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FORMULATION DEGIGN AND EVALUATION OF FAST DISSOLVING TABLET CONTAINING CARBAMAZEPINE NANOCRYSTALS FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT USING SOLUPLUS

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Abstract
Major problem to the development of highly effective formulation is poor aqueous solubility which affects stability and bioavailability of drugs. Therapeutic effectiveness depends upon bioavailability and ultimately upon the solubility of drug. Therefore there is need of systematic formulation approach tomake such poorly soluble drugs bioavailable. Attempt has been made in the present investigation to increase the solubility and dissolution of carbamazepine an antiepileptic class II drug. Nanocrystals of carbamazepin were prepared using graft copolymer soluplus by antisolvent precipitation technique. The prepared nanocrystals were characterized by Fourier Transform Infrared Spectroscopy (FTIR), Differential scanning calorimetry (DSC), X-ray diffractometry (XRD), Scanning electron microscopy (SEM), Particle size and saturation solubility. The optimized batch of prepared carbamazepine nanocrystals (0.938 mg/ml) showed remarkable increase in the aqueous saturation solubility i.e., 4.48 folds as compared to pure carbamazepine (0.209 mg/ml). The optimized carbamazepine nanocrystals withhighest solubility converted into fast dissolving tablet. The tablets were evaluated for different parametersand found to possess more dissolution as compared to pure drug. The rise in solubility and dissolutionmay be due to either increase in surface area due to nanocrystalization or micellization by soluplus.

Keywords: Carbamazepin, nanocrystals, solubility, Soluplus, fast dissolving tablet

INTRODUCTION
Amongst all of the routes of drug administration, oral route is the first choice for drug administration as it is convenient, having good patient compliance and lesser production cost as compared to others. [1,2] Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. [3]At the present time many of the pharmaceutical companies are facing an increasing number of poorly soluble new chemical entities (NCEs) in their development pipelines. [4] Currently about 40% of the drugs in development process are having poor solubility. [5, 6] Even up to 60% of compounds from the synthesis are poorly soluble. [5, 7, 8, 9] Solubility plays a key role in order to achieve maximum activity and effectiveness of a drug molecule through its bioavailability because the aqueous solubility becomes a major problem in formulation of new drug entities. [10] The low solubility of drugs leads to their low bioavailability and erratic absorption which is particularly pertinent to drugs within class II of the Biopharmaceutical Classification System (BCS). For drugs in BCS II,generally the rate-limiting step for absorption is its rate of dissolution arising from low solubility.

In spite of having high permeability, the poor solubility of these class II drugs results in a low concentration gradient across gut and blood vessel as a result of limitations of drug transport and absorption.[11] The bioavailability of class II and class IV compounds is highly dependent upon rate and extent of absorption which in turn depends on solubility. This is the major reason that solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility. [12] There is a definite need for smart technological formulation approaches to make such poorly soluble drugs bioavailable. Making such drugs bioavailable means that they show sufficiently high absorption after oral administration or they can alternatively be injected intravenously. [13] Hence improving drugs solubility will be one most challenging task in drug development in order to enhance the bioavailability of these drugs. Several strategies have been employed to overcome these limitations. The approaches to increase the solubility and the available surface area for dissolution are classified as physical and chemical modifications. For the physical modifications, the techniques include decreasing particle size (micronisation, nanonization), formation of polymorphs/ pseudo-polymorphs (including solvates), complexation / solubilization (by meansof using surfactants or cyclodextrins, conjugation to dendrimers, and an addition of co-solvents) and preparation of drug dispersions in carriers (eutectic mixtures, non-molecular solid dispersions, solid solutions). For the chemical modification the used technique is synthesis of soluble prodrugs and salts. [11] In order to combat the solubility problem of poorly soluble drugs, anumber of techniques have been developed, e. g. solubilization by using surfactants, self- emulsifying drug delivery systems (SEDDS), complex formation (e. g. cyclodextrins, macromolecules), microemulsions and especially for oral administration micronisation of drug

powders include nanosuspension, nanoemulsion, solid dispersion, nanocrystals, nanoparticles. [1, 13]

Nanoparticles

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the methods of preparation of nanoparticles, nanospheres or nanocapsules can be obtained. The devices and systems produced by chemical and/or physical processes having specific properties.[24]

There are wide advantages of nanoparticles like, better drug utilization, specific site of drug release, easy handling of nanoparticles prepared in the powder form, good control over size and size distribution, good protection on the encapsulated drug, longer clearance times increased therapeutic efficacy of drugs, limiting side effects, retention of drug at the active site, reduces size of drug nanoparticles, allowing for greater dissolution of the drug in water and improved bioavailability, significantly increases drug solubility in the supercritical solvent, improving productivity, particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration, control and sustain release of the drug during the transportation and at the site of localization, controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents and used by various routes of administration including oral, nasal, parenteral, intra- ocular etc. But some of the disadvantages like due to small size and large surface area can leadto particle aggregation and discontinuation of therapy is not possible, when administration of drugs by intravenously.

MATERIALS AND METHODS

Organoleptic properties of carbamazepin

A small quantity of drug powder was taken in butter paper and viewed in well illuminated place and color, odour and taste were noted.

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Melting Point Determination

Melting point determination of the obtained drug sample was done; as it is a first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range. Melting point of Carbamazepine was determined by using microprocessor based-programmable melting point apparatus (veego).

Determination of λ max:

A stock solution of drug (1000µg/ml) was prepared by taking accurately weighed 100 mg of model drug and dissolved in sufficient quantity of Methanol in 100 ml volumetric flask and volume was made up to 100 ml mark with Methanol. Further 1 ml of above solution was diluted to 100 ml with Methanol to get 10µg/ml. UV spectrum was taken using Shimadzu (UV-1800) spectrophotometer. The solution was scanned in the range of 200-400nm.

Solubility Determination

The solubility determination was carried out by adding a known excess amount of pure carbamazepine into 10 ml distilled water in separate Teflon facing screw capped vials. These samples were stirred by magnetic stirrer for 24 hours at a room temperature. The supernatant liquid was collected and filtered through Nylon syringe filter analyzed by UV-visible spectrophotometer at 284.9 nm wavelength.

Drug - Excipient compatibility study

FTIR and DSC data used to identify an incompatibility between drug and excipients and identification of compatible excipients for the formulation of drug or active principle was most often delivered to patient along with other chemical substance within a pharmaceutical formulation, which should comply with standard specification. In order to be approved a formulation should warrant well defined level of stability. Interaction between drug and excipients can be occurred by means of several mechanisms, including adsorption, complexation, chemical interaction, pH effect and eutectic formation, resulting in drug products with desired or undesired properties.

Preparation of standard calibration of carbamazepine

Preparation of standard calibration of carbamazepine in methanol

- *Preparation of Standard Solution:*

100mg of pure Carbamazepine was accurately weighed and dissolved into sufficient amount of Methanol in 100 ml volumetric flask and volume was made up to 100 ml to get 1000µg/ml solution. Further, 10 ml of above solution was diluted to 100 ml with Methanol to get 100 µg/ml solution (SS-I).

- *Preparation of working Standard Solutions:*

From SS-I aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml,1ml, 1.2ml were pipetted out into 10ml volumetric flasks. The volume was made up with Methanol to get the final concentrations of 2, 4, 6, 8, 10, 12µg/ml respectively. The absorbance of each concentration was measured at 284.9nm wavelength against Methanol as blank.

Preparation of standard calibration of carbamazepine in distilled water

- *Preparation of Standard Solution:*

5 mg of carbamazepine was accurately weighed and dissolved into 50 ml volumetric flask containing small volume of distilled water. The volume was made up with the distilled water to get a concentration of 100 µg/ml (SS-I).

- *Preparation of working Standard Solutions:*

From SS-I aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml,1ml, 1.2ml were pipetted out into 10ml volumetric

flasks. The volume was made up with distilled water to get the final concentrations of 2, 4, 6, 8, 10, 12µg/ml respectively. The absorbance of each concentration was measured at 284.9nm wavelength against distilled water as blank.

Preparation of standard calibration of carbamazepine in PBS pH 6.8:

- *Preparation of phosphate buffer solution (PBS) pH 6.8:*

50 ml of 0.2 M potassium hydrogen phosphate was taken in 200 ml volumetric flask, to which 22.4 ml of 0.2 M sodium hydroxide solution was added. Then volume was made up with distilled water.

- *Preparation of Standard Solution:*

5 mg of carbamazepine was accurately weighed and dissolved into 50 ml volumetric flask containing small volume of PBS (pH 6.8). The volume was made up with PBS (pH 6.8) toget a concentration of 100 µg/ml (SS-I).

- *Preparation of working Standard Solutions:*

From SS-I aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml,1ml, 1.2ml were pipetted out into 10ml volumetric flasks. The volume was made up with PBS (pH 6.8) to get the final concentrations of 2, 4, 6, 8, 10, 12µg/ml respectively. The absorbance of each concentration was measured at 284.9nm wavelength against PBS (pH) as blank.

Preparation of nanocrystals

Table 1: Formulation design of carbamazepine nanocrystals (CBZNs)

Ingredients → **Batches↓**	Carbamazepine (mg)	Soluplus(mg)	PVP K-30 (mg)	Drug:Polymer Ratio
NPC-1	200	100	100	1:0.5
NPC-2	200	200	100	1:1
NPC-3	200	400	100	1:2
NPC-4	200	600	100	1:3
NPC-5	200	1000	100	1:5
NPC-6	200	1400	100	1:7
NPC-7	200	1800	100	1:9
CPN-1	200	---	100	1:0.5
CPN-2	200	---	200	1:1
CPN-3	200	---	400	1:2
CPN-4	200	---	600	1:3

Carbamazepine nanoparticles were prepared by nanoprecipitation technique developed by Fessi et al., with some modifications. Preliminary studies were carried out to investigate the solubility of carbamazepine in various solvent like methanol, dimethylsulfoxide, dimethylformamide, and ethanol. The solvent in which carbamazepine showed highest solubility was used for preparing nanocrystals. The drug (carbamazepine) and polymer (soluplus) were dissolved in sufficient quantity of organic solvent [Dimethylsulfoxide (DMSO)] to form organic phase. The stabilizer (PVP K-30) was dissolved in sufficient quantity of water (50 ml), which forms aqueous phase. The organic phase was added dropwise into aqueous phase which is kept stirring at 1000 rpm using a magnetic stirrer (Remi Motor RQT-124A) at 50ºC temperature. Stirring was continuedfor 2 hours for evaporation of organic phase to form suspension. The milk like suspension was kept for some time to allow the foam to dissipate, then finally filtered and dried. The different ratios by weight of drug-polymer combination used for preparing nanocrystals are listed in table 1. Also, the nanoparticles were

prepared using only PVP K-30 using the same procedure, different ratios by weight of drug (carbamazepine) - polymer (PVP K-30) were used for preparing nanoparticles.

Evaluation of carbamazepine nanocrystals [54-69]

Entrapment efficiency

Entrapment efficiency of drug nanoparticles was determined by centrifugation of samples for 60 min. After centrifugation supernatant was separated and filtered through 0.45 Nylon syringe filter. Then filtrate was diluted suitably and analyzed by UV-visible spectrophotometer at 284 nm. The % entrapment efficiency (EE) was calculated by using the following equation.

Total drug content

Carbamazepine nanoparticles (10 mg) was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of methanol was added and shaken for 15 min, then volume was made up to 100 ml with same solution and kept it for 24 hours. The resulting solution was filtered, diluted suitably and analyzed by UV-visible spectrophotometer at 284 nm using methanol as a blank.

Determination of solubility

The solubility study was carried out by adding known excess amount of samples (Carbamazepine nanoparticle formulations) to 10 ml distilled water in separate Teflon facing Screw capped vials. These samples were stirred by magnetic stirrer for 24 hours at a room temperature. The supernatant liquid was collected and filtered through Nylon Syringe filter and analyzed by UV-visible spectrophotometer at 284.90nm wavelength.

Particle size

The particle size is an important parameter as it affects the physicochemical parameters of drug substances. Two techniques were thereby employed to measure both particle size and particlesize distribution. Indeed, the polydispersity index (PDI) is also an important factor as uniform particles are wanted with a narrow size range. A value of 0.3 is considered to be good for the characterization method used. In fact, the closest the PDI value is to zero the more similar the particles are in size. The prepared particles were dispersed in a water solution, added to a cuvetteand analysed by DLS (Malvern Zetasizer), in order to obtain the size and its dispersity.

Fourier-Transform Infrared (FT-IR) Spectroscopic Analysis

Shimadzu FT-IR spectrophotometer (IR-Affinity1S) was used for infrared analysis of samples. About 1-2 mg of samples were mixed with dry potassium bromide of IR grade in the ratio of 1:100 and examined at transmission mode over wave number range of 4000 to 400 cm^{-1} with a resolution of 4 cm^{-1}. FT-IR studies were carried out on pure Carbamazepine, Soluplus, PVP k-30, optimized carbamazepine nanoparticle formulation of drug: polymer ratio of (1:7).

Differential Scanning Calorimetry (DSC)

The DSC studies of pure drug (Carbamazepine) and optimized nanoparticle formulation was performed to access what changes had actually made when nanoparticles were formed. DSC thermogram was obtained using DSC (DSC-60 plus) at heating rate of 10ºC/min over a temperature range of 0-300°C in nitrogen atmosphere. The onset peak and end set peaks are recorded for pure drug and nanoparticle formulation.

X-ray Diffraction Studies (XRD)

X-ray powder diffraction patterns were used to detect possible polymorphic transition during the process of formation of nanoparticles. XRD study of carbamazepine and optimized CBZNs formulation were carried out to access the crystallinity. XRD patterns were recorded using (Miniflex

II, Rigaku) with Cu-kα radiation. The scanning angle ranged from 10º to 80º of 2

Scanning Electron Microscopy (SEM)

In order to examine the particle surface morphology and shape, filed emission scanning electron microscopy (FE-SEM) was used. A concentrated aqueous suspension was spread over a slab and dried under vacuum. The sample was shadowed in a cathodic evaporator with a gold layer 20 nm thick. Photographs were taken using a JSM-5200 Scanning Electron Microscope (Tokyo, Japan) operated at 10 kV.

***In vitro* dissolution Studies**

***In-vitro* dissolution of CBZ and CBZNs in phosphate buffer pH 6.8**

The dissolution test of pure carbamazepine and optimized CBZNs was carried out by using USP dissolution apparatus type II (Electrolab). 5 ml of aliquot was withdrawn at the specified time intervals, filtered through Whatman filter paper and an equal volume of fresh medium was replaced into the dissolution medium after each sampling to maintain the sink condition throughout the test. The withdrawn samples were diluted suitably and then the absorbance of solution was measured using UV-visible spectrophotometer at 284.9 nm.

***In-vitro* dissolution of CBZ and CBZNs in distilled water**

The dissolution study of CBZ and optimized CBZNs was carried out in distilled water (900ml), paddle RPM 100 and at 37ºC ± 0.5ºC temperature by using USP dissolution apparatus type-II, paddle type (Electrolab). The samples were withdrawn at intervals of 5, 10, 15, 20, 30, 45, 60 minutes and the volume replaced with fresh medium to maintain sink condition.

Preparation of fast dissolving tablet containing CBZ and CBZNs

Table 2: Formulation Design of fast dissolving tablet containing CBZ & CBZNs.

Formulations → **Ingredients ↓**	**F1** (mg)	**F2** (mg)	**F3** (mg)	**F4** (mg)
Pure Drug	---	---	---	100
CBZNs	109.6	109.6	109.6	---
SSG	12	18	24	24
Croscarmellose sodium	10	10	10	10
Microcrystalline cellulose	148.4	142.4	136.4	146
Magnesium stearate	6	6	6	6
Talc	4	4	4	4
Saccharine sodium	10	10	10	10
Total weight (mg**)/Tablet**	300	300	300	300

Carbamazepine (CBZ) and carbamazepine nanoparticles (CBZNS) tablets were prepared by direct compression method. The composition of each tablet is shown in table 2. The drug nanoparticles, diluents, superdisintegrants & sweetener were passed through sieve # 40. All the ingredients were properly mixed together. Talc & magnesium stearate were passed through mesh# 80, mixed, blended with initial mixture in a polybag. The powder blend was compressed by direct compression method into tablets on a multi-station rotary punch tableting machine Minipress II MT (Karnavati Pvt Ltd, Gujrat) using 8 mm punch.

Evaluation of fast dissolving tablets containing CBZ & CBZNsPrecompression evaluation

Precompression evaluation includes measurement of bulk density, tapped density, angle ofrepose,

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Carr's index (%compressibility) and Hausner's ratio of optimized carbamazepine nanocrystals (CBZNs) and Carbamazepine (CBZ) tablet formulations powder blends.

Post compression evaluation

Post compression evaluation includes measurement of thickness, weight variation, hardness, friability, drug content, disintegration time, *in-vitro* dissolution of prepared tablet formulation were performed as per IP.

Tablet thickness

Thickness of tablets was determined using vernier caliper. Five tablets form each batch wereused and average values were calculated.

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

Tablet hardness

Hardness of the tablet formulation was tested by using Pfizer hardness tester. The hardness was measured in terms of Kg/cm^2.

Friability test

Six tablets from each batch were selected randomly and weighed. These tablets were subjected to friability test using Roche friabilator (Electrolab) for 100 revolutions. After 100 revolutions (4 minutes), the tablets were taken out from the friabilator and, dedusted using a muslin cloth and reweighed. Following formula was used to calculate the % friability.

Where, W_0= Weight of tablets before test; W= Weight of tablets after test.

Drug content analysis

Drug content analysis was performed in order to study the amount of the drug incorporated in tablets. Three tablets were selected randomly from each formulation batch and powdered. The blend equivalent to 10 mg was accurately weighed and transferred into a 100 ml volumetricflask, initially; 10 ml methanol was added and shaken for 15 minutes. Then volume was made upto 100 ml with same solution and kept it for 24 hours. The resulting solution was filtered, diluted suitably and analyzed by UV-visible spectrophotometer at 284.9 nm using methanol as blank.

Disintegration test

The disintegration time of prepared tablet was determined by using disintegration test apparatus as per IP specifications. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. PBS (pH6.8) was used as the immersion liquid, which wasmaintained at 37ºC ± 2ºC. The assembly should be raised and lowered between 30 cycles per minute in the PBS (pH 6.8). The time taken for complete disintegration of tablet with no palpablemass in the apparatus was noted.

Dissolution of tablet containing CBZ and CBZNs

The *in-vitro* dissolution study of fast dissolving tablets containing CBZ and CBZNs were carried out in USP type-II dissolution test apparatus (Paddle type) using 900 ml of Phosphate buffer pH 6.8 as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals,5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analysed for the presence of the drug release by measuring the absorbance at 284.9 nm using

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UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

Stability studies

Stability study was performed to ensure that drug products remain stable for use until the end of their expiration dates. The purpose of stability study is to provide evidence on how the quality of a drug substance or product varies with time under influence of different environmental parameters such as temperature and humidity. Short-term stability study was carried out on optimized tablet formulation as per ICH guidelines. Tablets were stored at 40ºC ± 2ºC / 75 ± 5 %RH for 30 days. After 30 days tablets were removed and tested for *in vitro* drug release.

RESULTS AND DISCUSSION

Characterization of carbamazepine

Carbamazepin was found to be white to off white, odorless, bitter, crystalline powder.

Melting Point Determination

The melting point of obtained drug carbamazepin was found to be191.5 ºC, which is within the reported value of 189ºC – 193ºC. It complies with IP standards and thus indicating the purity ofthe sample.

Determination of λ max

Table 3: Wavelength of maximum absorption of Carbamazepine in Methanol

Sr. No.	Solvent	λ max
1	Methanol	284.9 nm

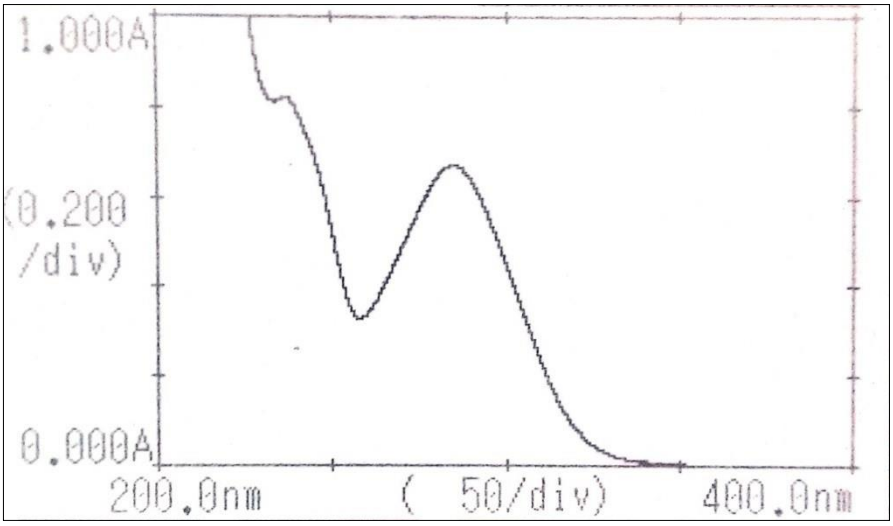

Figure1: Wavelength of maximum absorption of Carbamazepine in Methanol

Preparation of standard calibration curve of Carbamazepine

The calibration curves were obtained by plotting absorbance on Y-axis versus concentration onX-axis.

❖ **Preparation of standard calibration curve of Carbamazepine in Methanol**

Table 4: Standard calibration curve of CBZ in Methanol

Sr. No.	Concentration (µg/ml)	Absorbance

1	0	0
2	2	0.118
3	4	0.180
4	6	0.290
5	8	0.381
6	10	0.497
7	12	0.625

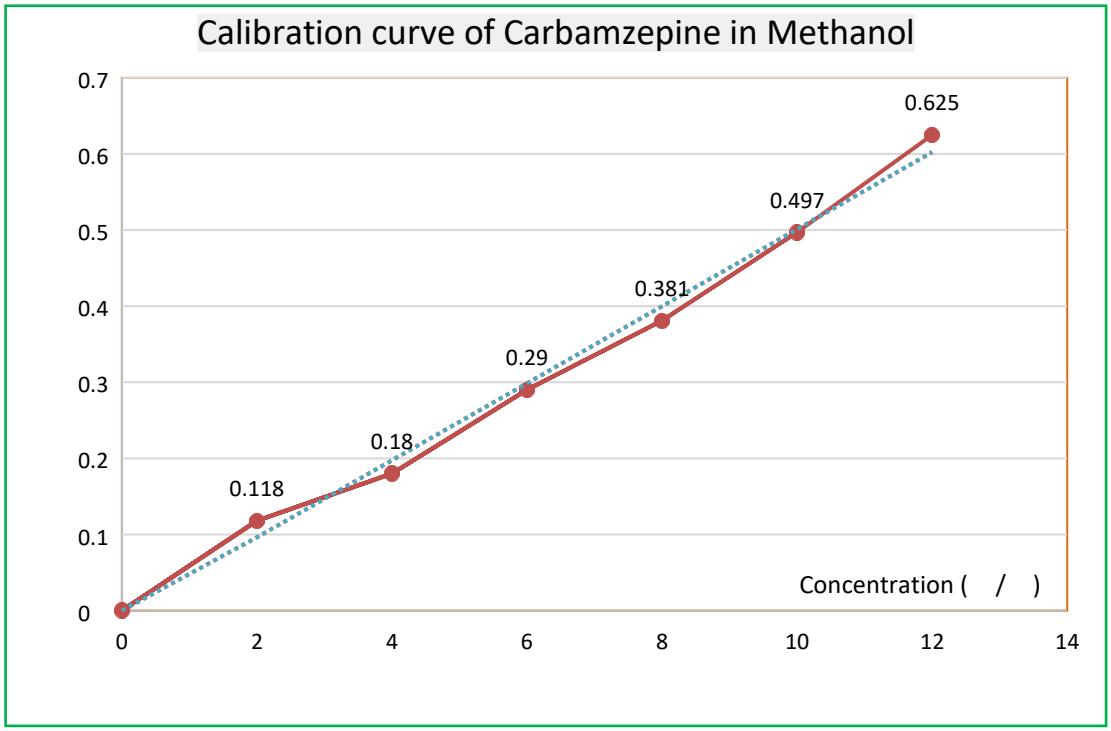

Figure 2: Standard calibration curve of CBZ in Methanol.

❖ **Standard calibration curve of carbamazepine in distilled water**

Table 5: Standard calibration curve of CBZ in distilled water

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.116
3	4	0.194
4	6	0.29
5	8	0.413
6	10	0.502

7	12	0.625

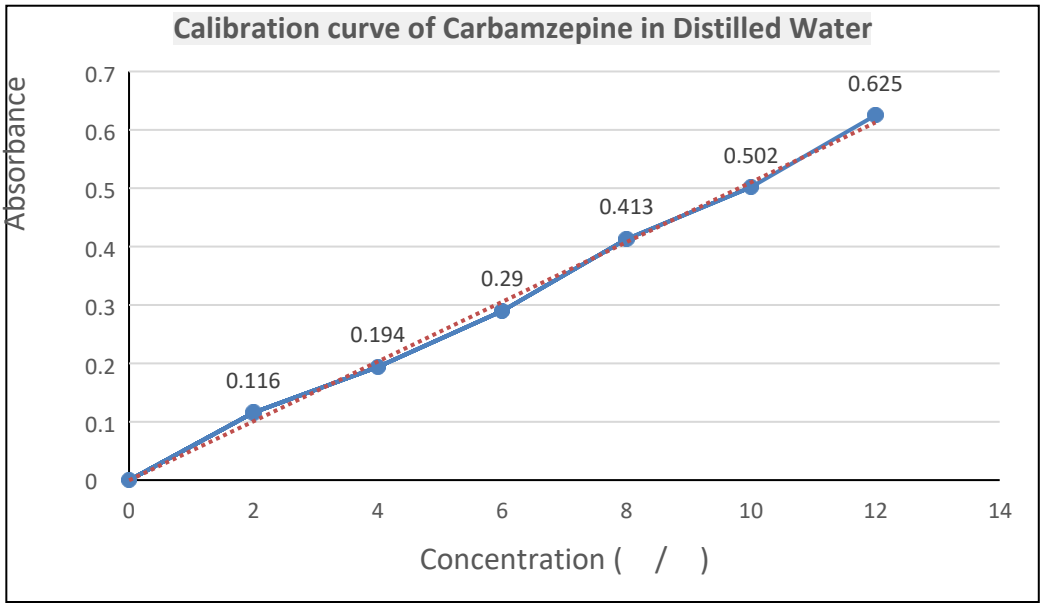

Figure 3: Standard calibration curve of CBZ in distilled water

❖ **Standard calibration curve of carbamazepine in PBS (pH 6.8)**

Table 6: Standard calibration curve of CBZ in PBS (pH 6.8).

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.116
3	4	0.178
4	6	0.29
5	8	0.402
6	10	0.51
7	12	0.608

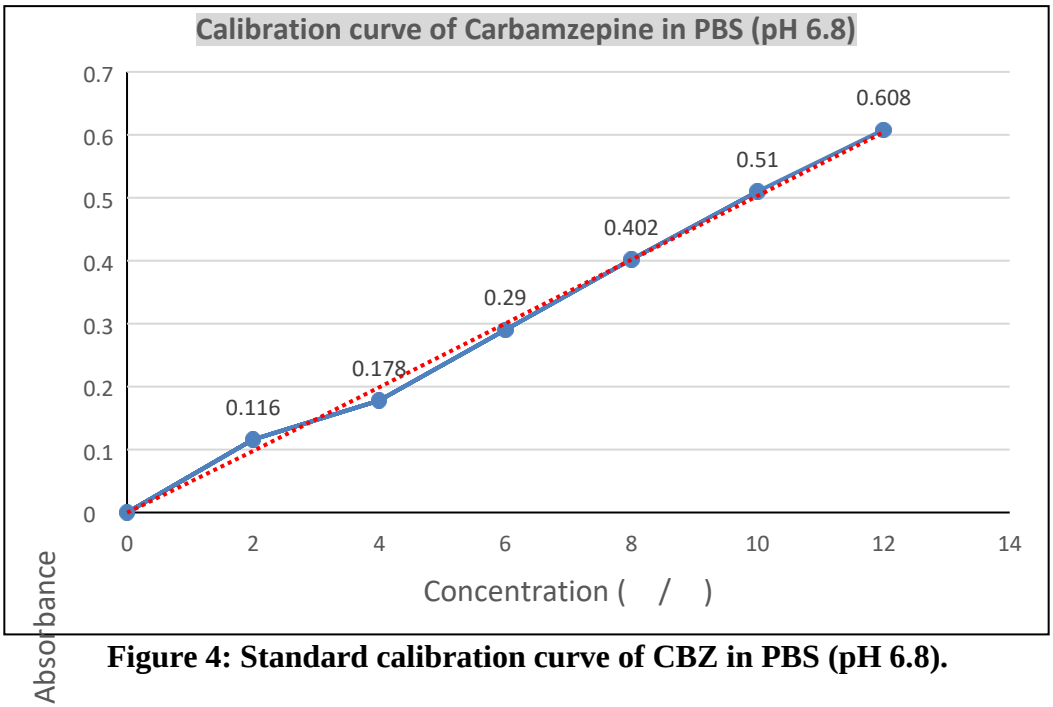

Figure 4: Standard calibration curve of CBZ in PBS (pH 6.8).

Evaluation of carbamazepine nanocrystals (CBZNs)Entrapment Efficiency

The entrapment efficiency of the CBZNs formulation was found to be 54.72 %.

Total Drug Content

Uniform distribution of drug in nanoparticle was determined by drug content analysis. The drug content in CBZNs formulation was found to be 91.2%.

Solubility Determination

Solubility studies gave the basis for selection of best formulation ratio that is to be forwarded for formulation. Hence, solubility study was carried on all CBZNs formulations. The results were shown in table 8 and figure 6.

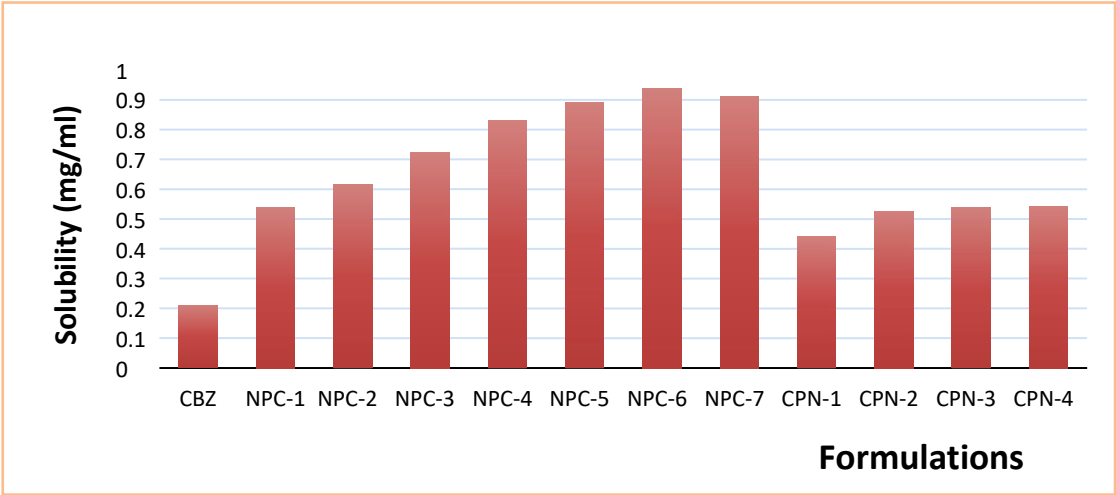

Figure 5: Solubility of CBZ and CBZNs formulations

Table 7: Solubility of CBZ and CBZNs formulations

FormulationCode	Drug: Polymer	Solubility(mg/ml)	Solubility Increased (In folds)
Carbamazepine	---	0.209	1
NPC-1	1:0.5	0.540	2.581
NPC-2	1:1	0.614	2.934
NPC-3	1:2	0.725	3.465
NPC-4	1:3	0.829	3.962
NPC-5	1:5	0.892	4.260
NPC-6	1:7	0.938	4.482
NPC-7	1:9	0.912	4.363
CPN-1	1:0.5	0.440	2.101
CPN-2	1:1	0.526	2.914
CPN-3	1:2	0.537	2.537
CPN-4	1:3	0.543	2.595

The prepared CBZNs formulations showed increased solubility than the pure CBZ in distilled water. The maximum solubility was found to be in CBZNs formulation NPC-6 showed solubility(0.938 mg/ml) about 4.482 fold increased in solubility as compared to CBZ (0.209 mg/ml).Drug: polymer ratio 1:7 was optimized and used for further formulation and evaluations. The increase in solubility of prepared CBZNs may be due to conversion to nanocrystalline state and may also due to the effect of soluplus.

Particle size determination

The particle size was analyzed by DLS method using Zetasizer (Malvern). The average size of 93.8% particles in optimized nanoparticle formulation (NPC-6) was found to be 158.8 nm. The polydispersity index was found to be 0.497 i. e. nearer to zero indicates similar particle size of nanoparticles in the formulation. Also, 6.2% particles with size more than 1000 micrometer were found.

Figure 6: Particle size analysis of optimized CBZNs formulation.

Drug-excipients compatibility study by FT-IR spectroscopic analysis

The FT-IR Spectrum of formulation NPC-6 shows that there was no significant shift in the peaksor no significant differences in the spectra and characteristic peaks of formulations are same as that of pure drug. There is no interaction between drug and polymer used in nanoparticleformulation indicating the compatibility between drug and polymer. The FT-IR spectrum of formulation shows same peak values when compared with the characteristic peak values of pure drug.

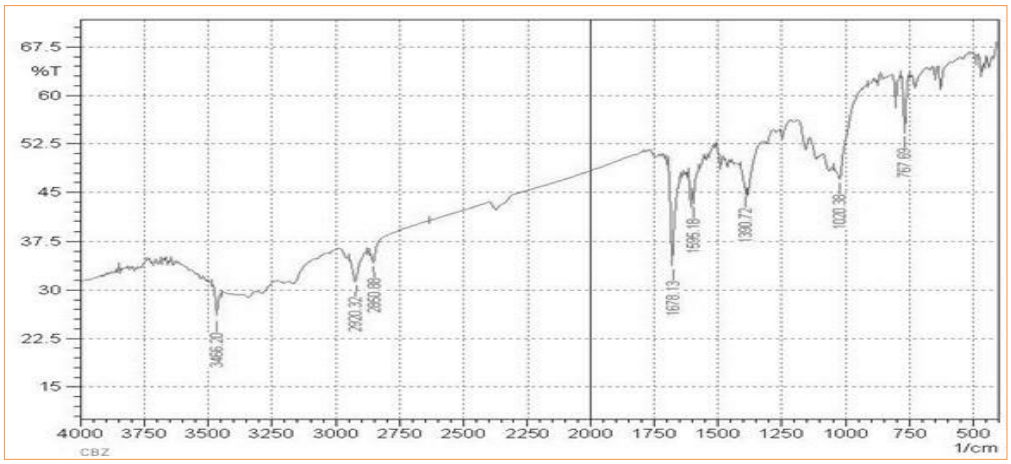

Figure 7: FTIR spectrum of CBZ

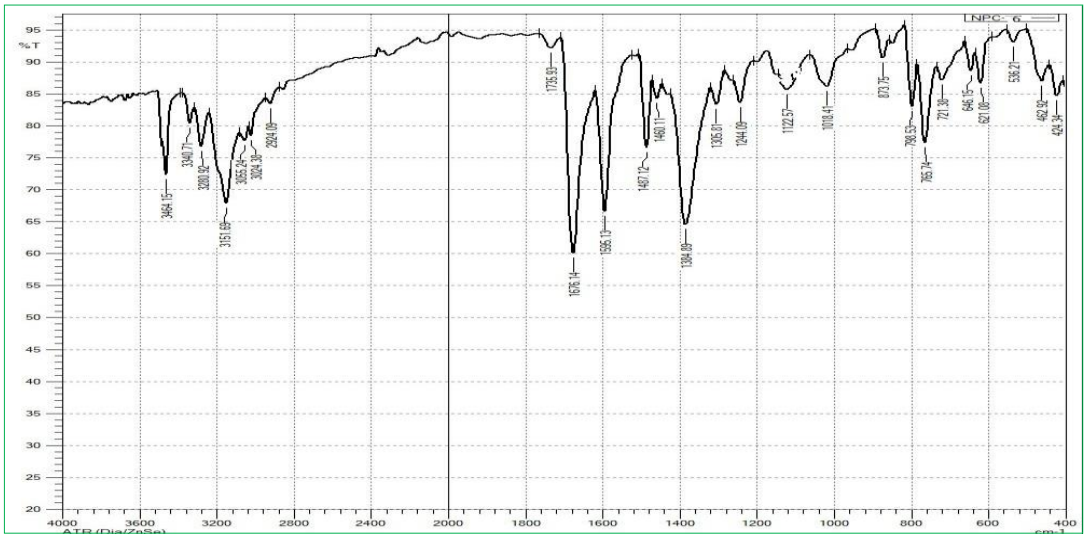

Figure 8: FTIR spectrum of CBZNs formulation

Scanning Electron Microscopy (SEM)

The SEM studies are generally done to study surface morphology of the drug particles. SEM images of CBZ and optimized CBZNs formulation are shown in figure 9 and figure 10 respectively.

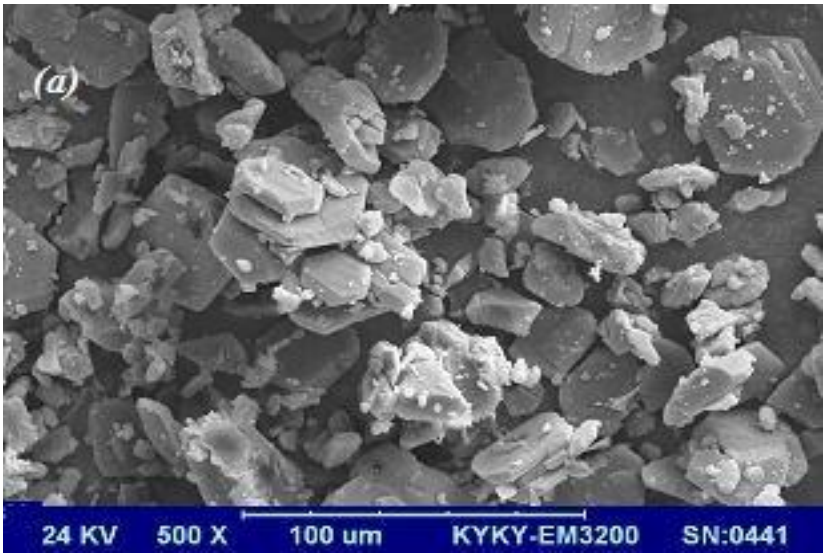

Figure 9: `SEM Micrographs of CBZ

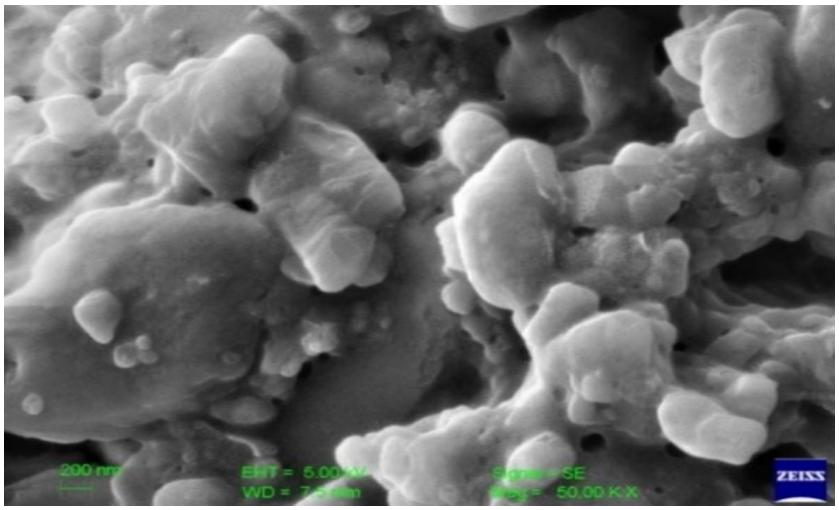

Figure 10: SEM micrograph of CBZNs

SEM micrographs clearly showed differences between carbamazepine (CBZ) and optimized carbamazepin nanocrystals (CBZNs). The particles of CBZ were found to be large and irregular shaped. However, in optimized CBZNs, the particles became smaller and uniform in size and smooth surface. The particle size falls below 200 nm, which was also supported with particlesize analysis by Zetasizer (Malvern).

Differential Scanning Calorimetry (DSC)

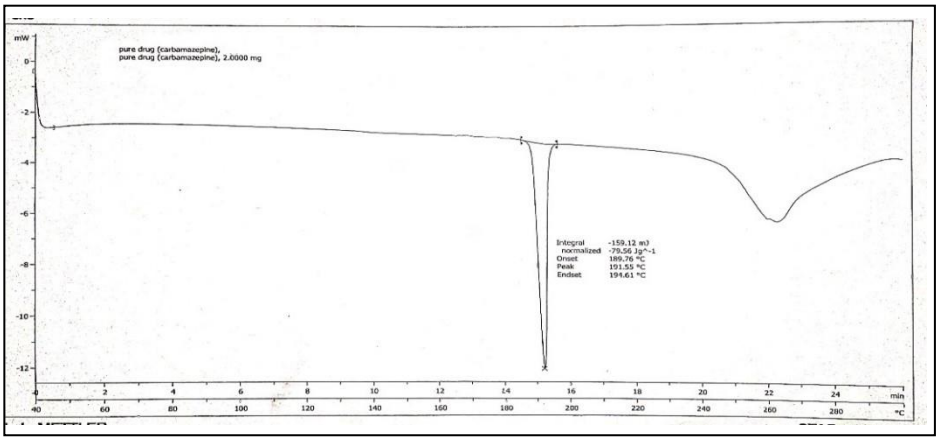

Figure 11: DSC thermogram of CBZ

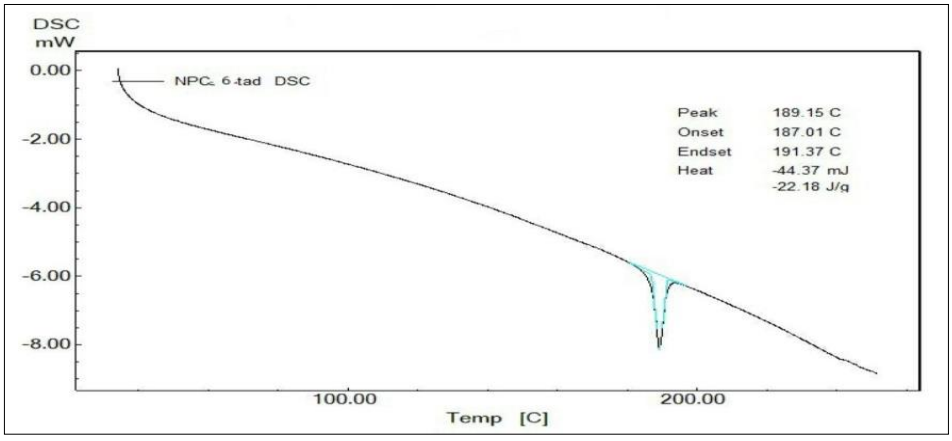

Figure 12: DSC thermogram of CBZNs

The DSC thermogram of CBZ showed a single sharp endothermic peak at 191.55ºC corresponding to melting point of CBZ indicating the crystalline nature of the drug. DSCthermogram of optimized CBZNs formulation showed melting endotherm at 189.15ºC ascribed to the melting point of carbamazepine. This indicates that there is no interaction between drug and excipients, also characteristic endothermic peak showed crystalline nature of CBZNs.

Powder X-ray Diffraction Studies (PXRD)

The X-ray diffraction patterns of CBZ and CBZNs formulation were studied in order to gain insights into the crystallinity.

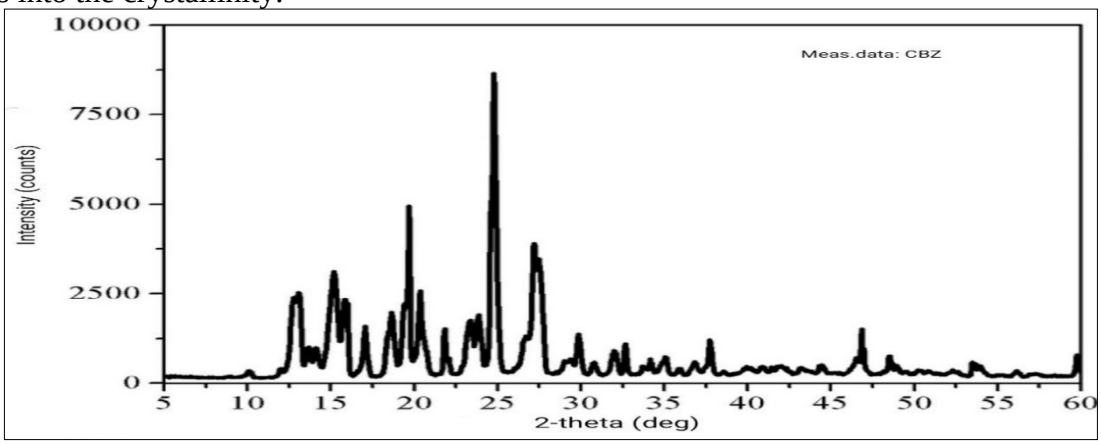

Figure 13: XRD pattern of CBZ

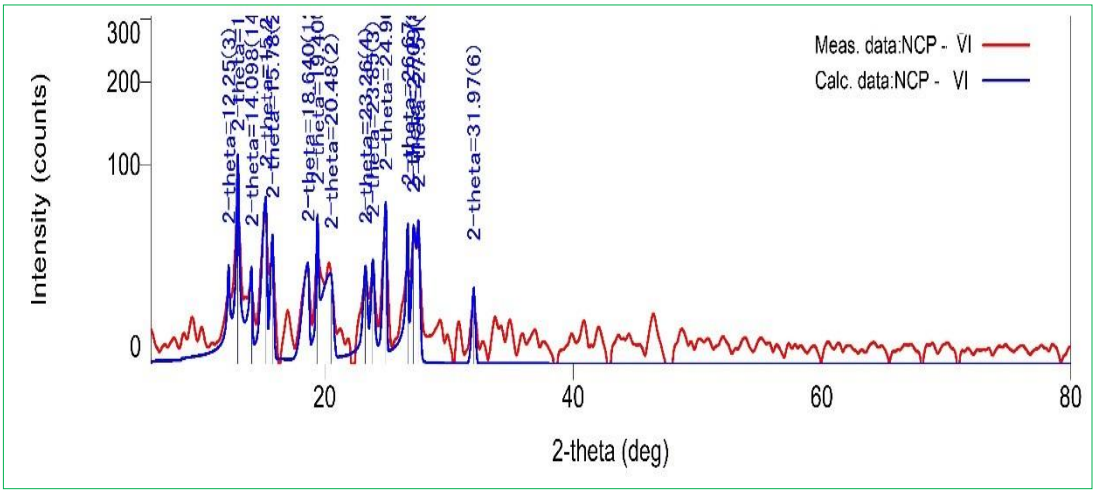

Figure 14: XRD pattern of CBZNs

The X-ray diffractograms of CBZ shows characteristic crystalline peaks at 12.55º, 16.10º, 19.5º, 24.9º, 27.01º and CBZNs shows characteristic crystalline peaks at 12.98º, 15.24º, 19.40º, 24.90º, 26.67º and 27.50º with less intensity indicating reduction in crystallinity. This may be due the reduction in particle size of carbamazepine to nanocrystalline form.

Powder Dissolution Studies

The release profile of drug predicts how a delivery system might function and gives valuable insight into its *in vitro* behavior. Optimized CBZNs and CBZ were subjected to *in vitro* dissolution studies by using USP apparatus type I (basket type) at 100 rpm. The dissolution medium was 900 ml phosphate buffer pH 6.8 maintained at 37° ± 0.5°C. The drug release rate obtained for CBZNs and CBZ in different dissolution media were shown in table 8, 9 and Figure 15, 16.

Table 8: Dissolution of CBZ and CBZNs in PBS pH6.8

Sr. No.	Time (min)	% Cumulative Drug Release	
		CBZ	CBZNs
1	0	0	0
2	5	4.3944828	5.13088
3	10	9.7944828	10.5676
4	15	16.013793	16.7858
5	20	22.866207	24.2952
6	30	30.798621	35.3385
7	45	40.183448	47.6391
8	60	51.393103	65.0365

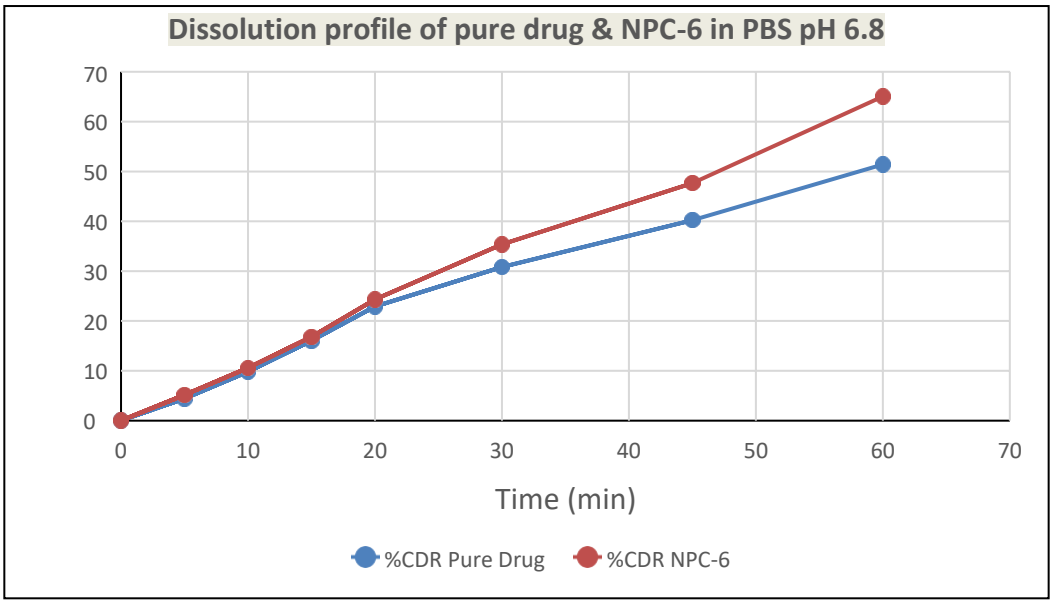

Figure 15: Dissolution profiles of CBZ and CBZNs in PBS pH 6.8

Table 9: Dissolution of CBZ and CBZNs in Distilled Water

Sr. No.	Time (min)	% Cumulative Drug Release	
		CBZ	CBZNs
1	0	0	0
2	5	4.282759	5.028945
3	10	9.571034	10.73748
4	15	15.64138	17.15958
5	20	22.27034	24.77095
6	30	30.09103	35.33854
7	45	39.58759	47.63906
8	60	50.83448	64.01712

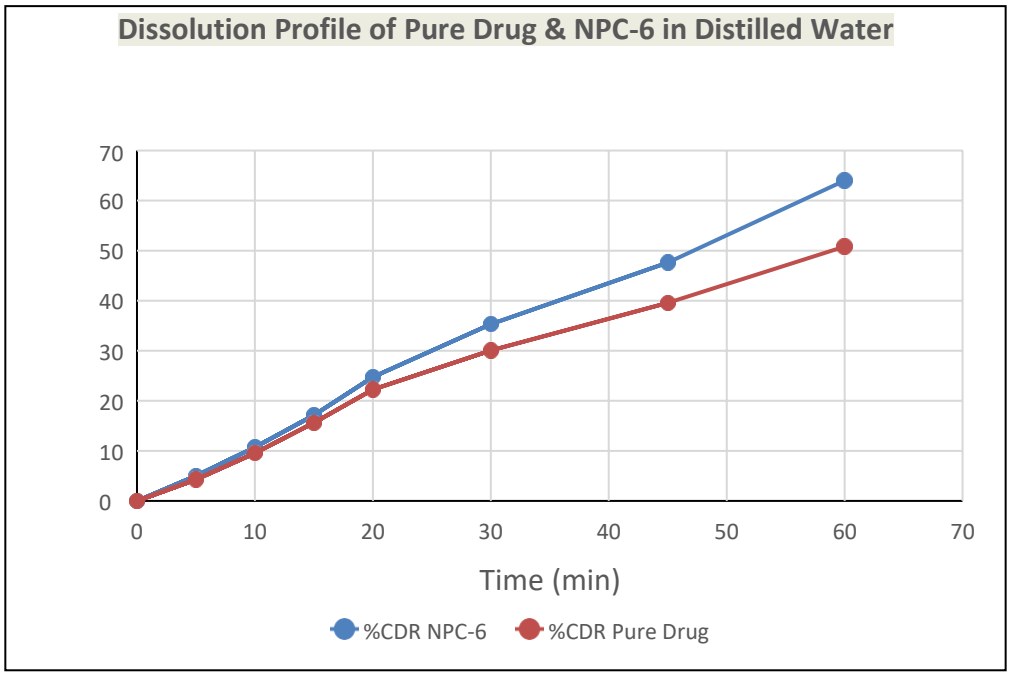

Figure 16: Dissolution profiles of CBZ and CBZNs in Distilled water

Optimized CBZNs showed almost 65.03% drug release in 60 minutes while CBZ showed51.39% drug release in PBS pH 6.8. Also, the optimized CBZNs formulation and CBZ showed almost 64.01% and 50.83% drug release in distilled water. The optimized CBZNs formulation exhibited improved dissolution behavior than the pure carbamazepine. This might be due to nanocrystallization and also may due to solubilizing effect of soluplus.

Evaluation of fast dissolving tablets containing CBZNsPrecompression evaluation

Three different tablet powder blends of F_1, F_2, F_3, F_4 were prepared and analyzed for various micromeritics and flow properties. Values of carr's index was found in the range of 12.07%, 13.15%, and 13.50%, 12.01%respectively i. e. <15 % indicating good flow properties. The angle of repose of different powder blends were found to be in the range of 25°31', 26°7', 27°21', 27° respectively i. e. <30 indicates good flow. The bulk densities of F_1, F_2, F_3, F_4 were found to be 0.351, 0.371, 0.78, 0.365 gm/cm^3 and measured values of tapped densities for the same were found to be 0.425, 0.441, 0.450, 0.451 gm/cm^3 respectively. The Hausner's ratio of powder formulation F_1, F_2, F_3, F_4 were found to be 1.20, 1.19, 1.18 and 1.23. From these values it was concluded that the prepared powder exhibited good flow properties.

Post compression evaluationThickness

The thickness of formulations F_1 to F_4 found to be 3.41 - 3.46 mm.

Table 10: Post compression parameters of tablet formulations

Formulations	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)	Weight Variation	Disintegration time (Sec)
F_1	3.3 ± 0.14	0.25 ± 0.9	99.5 ± 0.5	300 ± 1.8	52 ± 3
F_2	3.2 ± 0.11	0.54 ± 0.6	99.8 ± 0.3	301 ± 15	48 ± 2
F_3	3.1 ± 0.09	0.59 ± 0.6	99.23 ± 0.1	299 ± 1.4	31 ± 2
F_4	3.1 ± 0.05	0.58 ± 0.5	99.65 ± 0.2	300 ± 1.6	32 ± 1

(n*=3)

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Hardness, Friability, drug content, weight variation and disintegration time were found to be acceptable and within the limit as per IP.

In vitro dissolution study of CBZNs fast dissolving tablets

The fast dissolving tablets containing CBZNs was evaluated for *in vitro* drug release for a periodof 60 minutes and the results were shown in the Table 11 and figure 17.

Table 11: Dissolution of fast dissolving tablet containing CBZ & CBZNS

Sr. No.	Time (min)	% Cumulative Drug Release			
		F1	F2	F3	F4
1	0	0	0	0	0
2	5	8.53	7.03	11.37	6.88
3	10	18.35	18.48	24.39	14.04
4	15	31.70	32.10	38.28	21.30
5	20	45.73	47.49	52.52	28.67
6	30	60.21	63.09	67.91	36.79
7	45	77.20	79.43	83.34	49.82
8	60	94.45	96.45	98.93	72.13

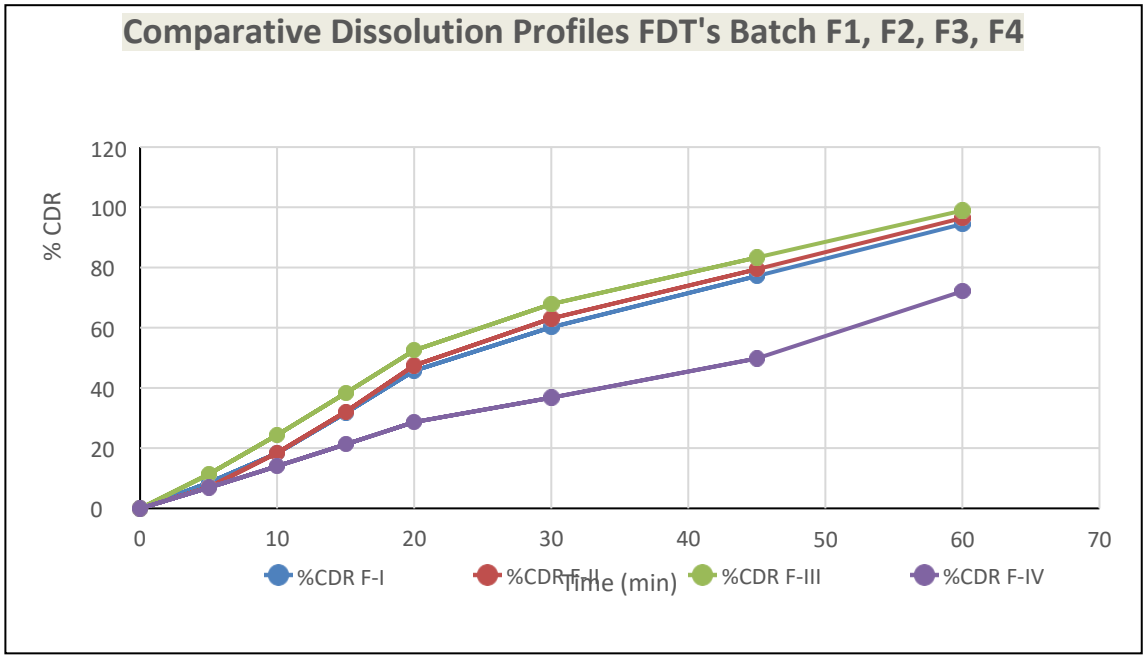

Figure 17: Dissolution of fast dissolving tablet containing CBZ & CBZNS

All tablet batches were subjected for *in vitro* dissolution studies for a period of 60 minutes table 11 and Figure 17. The tablet batch F3 showed 98.93% drug release which is more than the drug release shown by F1, F2, F4 which showed 94.45%, 96.45%, 72.14% drug release respectively. Hence batch F3 was considered as optimized batch and subjected for stability studies. The fast- dissolving tablet (F1, F2, F3) containing CBZNs showed greater drug release as compared to fast dissolving tablet (F4) containing CBZ. The increased rate and extent of dissolution may due tothe nanocrystallization with increased surface area and also may attributed to the solublizing effect of Soluplus.

CONCLUSION

The nanoprecipitation technique was employed to produce nanocrystals of carbamazepine, a poorly water-soluble drug, for the enhancement of solubility and dissolution velocity. With water as antisolvent, DMSO, Soluplus and PVP K-30 were found to be the suitable solvent, polymer and stabilizer, respectively. Carbamazepine nanocrystals prepared by nanoprecipitation exhibited significantly,

- Smaller particle size observed in case of optimized CBZNs as compared to CBZ.
- XRD data, showed significant crystallinity in both CBZNs and CBZ.
- Solubility was enhanced in CBZNS compared to CBZ, may be due to nanocrystallization or solubilizing effect of soluplus and hydrophilic stabilizer.
- *In-vitro* dissolution studies showed enhanced drug release in CBZNs and fast dissolving tablet (F1, F2, F3) containing CBZNs as compared to CBZ and FDTs containing CBZ (F4) in required time period.

From the obtained results of this study it can be concluded that the nanoparticles of poorly water-soluble drugs such as carbamazepine are easy to prepare and represent a promising new drug formulation strategy for oral delivery.

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