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Research Article

FORMULATION AND *IN-VITRO* EVALUATION OF CARBAMAZEPINE NANOSPONGE

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ABSTRACT

The main purpose of this investigation study was to fabricate nanosponges with good entrapment efficiency and percentage of yield to enhance the solubility and dissolution rate of poorly water-soluble antiepileptic molecules of Carbamazepine. Molecule was selected as the choice of drug as it belongs to BCS class II with low solubility and high permeability. Carbamazepine nanosponges were prepared to enhance the solubility and dissolution rate using the Emulsion solvent diffusion technique. Nanosponges were formulated using different polymers ratio like Ethyl cellulose and polyvinyl alcohol. The batch-containing ratio 2:1:2 of Drug, Ethyl cellulose and PVA gave maximum entrapment efficiency and percentage of yield. Reduced size up to nano levels of nanosponges are confirmed through particle size analysis. Optimized nanosponges were further mixed with common excipients and compressed in to oral tablets. The optimized nanosponges were subjected for Practical yield, Drug content, Saturation solubility, Zeta potential (ZP), Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-ray powder Diffractometry and Scanning electron microscopy (SEM). Pre and post compression parameters were also studied. FT-IR revealed no chemical incompatibility between drug and polymer. Solubility and increase in dissolution rate as compared to the plain drug were also demonstrated for nanosponge formulation. The tablets of Carbamazepine nanosponges were successfully prepared and the formulation was found to be stable.

Keywords: Carbamazepine, Nanosponges, Solubility enhancement, Kinetic, Dissolution rate.

1. INTRODUCTION

Despite of having good therapeutic efficiency, many available drugs molecules are still recognized as poorly aqueous soluble drugs leading to incomplete absorption and giving low bioavailability. In such cases, solubility is the main criteria that limit the potential of such drugs. The drugs which are poorly soluble cause a failure of the formulation during development processes. Poor water solubility in turns low dissolution rate profile of the drug candidate in aqueous gastrointestinal fluid relates to insufficient bioavailability. Dissolution is a process in which a solid substance goes into solution. As per equation provided by Noyes-Whitney the rate of dissolution is directly proportional to the solubility of the drug. Hence, the drug solubility is important factor for dissolution profile which mean for good absorption and bioavailability of the drugs. Dissolution is a process that determines the degree and the rate of absorption of the drugs [1].

Anti-epileptic drugs (AEDs) are the most sort of treatment for the people with epilepsy. And up to 70% (7 in 10) people with epilepsy could have their seizures completely controlled with AEDs. There are around 26 AEDs are available to treat seizures, and different AEDs work for various type of seizures. Anticonvulsants medicines are usually work by calming hyperactivity in the brain in various ways.

Carbamazepine is usually used for the treatment of seizure disorders and neuropathic pain. It also be used off-label as a second-line treatment for bipolar disorder and in combination with an antipsychotic in some cases of schizophrenia when treatment with a

conventional antipsychotic alone has failed. The drug is also claimed to be effective for Attention deficit hyperactivity disorder (ADHD). This antiepileptic molecule is having BCS class II, water insoluble [2, 3].

An advance version of nano-particulate systems is entitled as nanosponges. These are designed with hyper cross-linked polymer based colloidal structure. Nanosponges are mostly spongy polymeric delivery systems, which are minor sphere-shaped particles with great porous external. These are not really sponge like structured shape, more like a network of molecule in three dimensional structures. Nanosponges are very small with a size of about virus having diameter below 1 μ. These are complexes in solution along with tiny molecules coined as cross-linkers that helps to break different parts of the polymer collectively. There are many different techniques available for nanosponge preparation, but in current research "Emulsion solvent diffusion method" is used to formulate nanosponges [4-13].

2. MATERIAL AND METHODS

Carbamazepine was obtained from INTAS Pharmaceuticals Ltd., Ahmedabad, and Gujarat, India. Magnesium stearate and microcrystalline cellulose were obtained from S.D. Fine Chemical, Mumbai, India. Ethyl cellulose (EC) and Polyvinyl alcohol (PVA) was obtained from S.D. Fine Chemical, Mumbai, India. Pluronic F68 was obtained from BASF Corporation, Mumbai, India. Dichloromethane was obtained from Finar Lab, Ahmedabad, India. Crosscarmellose Sodium was obtained from Roquette, Mumbai, India.

2.1. Preparation of Carbamazepine NS using emulsion solvent diffusion technique

Drug loaded nanosponges were prepared by different proportions of ethyl cellulose, polyvinyl alcohol and Pluronic F68 by emulsion solvent diffusion technique. The disperse phase consisting of 100 mg of carbamazepine and specified quantity of ethyl cellulose dissolved in 30 mL of dichloromethane was slowly added to a definite amount of PVA in 100 mL of aqueous continuous phase. The mixture was stirred at 1000 rpm on a magnetic stirrer for two hours. The formed nanosponges were collected by vacuum filtration and dried in an oven at 40 °C for 24 h. [14-17]

Table 1: Formulations of Nanosponges of Carbamazepine

Ingredient	F1	F2	F3	F4	F5	F6
Carbamazepine (CBZ)	160	160	160	160	160	160
Polyvinylalcohol (PVA)	160	320	480	160	320	480
Ethylcellulose (EC)	80	80	80	160	160	160
Pluronic F68	100	100	100	100	100	100
Dichloromethane (DCM)	30	30	30	30	30	30
Water (up to)	100	100	100	100	100	100
Calcium Chloride (5%)	QS	QS	QS	QS	QS	QS

Table 2: Formulations of Immediate Release Tablets of Carbamazepine

Name of the Ingredient	Mg/tablet
Carbamazepine Nanosponges equivalent to Carbamazepine 160mg	500.000
Microcrystalline Cellulose	175.000
Crosscarmellose Sodium	21.500
Magnesium Stearate	3.500
Total Weight of Tablet (mg)	700.000

2.2. Evaluation and characterization of Carbamazepine Nanosponges [18-20]

2.2.1. Percentage yield

The percentage of production yield was calculated from the weight of dried nanosponges recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

% Yield = Practical mass (Nanosponges)/Theoretical mass (Polymer+Drug) × 100

2.2.2. Drug entrapment efficiency

Powdered nanosponges were suspended in 10 ml of phosphate buffer (pH 6.8). After 24 h, the solution was

filtered, the filtrate was centrifuged at 2000 rpm for 3 min, and then analyzed for drug content spectrophotometrically (Shimadzu UV-1800, Japan)), and the concentration of soluble drug was calculated. The amount of drug entrapped in the nanosponges was calculated by the following formula:

Entrapment efficiency = {(Weight of drug added formulation - weight of drug recovered from Nanosponges) /Weight of drug added during formulation}

2.2.3. Particle size analysis

The average particle size of Carbamazepine nanosponges were determined by photon correlation spectroscopy (PCS) using a Nano ZS-90 (Malvern Instruments limited, UK) at a fixed angle at 25°. Sample was diluted 10 times with distilled water and then it was analyzed for particle size.

2.2.4. Zeta potential

The zeta potential was measured for the determination of the movement velocity of the particles in an electric field and the particle charge. In the present work, the nanosponges was diluted 10 times with distilled water and analyzed by Zetasizer using Laser Doppler Micro electrophoresis (Zetasizer nano ZS, Malvern instruments Ltd., UK).

2.2.5. Particle shape and morphology

The shape and morphology of nanosponges was examined using Scanning Electron Microscopy (LEO 440I). Sample was deposited on a glass slide, and was kept under vacuum. The samples were coated with a thin gold/palladium layer using a sputter coater unit. The scanning electron microscope was operated at an acceleration voltage of 10 kV.

2.2.6. Fourier transforms infrared spectroscopy studies

The FTIR spectral measurements were taken at ambient temperature using a Perkin Elmer Model 1600 (USA). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

2.2.7. Differential scanning calorimetric studies

Differential scanning calorimetry (DSC-60, Shimadzu Corporation, Japan) studies were carried out to check compatibility between drug and polymers. DSC was used after calibration with Indium and lead standards, samples (3-5 mg) were heated (range 40-220 ºC, 10 ºC /min) in crimped aluminium pans under a nitrogen atmosphere. The enthalpy of fusion and melting point were automatically calculated.

2.2.8. In-vitro dissolution studies

900 ml of 0.1 N HCl was placed in vessel and the USP apparatus type II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37 ºC±0.5 ºC. Nanosponge powder was placed in the vessel and operated for 240 minutes in 0.1 N HCl at 50 rpm. At definite time intervals, 5 ml of the receptor fluid were withdrawn, filtered, diluted and analyzed spectrophotometrically.

2.3. Preparation of Immediate Release Tablets

Immediate Release Tablets of the Carbamazepine was prepared by optimized Nanosponges formulation equivalent to 160 mg with MCC, CCS and magnesium stearate and were compressed by direct compression method. The prescribed quantities of nanosponges, diluent, disintegrant and lubricant were mixed homogeneously and the mixture was then compressed into tablets using a 12mm, biconcave punches on a 'Eliza Press 10 station rotary single layer compression machine.

2.4. Pre-compression Parameters for Nanosponges [21, 22]

2.4.1. Bulk density

It is the ratio of mass to the bulk volume of the powder. It is useful in the determination of compressibility index. Bulk density is significant parameter which influences the pack size of the container. One gm nanosponge loaded carbamazepine and nanosponge powder blend were weighed and placed in a measuring cylinder; the volume occupied by it is noted.

It is defined mathematically as: Bulk density = Mass of powder / Bulk volume

2.4.2. Tapped density

It is the ratio of mass to the tapped volume of the powder. One gm nanosponge loaded carbamazepine and nanosponge powder blend were weighed and placed in a measuring cylinder and then it is tapped on a wooden base for about 500 times and finally the volume occupied by it is noted. Tapped density = mass of powder / tapped volume

2.4.3. Powder flow properties

The wide variety of methods for characterizing the powder flow are generated in the wide spread use of powders in the pharmaceutical industry because no single and simple test method can adequately characterize the flow properties of pharmaceutical powders. Four commonly reported methods for testing powder flow are Angle of Repose, Compressibility Index and Hausner's Ratio and Shear Cell. In the current research powder flow properties were determined by first three methods.

2.4.3.1. Angle of repose

The angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. It is the constant, three dimensional angle (relative to the horizontal base) assumed by a cone – like pile of material. The maximum angle which is formed b/w the surface of a pile of powder and horizontal surface is called the angle of repose. The nanosponge loaded carbamazepine and nanosponge powder blend were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed. It is calculated by using the formula: $\theta = \tan^{-1}(h/r)$

2.4.3.2. Compressibility index/consolidation index/ carr's index

The bulk density and tapped density were measured for and then compressibility index was calculated using the formula: Consolidation index [C] (%) = {(Tapped density – Bulk density)/ Tapped density} x 100

2.4.3.3. Hausner's ratio

Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula:
Hausner's ratio [H) = Tapped density / Bulk density
The relationship between Carr's index and Hausner's ratio is given below:
H = 100/100-C

2.5. Evaluation of Immediate release tablets [19]

2.5.1. Weight variation

The weight variation test was performed according to specifications given in the Indian Pharmacopoeia on 20 tablets. The maximum acceptable limit is ±5.0% deviation of an individual weight from average weight.

2.5.2. Thickness

The thickness of 20 randomly selected tablets from each formulation was determined in mm using a vernier caliper (Pico India).

2.5.3. Hardness

Twenty tablets were randomly selected from each formulation and measured hardness in kg/cm^2 using Monsanto type hardness tester.

2.5.4. Friability

Tablet friability was measured using the Roche Friabilator. Randomly selected twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The friability was determined as the mass loss in percent with = {(Initial weight – Final weight)/Initial weight} ×100, where the acceptable limits of the weight loss should not be more than 1%.

2.5.5. Assay

Ten tablets were randomly selected from each formulation and crushed to a fine powder in mortar with pestle. Weigh accurately equivalent to unit dose of drug from fine powder then transfer in 100 mL volumetric flask, 100 mL of methanolic HCL was added to dissolve and sonicated for 20 minutes. Drug was extracted by centrifuging at 1000 rpm for 30 min. The samples were filtered, diluted and analyzed UV spectrophotometrically.

2.5.6. In-vitro dissolution studies

900 ml of 0.1 N HCl was placed in vessel and the USP apparatus type II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37 °C±0.5 °C. Compressed nanosponge loaded powder tablets were placed in the vessel and operated for 240 minutes in 0.1 N HCl at 50 rpm. At definite time intervals, 5 ml of the receptor fluid were withdrawn, filtered, diluted and analyzed spectrophotometrically.

2.5.7. Stability Studies

The stability testing studies were performed for optimized batch of formulation as per the ICH (International Conference on Harmonization) guide-lines. The guidelines were followed for stability testing. The optimized batch of tablets was stored in aluminium foil and the stability testing was carried for 3 months. According to ICH guidelines the temperature was kept 40°C ± 2°C and relative humidity of 75% RH ± 5%.

The samples were tested after every one month and analyzed for changes like in its appearance and drug content. The changes observed were noted.

3. RESULTS AND DISCUSSION

From the results it was observed that all formulations have shown the size in Nano level with negative zeta potential, however formulation F1 has shown very less size and more zeta potential with more percentage yield and entrapment efficiency than others. However, dissolution was performed for all formulation to select best formulation.

Table 3: Results of Carbamazepine loaded NS

Formulation	Percentage Yield	Entrapment Efficiency	Assay (%)	Particle Size (nm)	Zeta Potential (mV)
F1	97.8 ± 2.32	93.5 ± 0.45	99.8 ± 1.05	113.0	-9.03
F2	94.2 ± 1.23	88.5 ± 1.42	98.8 ± 0.95	114.4	-7.15
F3	86.8 ± 1.44	73.9 ± 2.11	99.4 ± 1.56	125.6	-6.24
F4	84.6 ± 0.88	88.9 ± 0.85	99.5 ± 155	132.4	-5.46
F5	82.5 ± 3.22	81.2 ± 0.88	98.9 ± 1.22	145.7	-4.35
F6	73.6 ± 3.42	80.3 ± 1.18	97.9 ± 0.55	156.9	-3.46

(Mean ± SD, n=3)

Table 4: Results of pre-compression Parameters for Carbamazepine loaded NS & NS powder blend

Parameters	Bulk Density*	Tapped Density*	Angle of repose*	Compressibility index	Hausner's ratio
Carbamazepine Nanosponges	0.34 ± 2.55	0.42 ± 2.85	32 ± 2.55	19.05	1.24
Nanosponges powder blend	0.47 ± 1.96	0.54 ± 2.25	27 ± 1.85	12.96	1.15

*(*Mean ± SD, n=3)*

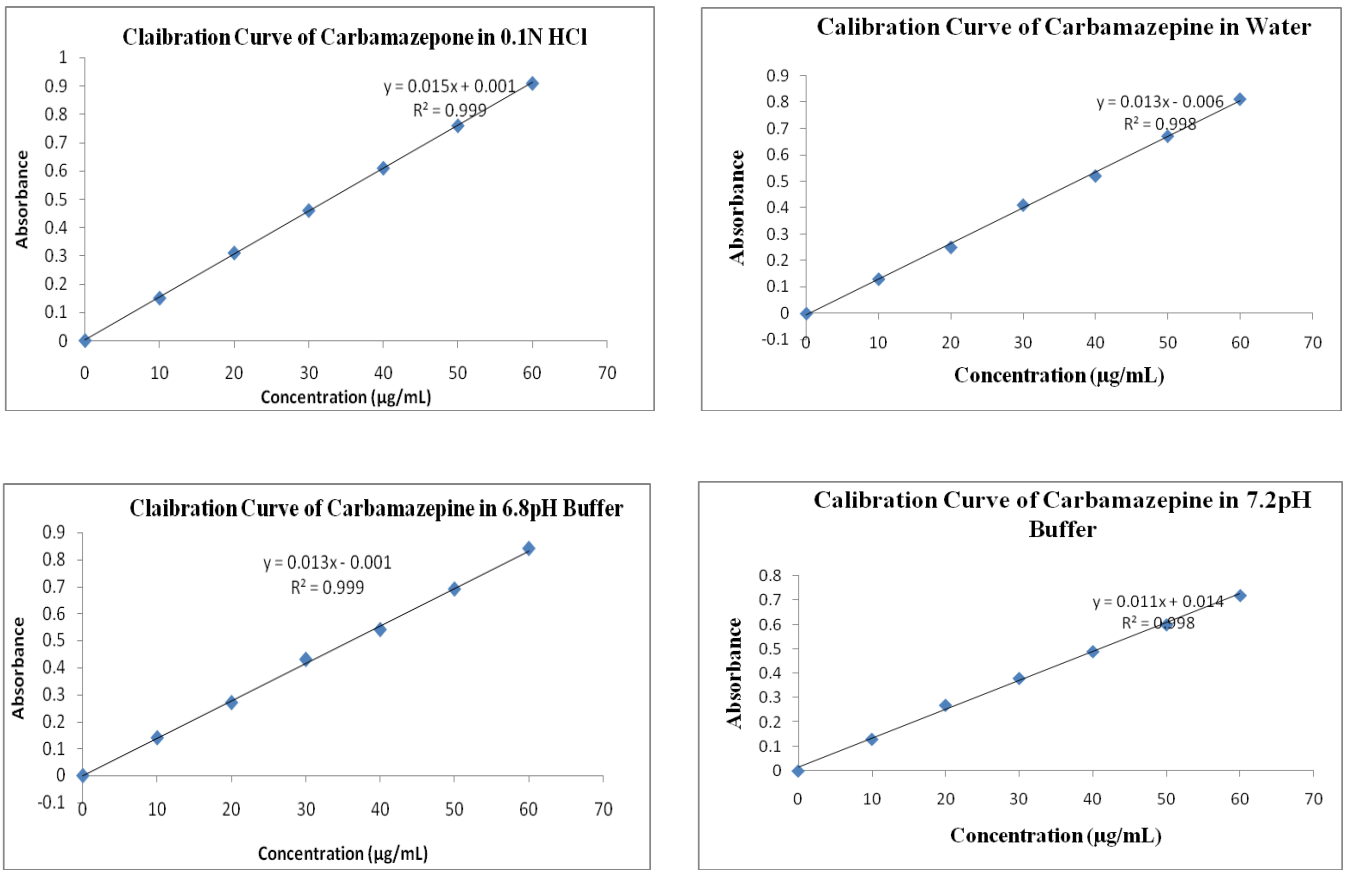
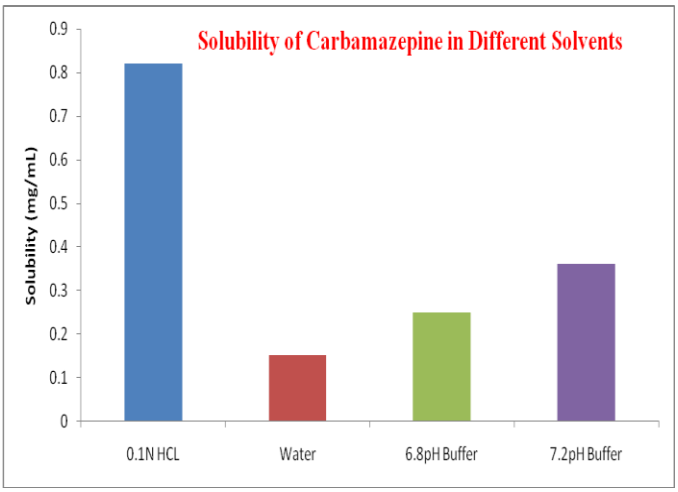


Fig. 1: Calibration plot of Carbamazepine in different solvents

Table 5: Comparative results of Saturation Solubility Studies of pure drug (CBZ) and optimized nano-sponge formulation using CBZ

0.1N HCl		Water		6.8pH Buffer		7.2pH Buffer	
Pure Drug	Optimized formulation	Pure Drug	Optimized formulation	Pure Drug	Optimized formulation	Pure Drug	Optimized formulation
0.82±1.55	4.75±1.08	0.15±0.66	2.56±1.28	0.25±0.98	3.24±1.22	0.36±1.42	3.84±0.85

(Mean ± SD, n=3)



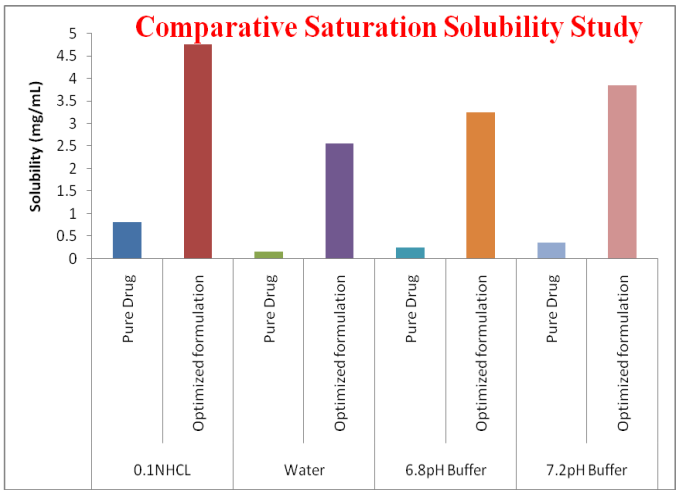


Fig. 2: Comparative results of Saturation Solubility Studies of carbamazepine and optimized nanosponge formulation

Table 6: Results of In vitro dissolution study of pure drug (CBZ) and Carbamazepine loaded Nanosponges

Time (min.)	% Drug Release						
	Pure Drug (CBZ)	F1	F2	F3	F4	F5	F6
30	11.4 ± 6.55	54.8 ± 4.35	45.9 ± 5.55	44.8 ± 5.35	27.5 ± 7.55	25.2 ± 6.54	22.2 ± 7.25
60	22.4 ± 5.35	86.4 ± 2.12	76.5 ± 2.32	75.9 ± 2.45	52.8 ± 5.45	48.2 ± 4.55	41.8 ± 4.65
90	49.3 ± 4.55	99.8 ± 1.21	88.6 ± 1.55	86.5 ± 2.25	63.2 ± 5.25	61.8 ± 4.95	55.8 ± 3.85
120	68.6 ± 2.65	99.5 ± 0.75	99.8 ± 0.75	99.8 ± 1.65	79.8 ± 2.95	77.8 ± 3.95	72.8 ± 3.55
180	84.5 ± 1.98	99.8 ± 0.95	99.9 ± 0.55	99.9 ± 1.05	99.9 ± 1.95	99.9 ± 0.95	89.9 ± 1.95
240	99.1 ± 1.75	99.9 ± 0.45	99.9 ± 0.85	99.8 ± 0.55	99.8 ± 0.75	99.9 ± 0.65	99.9 ± 0.65

(Mean ± SD, n=3)

3.1. Solubility Studies of Carbamazepine

Saturation solubility studies was done in different solvents for Carbamazepine and carbamazepine loaded NS. Findings of solubilities are tabulated below. It was found that the drug is practically insoluble in all the solvents.

3.1.1. Calibration plot of Carbamazepine in different solvents

Calibration curve of API in 0.1N HCL, 6.8pH buffer, Water and 7.2pH Buffer were plotted and graphs are shown below along with absorbance values

From the above saturation solubility studies it was observed that the solubility of optimized Carbamazepine loaded NS formulation is significantly improved when compared to the pure drug (CBZ).

From the results, it was observed that all NS formulations have faster release than pure drug. 2:1:2 ratio Drug, EC and PVA formulation is the best one and having good entrapment efficiency compared to all other formulations. Hence, the same has been selected as best formulation for converting in to tablets. Further increase in the ethyl cellulose concentration may retard and sustain the release profile.

Compressed tablets of Carbamazepine Loaded Nanosponges dissolution has been performed and found to be faster rate of release than pure drug.

From the comparative FTIR spectra of Pure drug (CBZ), Optimized NS (F1) and compressed NS tablets, it was found that the drug is compatible with excipients.

From the DSC results, it was observed that the endothermic peak of API has been disappeared in formulations, indicating that the drug is inglobated within the polymer matrix of nanosponges at nano level.

From the above XRD spectra it is understood that, API is in crystalline in nature and is been converted to amorphous form as its being embedded in nanosponges formulation.

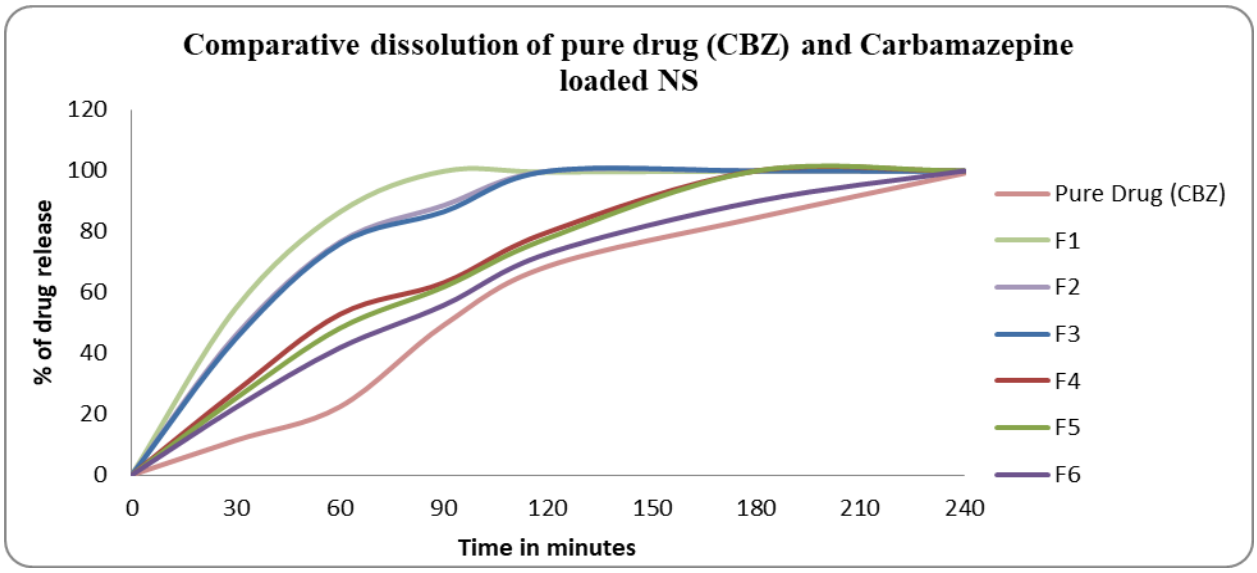


Fig. 3: Comparative dissolution of Pure drug and Carbamazepine Loaded Nanosponges

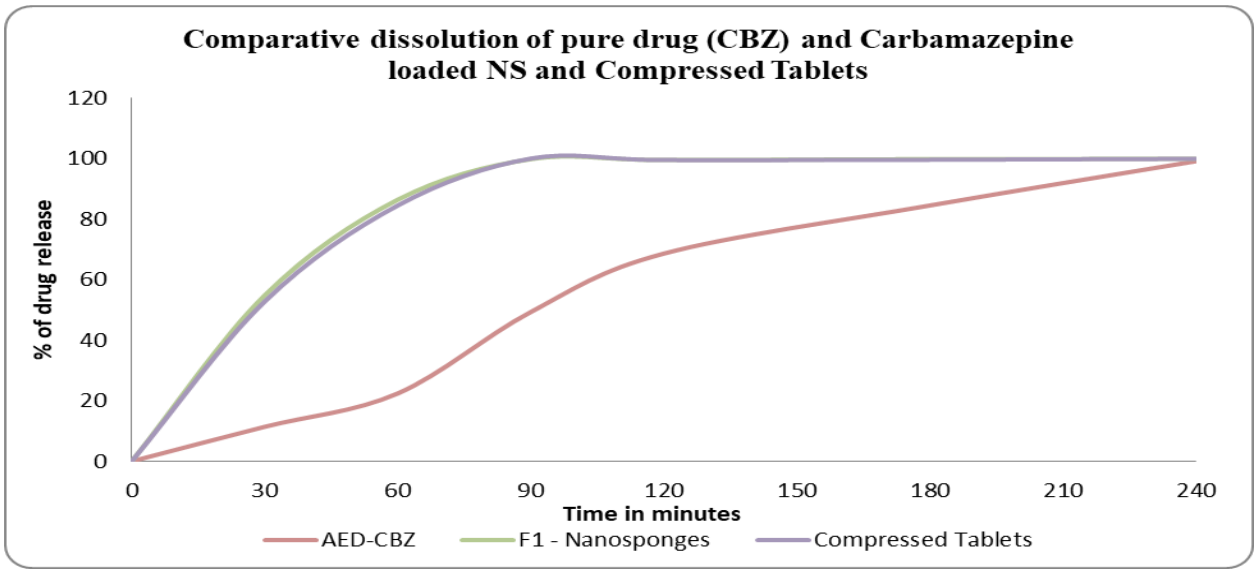


Fig. 4: Comparative dissolution of Pure drug, Carbamazepine Loaded Nanosponges and Compressed Tablets

Table 7: Results of Compressed Tablets

Hardness* (kP)	Thickness* (mm)	Friability (%)	Weight Variation*	Assay (%)
13.8 ± 9.55	5.3 ± 4.85	0.3	Complies	99.6 ± 0.75 (n=3)

*(Mean ± SD, *n=20)*

Table 8: Comparative in-vitro dissolution results of pure drug (CBZ) and Optimized Nanosponges (F1) and compressed tablets

Time (Mins)	% Drug Release		
	Pure Drug (CBZ)	F1 - Nanosponges	Compressed Tablets
30	11.4 ± 6.55	54.8 ± 4.35	52.8± 3.95
60	22.4 ± 5.35	86.4 ± 2.12	84.5± 1.85
90	49.3 ± 4.55	99.8 ± 1.21	100.0± 0.65
120	68.6 ± 2.65	99.5 ± 0.75	99.5± 0.65
180	84.5 ± 1.98	99.8 ± 0.95	99.6± 0.85
240	99.1 ± 1.75	99.9 ± 0.45	99.9± 0.55

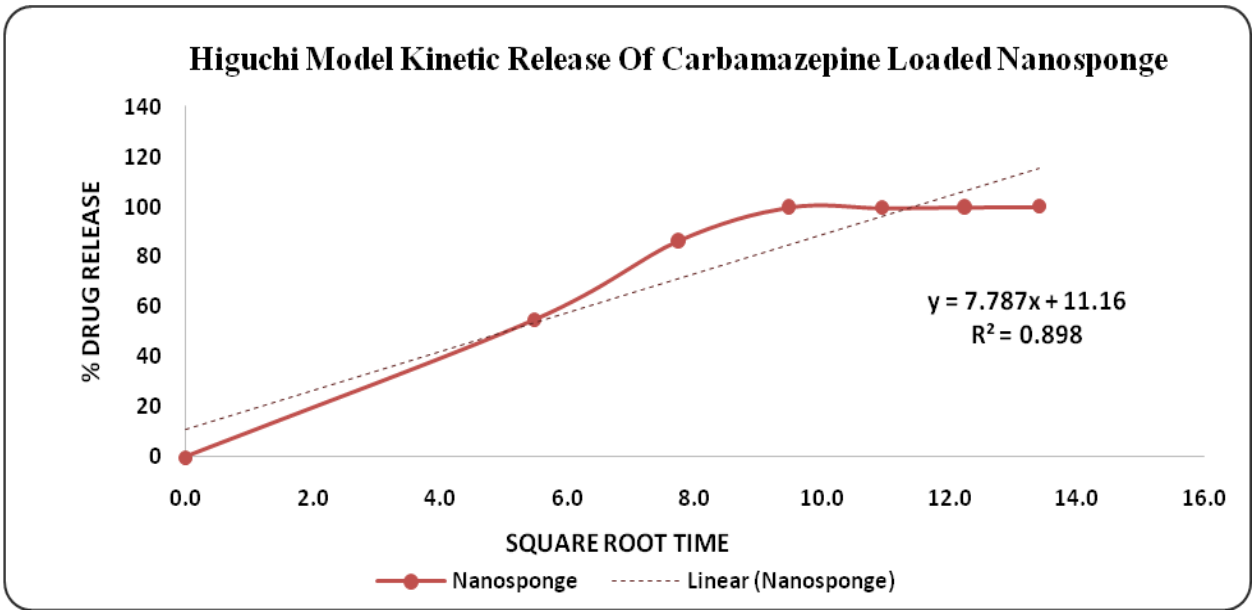


Fig. 5: Higuchi model kinetic release of carbamazepine loaded nanosponges

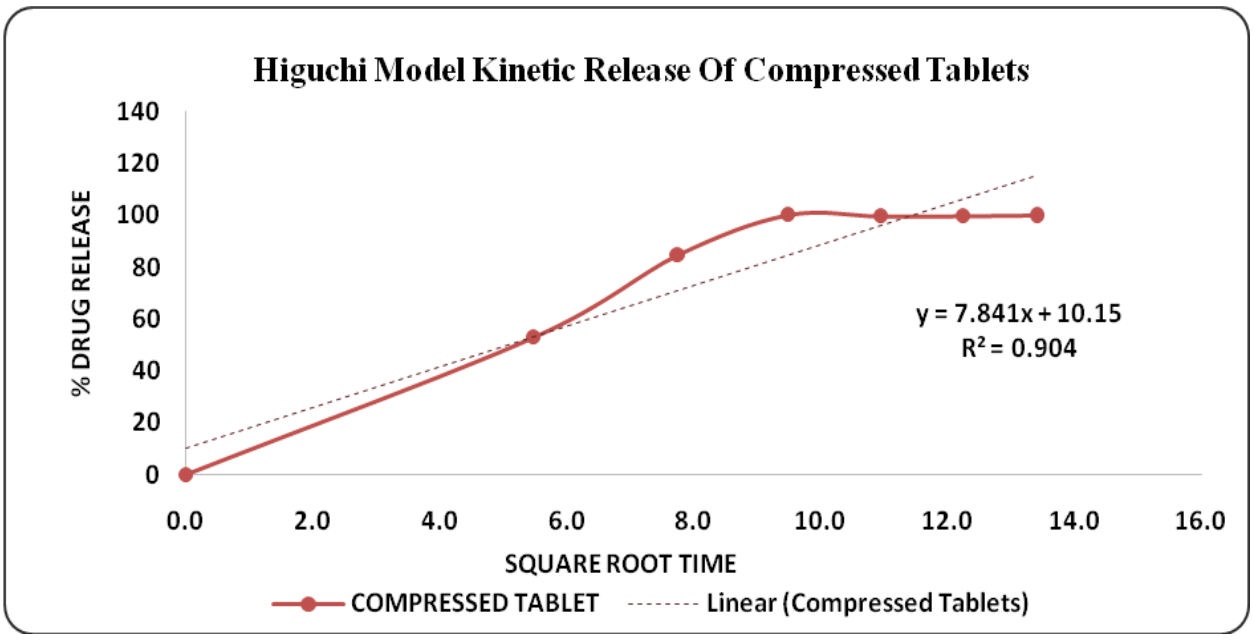


Fig. 6: Higuchi model kinetic release of compressed tablets

			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	113.0	Peak 1:	4.914	57.3	1.087
PdI:	0.311	Peak 2:	310.1	37.7	69.83
Intercept:	0.924	Peak 3:	53.70	5.0	9.601
Result quality :	Refer to quality report				

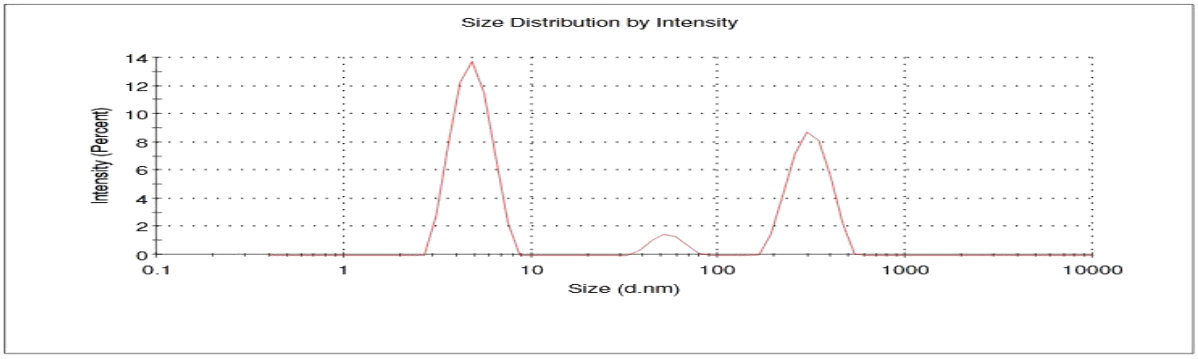


Fig. 7: Particle Size distribution of Carbamazepine Loaded F 1 Nanosponges

			Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-9.03	Peak 1:	-9.03	100.0	3.85
Zeta Deviation (mV):	3.85	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm):	0.377	Peak 3:	0.00	0.0	0.00
Result quality :	Good				

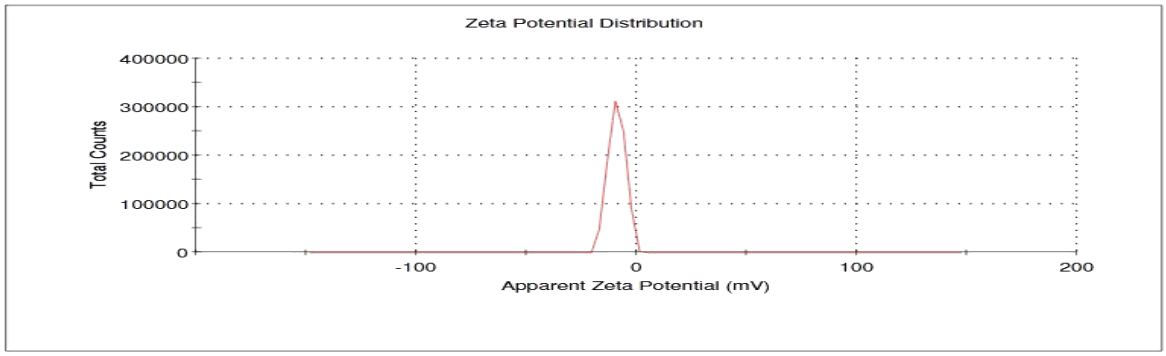


Fig. 8: Zeta Potential of Carbamazepine Loaded F 1 Nanosponges

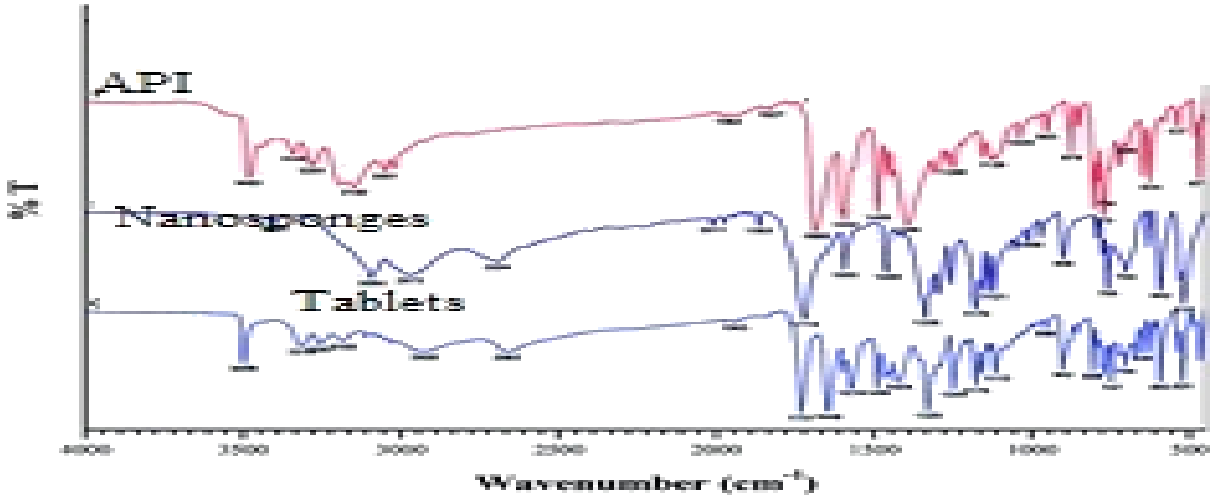


Fig. 9: FTIR graph of Carbamazepine pure drug, Carbamazepine Loaded F1 Nanosponges and Nanosponges Compressed Tablets

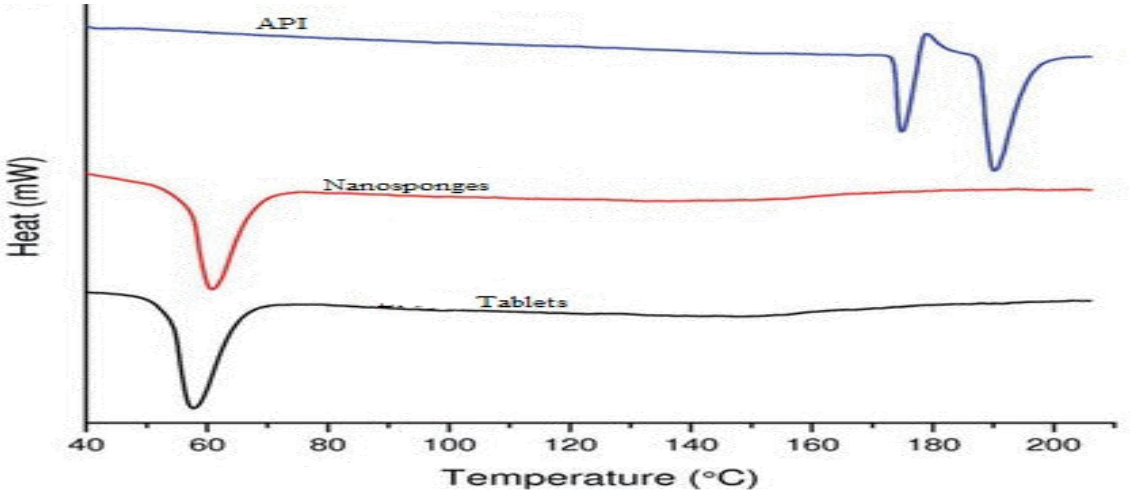


Fig. 10: DSC graph of Carbamazepine pure drug, Carbamazepine Loaded F1 Nanosponges and Nanosponges Compressed Tablets

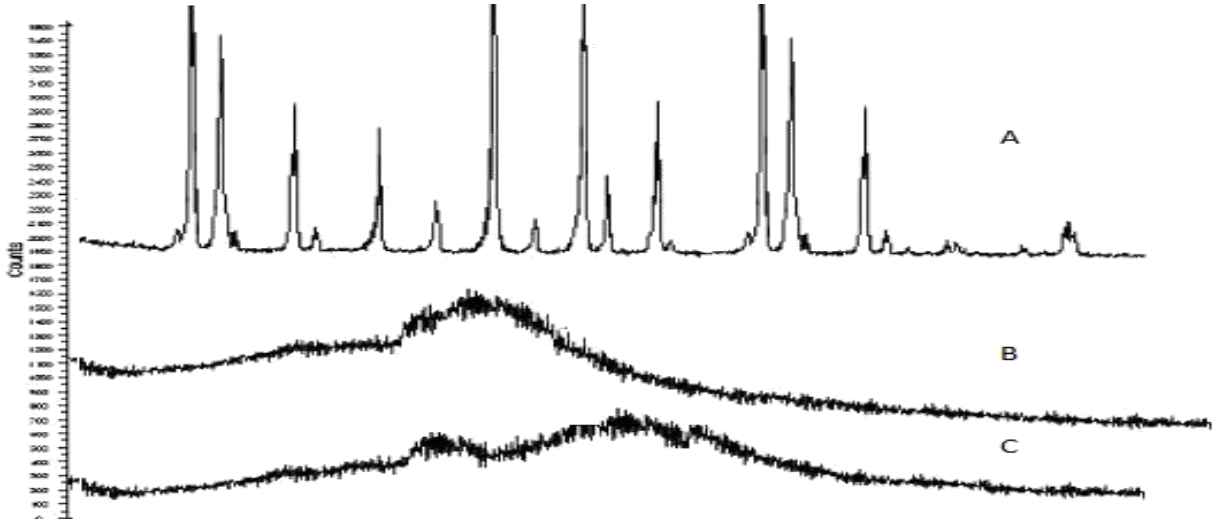


Fig. 11: XRD graph of Carbamazepine pure drug (A), Carbamazepine Loaded F1 Nanosponges (B), Compressed Tablets (C)

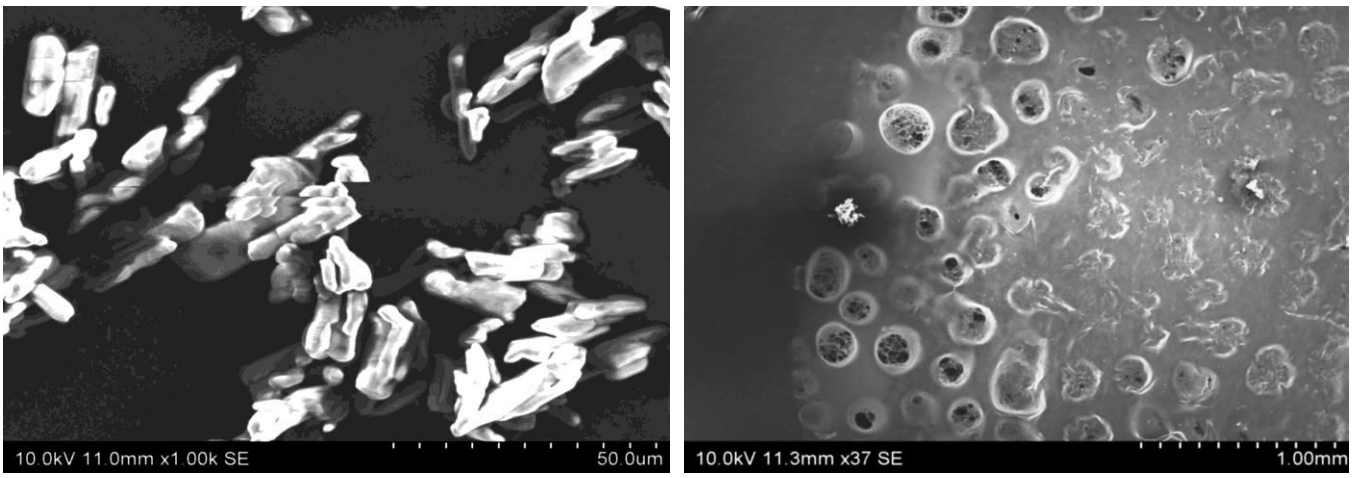


Fig. 12: SEM Image of Carbamazepine API and Carbamazepine Nanosponges

3.2. Stability Studies

The batch of compressed carbamazepine loaded NS tablets were observed for stability parameters for three months. The formulation subjected to stability testing till 3 month stated that there were no such changes observed in the formulation's physical appearance and drug contents. The test results are shown in Table 9. Hence, it proved that formulation of compressed carbamazepine loaded NS tablets had good stability for 3 months.

Table 9: Stability results of compressed Carbamazepine loaded NS tablets

Parameters	Initial	1 M 40deg C & 75% RH	3 M 40deg C & 75% RH
Physical appearance	No changes	No changes	No changes
Assay (%)	99.6 ± 0.75	99.8 ± 0.95	99.5 ± 0.85

(Mean ± SD, n=3)

4. CONCLUSION

The data obtained from all the studies stated that the solubility and dissolution rate of carbamazepine molecule improved by preparing Nanosponge formulation. Nanosponges were formulated using different polymers ratio like Ethyl cellulose and PVA. The batch containing ratio 2:1:2 of Drug, Ethyl cellulose and PVA by using the Emulsion solvent diffusion technogogy gave maximum entrapment efficiency and percentage of yield. Reduced size up to nano levels of nanosponges are confirmed through particle size analysis. The formulation F1 showed minium particle (113.0 nm), good zeta potential (-9.03 mV), maximum solubility and also an increase in dissolution rate as compared to the pure drug. Further compressed tablets of the selected nanosponge also gave higher dissolution rate i.e approx 85% drug release in 60 min when compared with pure drug which is only 22% drug release in 60 min . Therefore it can be beneficial such as dose reduction, reduced frequency of administration and avoiding related systemic side effects. Stability studies also proved that the formulation was found to be stable. Hence it can be concluded that the developed nanosponges of carbamazepine is considered to be an ideal and effective in the management of epileptic conditions. Release kinetic from nanospong formulation and compressed tablets are best fitted with higuchi model of kinetic release. From the concluded experiments this also clinched that any additional increase of hydrophobic polymer concentration may alter the dissolution profille in controlled manner, which will also help to provide a sustained dissolution profile for longer periord of time.

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Conflict of interest

There is no conflict of interest associated with this work.

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