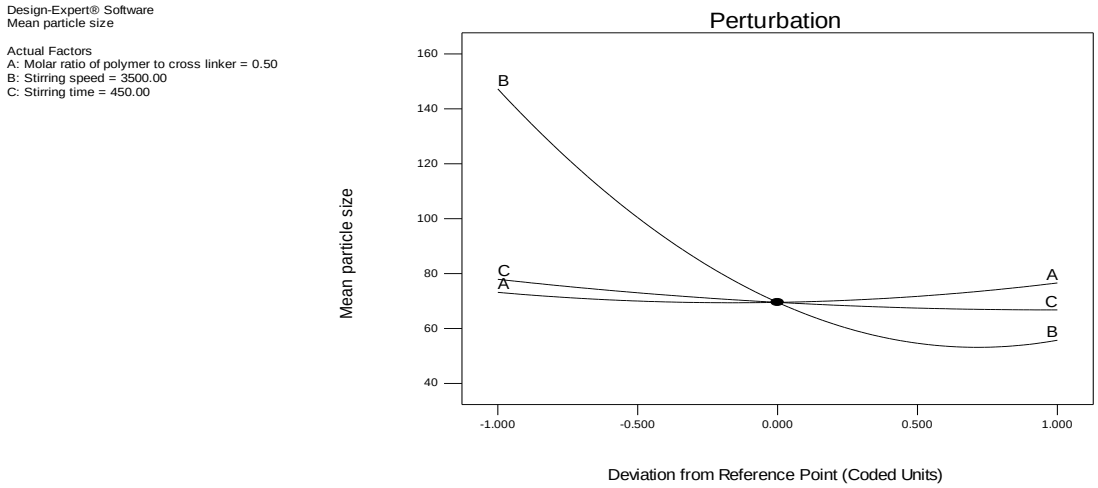
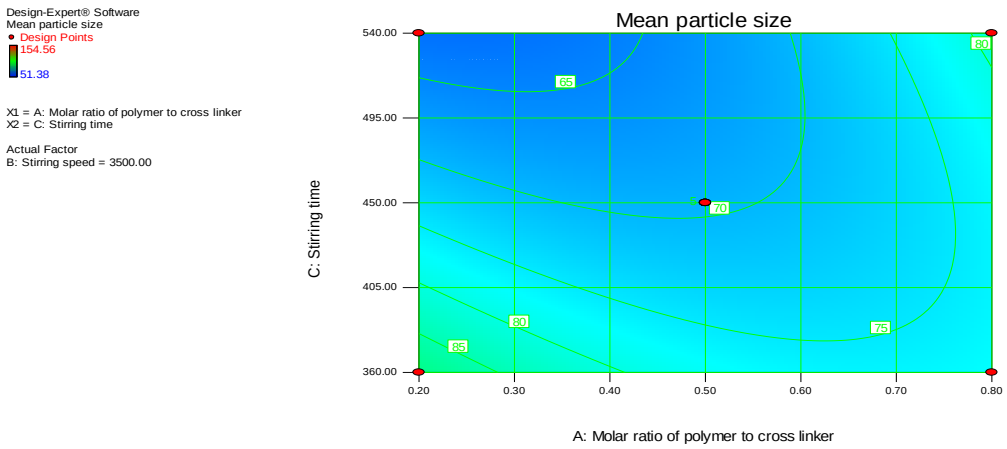
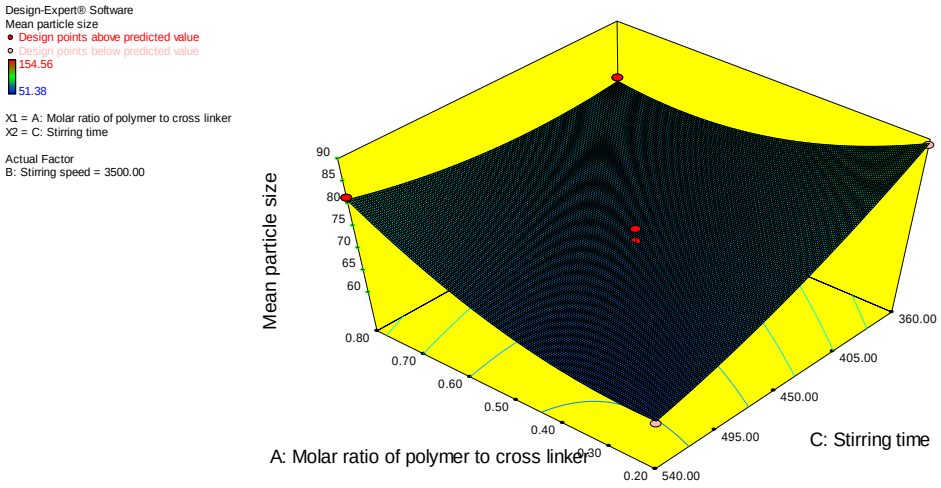


Figure 1. Two-dimensional Perturbation plot- Effect of A, B and C on mean particle size

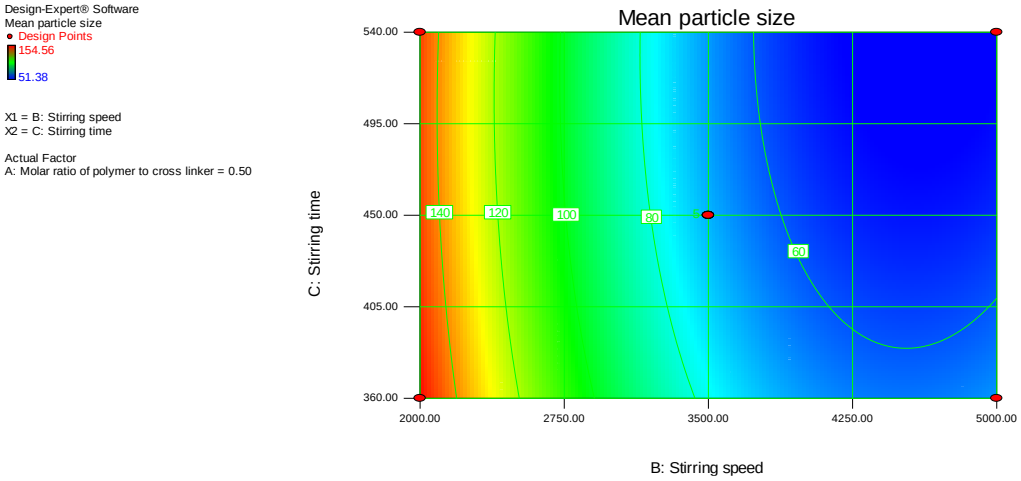


(a)

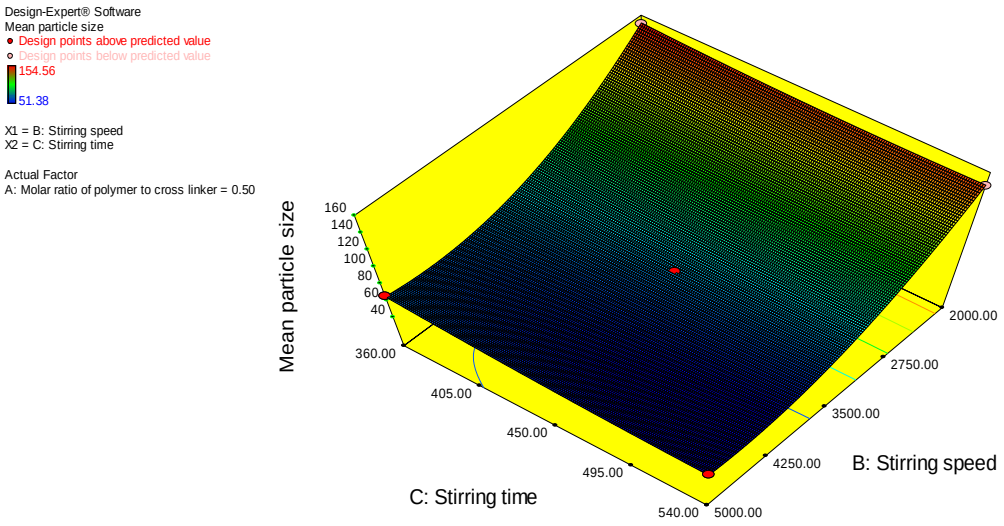


(b)

Figure 2. (a). 3D- Contour plot showing the interactive effect of A and Cand (b). 3D- response surface plot showing the interactive effect of A and C on mean particle size at constant level of Brespectively.



(a)



(b)

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

Encapsulation efficiency:

The encapsulation efficiency of nanosponges was found to be in the range of 51.12 to 92.56 %. The mathematical model of encapsulation efficiency was found to significant with model F-value 1106.13. The model terms A, B, C, AB, A^2 and B^2 were found to be significant with p value less than 0.0500. The effect of individual variables on encapsulation efficiency was described by using perturbation plot (Figure 4). The interactive effect of AB on encapsulation efficiency at constant level of Cis as shown in figure 5a and 5b.

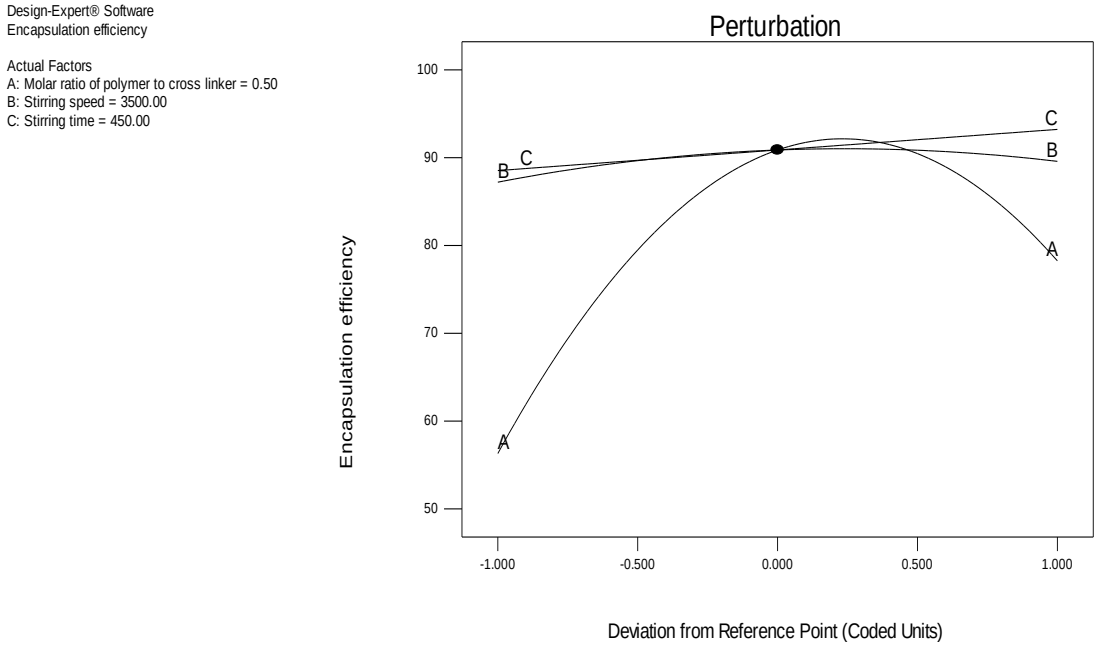
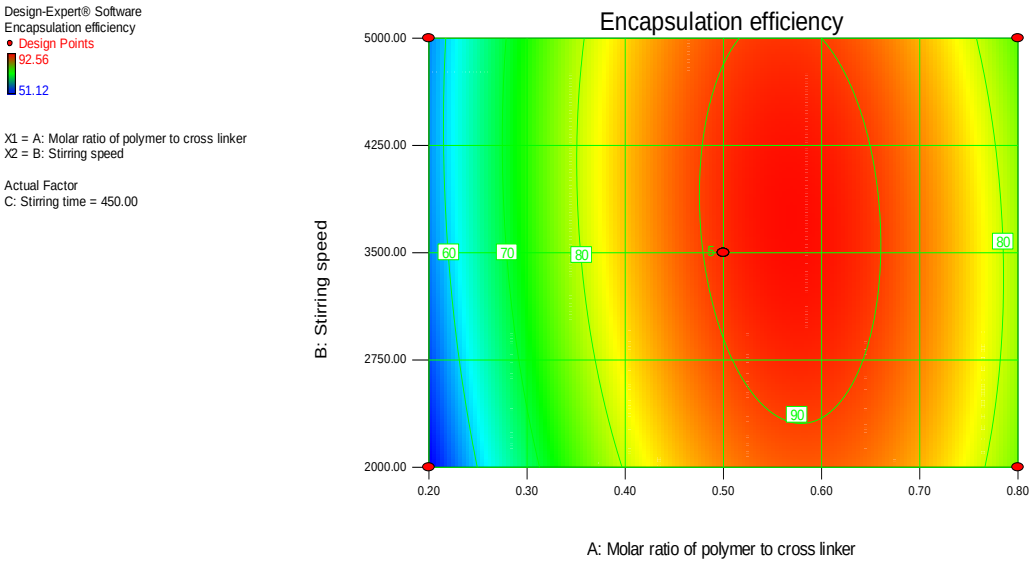
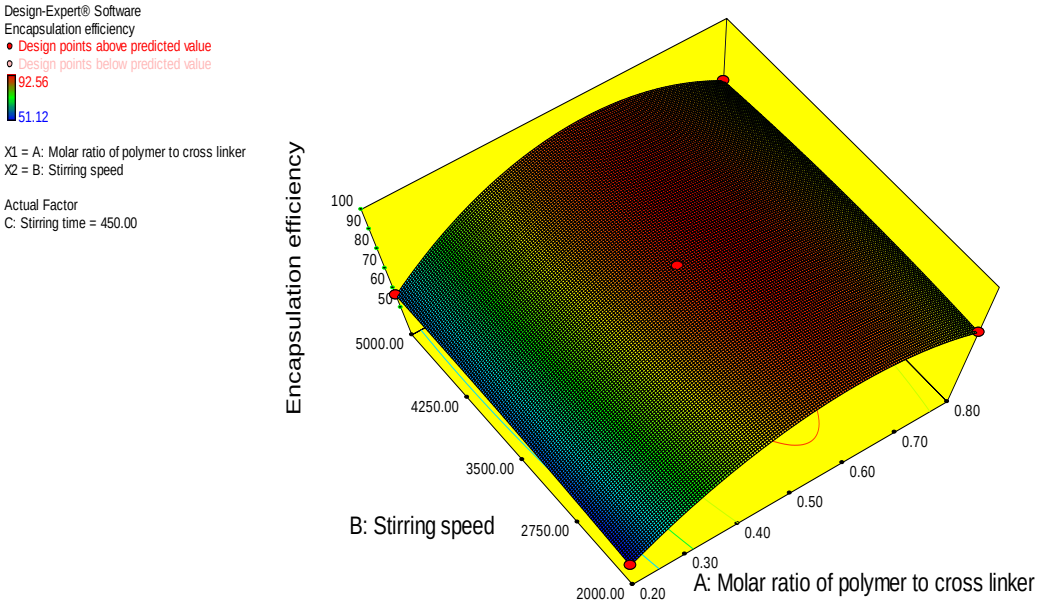


Figure 4. Two-dimensional Perturbation plot- Effect of A, B and C on encapsulation efficiency



(a)



(b)

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

Percent drug release at 6h:

Percent drug release from the nano formulation ranges from 51.62 – 82.34 %. The mathematical model of percent drug release at 6h (Y3) was found to be significant with model F-value 425.98. The model terms A, B, C, A^2, B^2 and C^2 were found to be significant with p value less than 0.0500. (Figure 6).

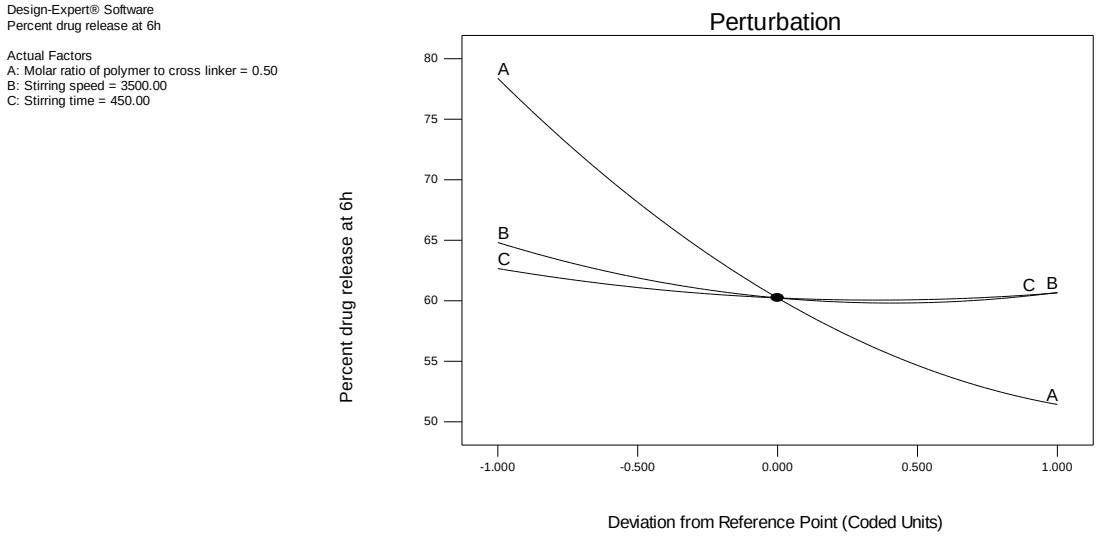


Figure 6. Two-dimensional Perturbation plot- Effect of A on percent drug release at 6h

Derringer's desirability function (D) was used to optimize the selected variables which influences the response parameters. Table5.

Table 5 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 (Y_1) nm	Encapsulation efficiency (Y_2) %	Percent drug release at 6h (Y_3)
Molar ratio of polymer to cross linker	0.64	55.09	91.87	54.52	F1	61.3 ± 2.68	90.42 ± 2.06	55.78 ± 1.78
Stirring speed	4332				F2	59.2 ± 3.12	91.12 ± 1.54	54.98 ± 1.89
Stirring time	518 min				F3	53.4 ± 2.28	90.76 ± 3.12	56.12 ± 2.12

Morphology and sizes of the tapentadol loaded nanosponges

The particle size analysis oftapentadol loaded nanosponges revealed that the average particle size measured by laser light scattering method is around 50- 60 nm with low polydispersity index.

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

The percent drug loading and encapsulation efficiency of prepared tapentadol nanosponges were determined and are presented in table 6.

Table 6. Particle Size, polydispersity index and zeta potential of plain nanosponges and drug loaded na[50nosponge formulation

Sample	Mean particle size ± SD (nm)	Polydispersity Index	Zeta potential (mV)	Drug pay load	Encapsulation efficiency
Plain NS	113.14 ± 5.6	0.32 ± 0.005	-21.76 ± 1.2	-	-
F1	61.3 ± 2.68	0.10 ± 0.005	-24.7 ±1.9	45.78	90.42 ± 2.06
F2	59.2 ± 3.12	0.32 ± 0.005	-25.3 ± 2.12	46.12	91.12 ± 1.54
F3	53.4 ± 2.28	0.22 ± 0.005	-26.8 ± 3.1	46.86	90.76 ± 3.12

(All determinations are expressed as mean ± S.D., n=3)

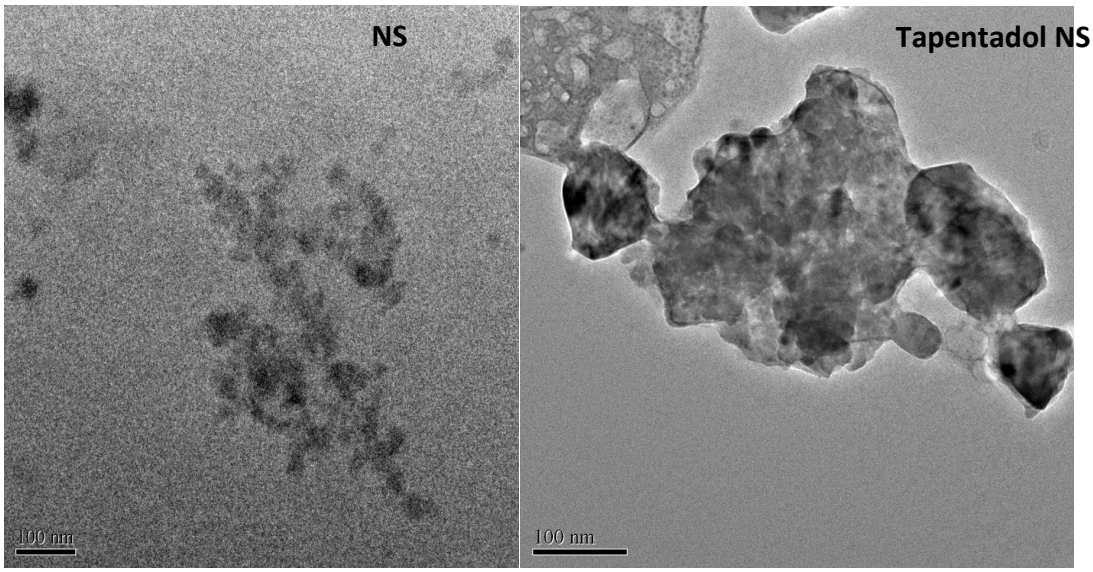


Figure7. A. TEM image of plain nanosponges B.Tapentadol loaded nanosponge complexes

FTIR spectra of free drug had characteristic peaks at 3421.83, 3167.22, 3024.48, 3010.96, 2962.76, 2931.90, 2875.96, 2683.07, 2521.05, 1597.11, 1450.52, 1278.85, 1253.55, 1217.12, 1178.55, 1089.82, 949.01, 877.64, 833.28, 796.63, 711.76 and 682.82 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 Comparison of FTIR spectra of tapentadol and tapentadol complexshowed that there is a major change in the fingerprint region i.e., 900 to 1,400 cm^{-1} as shown in figure 8. The main characteristic peaks of tapentadol were disappeared in the formulations suggesting definite interactions between tapentadol and nanosponges [18].

The DSC thermogram of free drug shows a sharp melting point at approximately 209.25 °C indicating the crystalline nature of the drug. The DSC thermogram of plain nanosponges (NS2) showed exothermic peaks at around 350 °C.Tapentadol nanosponge complex also exhibited a broad

exothermic peak at around at 350 °C. The complete disappearance of tapentadol endothermic peak was observed for the formulation. This phenomenon can be assumed as proof of interactions between the components of the formulation. This can be considered as indicative of drug amorphization and/or inclusion complex formation [19].(Figure 9)

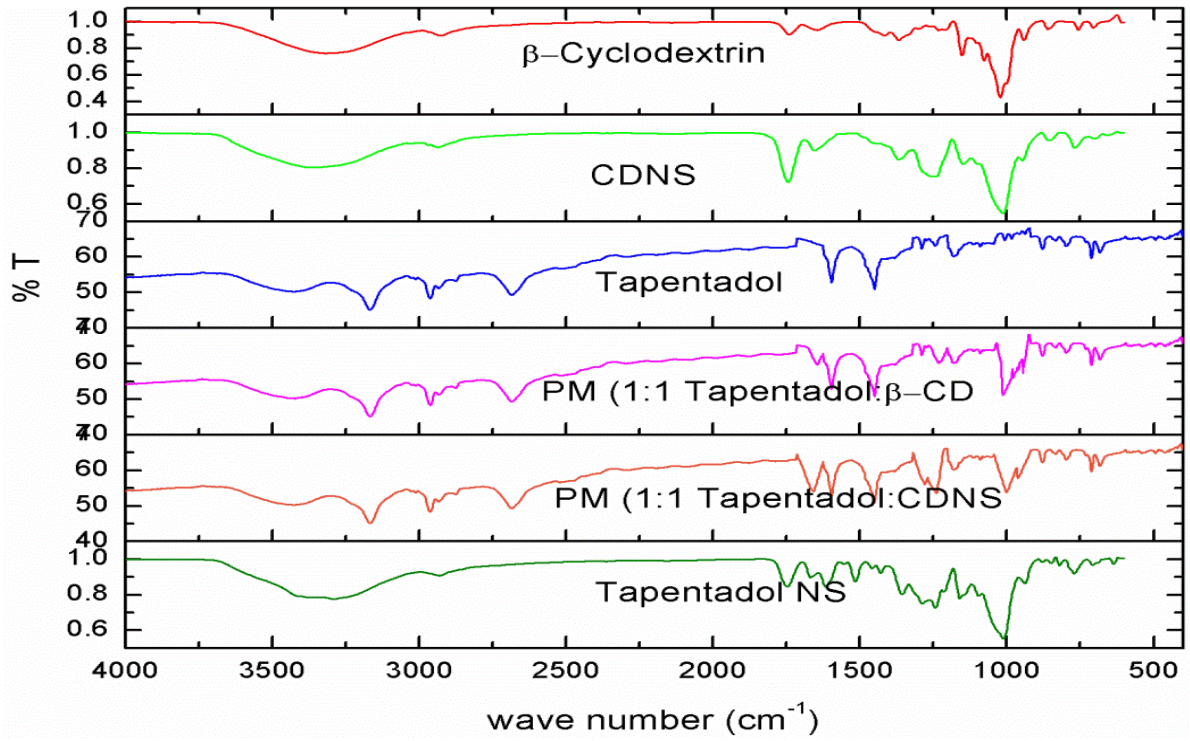


Figure 8. FTIR spectra of β-Cyclodextrin, plain nanosponges, Tapentadol, Physical mixture and Tapentadol loaded nanosponges

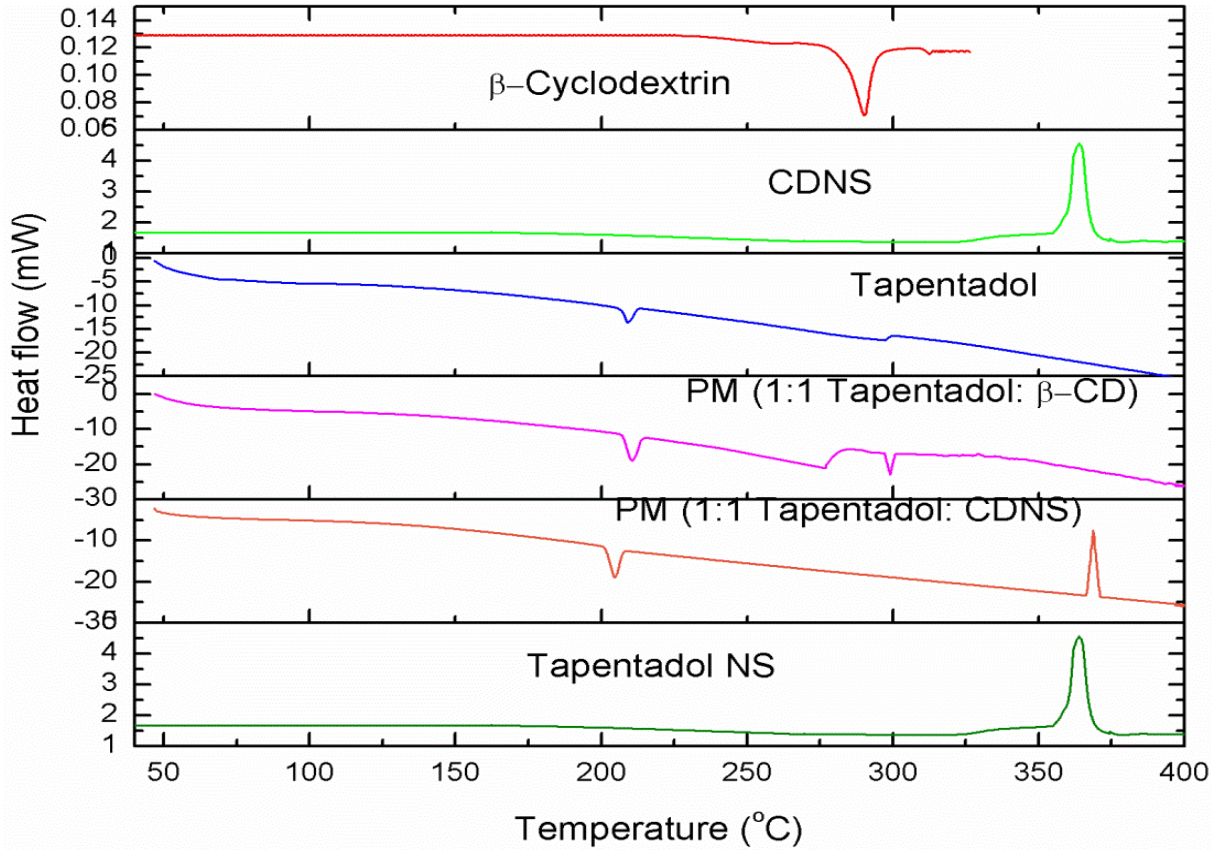


Figure9. DSC thermograms ofβ-Cyclodextrin, plain nanosponges, Tapentadol, Physical mixture and Tapentadol loaded nanosponges

The x-ray diffractograms of plain tapentadol exhibited sharp intense peaks at 2θ values of 14.87, 16.11, 18.50, 20.44, 22.31, 24.96 and 26.21 confirming the drug's crystal form as shown in figure 10. The absence of such crystalline peaks of tapentadol in nanosponge complex clearly indicates that the drug is encapsulated in nanosponges [20].

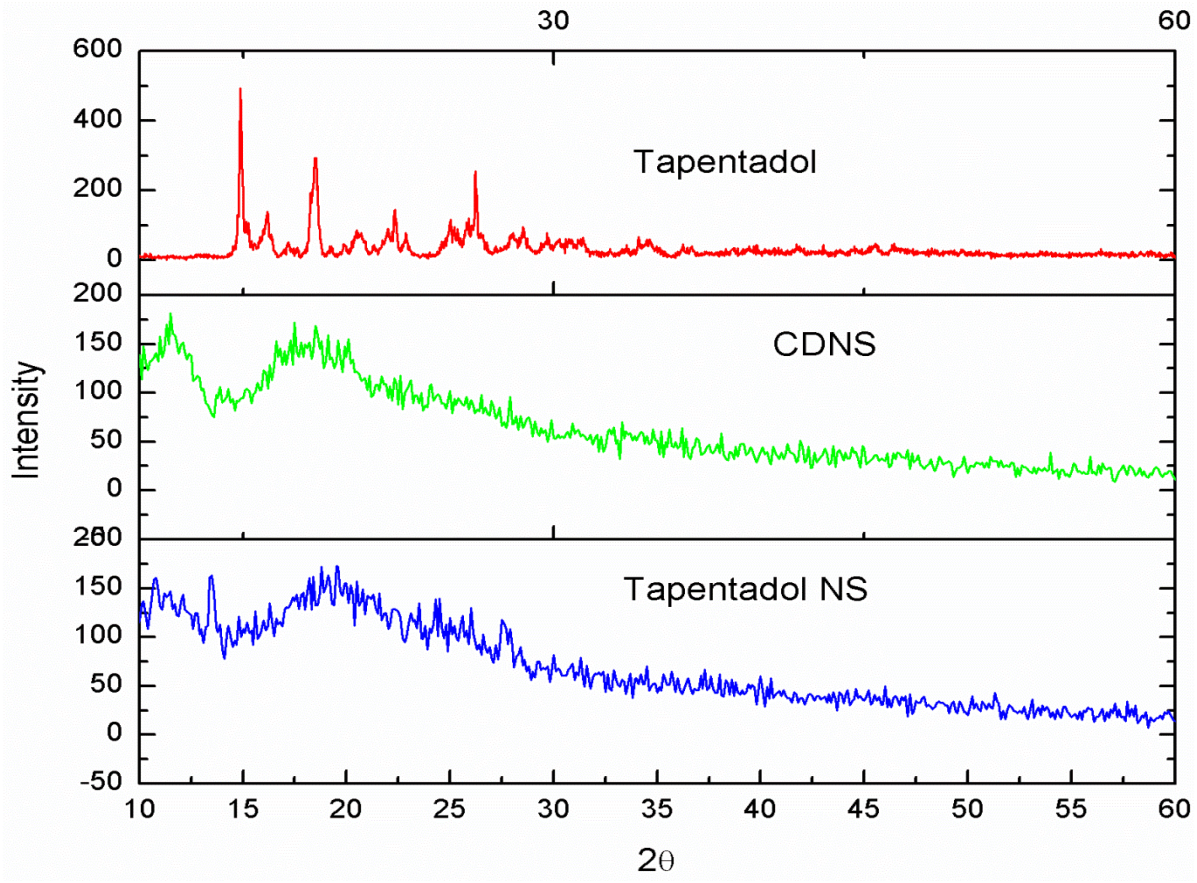


Figure10. XRPD pattern of Tapentadol, plain nanosponges (NS2) and tapentadol loaded nanosponge complexes (IBNS)

Preparation of Tapentadol loaded nanosponges tablets

The mean weight ranged from 298.56 mg to 302.12 mg.

The mean thickness ranges from 4.98 mm to 5.22 mm.

The mean hardness ranges from 5.08 kg/cm^2 to 5.46 kg/cm^2.

The mean friability values range from 0.29 % to 0.76 % and the average percentage drug content ranges from 98.92 % to 99.58 %, as shown in Table 7. The prepared tablets completely disintegrated within 5 min.

Table 7. Evaluation parameters of tapentadoltablets

Formulation	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
T1	300.19	5.14	5.46	0.29	99.34
T2	302.12	4.98	5.08	0.76	98.92
T3	298.56	5.22	4.86	0.59	99.58

In vitro release study

Maximum amount of the drug was released within 2 hrs from the marketed tablet of tapentadolas shown in figure 11. A biphasic release pattern of tapentadol from the prepared nanosponges tablets was observed. The initial burst release was ranged from 14.68 % of drug within 1 h, followed by

sustained release of the drug for 12 h. The percent of tapentadol released from nanosponges tablets after 12 h was 86.58 %.

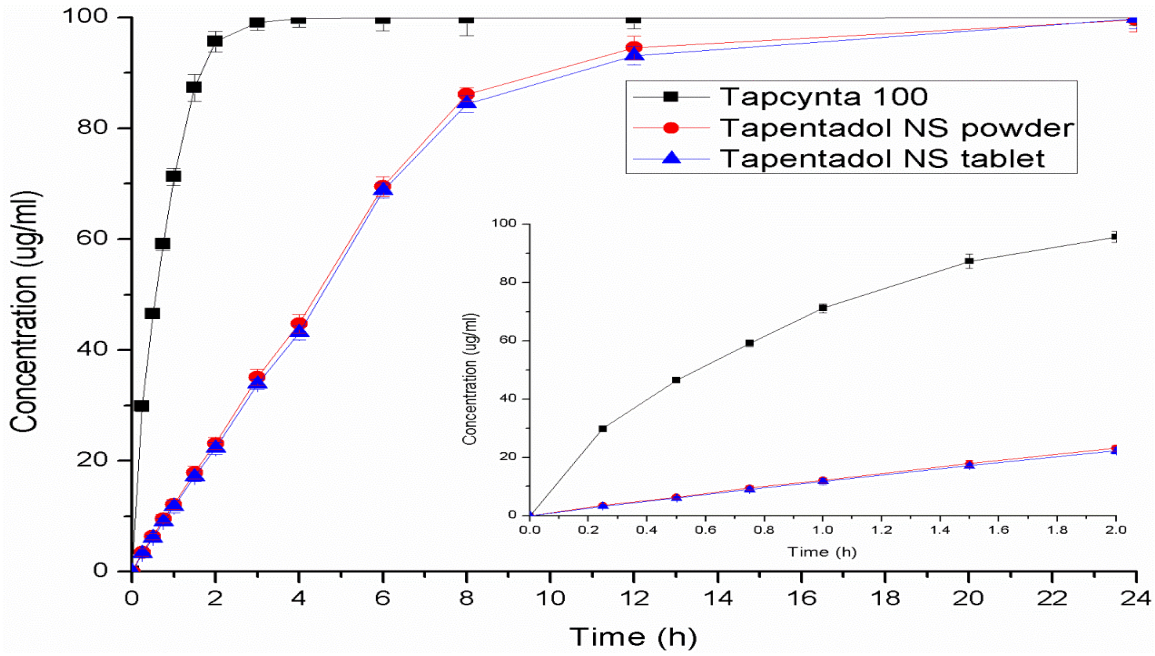


Figure11. In vitro release of Tapentadol nanosponges tablets and marketed tablets

Short Term Stability Studies

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

Table 8. Results of stability studies of the Tapentadoltablets (T3)

Condition	Days	Appearance	Hardness	Disintegration time (min)	Percent dissolution at 6 h	Drug content
25 ± 2 °C, 60% ± 5 % RH	0	White	5.14 ± 0.24	2.5 ± 0.1 min	68.78 ± 1.32	99.34 ± 0.24
	90	White	5.26 ± 0.18	2.4 ± 0.3 min	67.76 ± 0.88	98.88 ± 0.38
	180	White	5.32 ± 0.20	2.6 ± 0.2 min	69.12 ± 2.32	98.56 ± 0.42
30 ± 2 °C, 65% ± 5	0	White	5.14 ± 0.24	2.5 ± 0.1 min	68.78 ± 1.32	99.34 ± 0.24
	90	White	5.32 ± 0.28	2.7 ± 0.3 min	67.87 ± 2.22	99.18 ± 0.48
	80	White	5.44 ± 0.16	2.6 ± 0.2 min	68.34 ± 2.54	99.04 ± 0.18
40 ± 2 °C, 75% ± 5	0	White	5.14 ± 0.24	2.5 ± 0.1 min	68.78 ± 1.32	99.34 ± 0.24

	90	White	5.26 ± 0.18	2.8 ± 0.4 min	67.98 ± 0.78	98.78 ± 0.42
	180	White	5.34 ± 0.20	2.7 ± 0.1 min	68.32 ± 1.56	99.12 ± 0.36

CONCLUSION

In this study, tapentadol-loaded nanosponges were prepared using the freeze-drying method. The spherical shape of drug-loaded nanosponges was revealed by TEM imaging. FTIR, DSC, and XRD analyses indicated the development of a tapentadol inclusion complex with nanosponges. The freeze-drying procedure results in a fluffy mass powder with a highly porous structure that has lost all its crystallinity, as validated by an XRPD investigation. The dissolution of tapentadol nanosponges tablets was substantially greater than that of the marketed due to the decreased drug particle size, the formation of a high-energy amorphous state, and intermolecular hydrogen bonding. The drug may be maintained and released relatively slowly by the nanosponge structure. Stability studies indicated the formulation was stable for 6months. The findings of this study imply that tapentadol nanosponges are potential for regulated medication administration, which can minimise dose frequency.

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