RESEARCH ARTICLE

# Formulation and Evaluation of Carbamazepine Nanosuspension with the Help of Cosolvent Technique

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***Received: 05th February, 2022; Revised: 20th April, 2022; Accepted: 13th May, 2022; Available Online: 25th June, 2022***

**ABSTRACT**

The nanosuspensions of carbamazepine (CZ) were developed by cosolvent technique. Various formulations were optimized to achieve desired size and solubility. Characterization of the prepared nanosuspension was done with respect to particle size, zeta potential, solubility, and dissolution rate. The results indicated that the optimized formulation showed more dissolution rate than a pure drug. Hence nanosuspension is a promising approach for bioavailability enhancement.

**Keywords:** Cosolvent, Dissolution, Nanosuspension, Particle size.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.2.2

**How to cite this article:** Sahoo CK, Mishra AK, Moharana AK. Formulation and Evaluation of Carbamazepine Nanosuspension with the Help of Cosolvent Technique. International Journal of Drug Delivery Technology. 2022;12(2):472-475.

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

One of the most persistent problems faced by drugs with poor[1] aqueous solubility is that their oral delivery is frequently associated with implications of low bioavailability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of such lipophillic drugs to increase their clinical efficacy. For the sake of therapeutic responses, the concentration of drug in plasma is important. Oral bioavailability[2] of drugs is affected by a variety of factors, which influence their absorption from the gastrointestinal tract. The therapeutic success depends on the concentration of the drug in the plasma which is within the minimum effective concentration and maximum toxic concentration. So, the therapeutic success depends upon various absorption factors. Varieties of methods have been developed over the years to improve the release and dissolution[3] of such as like pH adjustment method, cosolvent technique, micro emulsification method, self-emulsification, micelle formation etc. Out of various methods cosolvent technique is the easiest method to enhance solubility.

Nanosuspension[4] technology offers novel solutions for the poorly soluble drugs. Nanosuspensions are sub-micron colloidal dispersions of pure particles of drug which are stabilized by surfactants. Cosolvent technique has been proved to be capable of providing in situ nanosuspension. Cosolvent system can alter the thermodynamics of system and nucleation kinetics which would result in reducing particle size. This technique creates highly supersaturated systems which tend to crystallize by spontaneous reaction. The presence of polymers which function as anti-nucleating agents prevents crystal growth and enhances the overall stability of the formulation. Cosolvents are the mixtures of misicible solvents often used to solubilize lipophillic drugs. Currently, the water-soluble organic solvents are polyethylene glycol, ethanol, propylene glycol and glycerin. The water insoluble solvents include chain triglycerides like (i.e., peanut oil, corn oil, soyabean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil and hydrogenated soyabean oil), medium chain glycerides (miglycol 812), beeswax, d- a-tocopherol (vitamin E), and oleic acid.

According to Biopharmaceutic classification system (BCS), there are four categories of drugs. Dissolution is the rate limiting step for class II drugs. Carbamazepine[5] belongs to class II drugs. Carbamazepine is a white or yellowish-white crystalline powder, odorless and exhibits polymorphism. Oral absorption of is slow and variable due to its poor water solubility. Peak concentrations in plasma is observed after about 4 to 8 hours after oral ingestion, but may be delayed by as much as 24 hours following administration of a larger dose. The dose is 200 mg daily increasing 1.2 g daily in divided doses, in accordance with the needs of the patient. The present research is to develop CZ nanosuspension to avoid shortcomings of conventional dosage forms.

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## MATERIALS AND METHODS

### Materials

The CZ was obtained from Gift sample from Torrent Pharmaceuticals Ltd., Polyvinylpyrrolidone, and HPMC were purchased from S.D. Fine Chemicals Ltd, Mumbai, India., Poloxamer was purchased from Signet Pharma, Mumbai, India. Pluronic F-68 was obtained from HIMEDIA. PEG-200 was purchased from Loba Chemie Pvt. Ltd, Mumbai, India). All other solvents and reagents used were of analytical grade.

### Methods

*Calibration Curve*

The 10 mg of CZ was dissolved[6] in 0.1N HCl (10 mL), to get a 1-mL/mg concentration which can also be said to be 1000 µg/mL and is referred as stock solution. From the above stock solution 2.5 mL was taken and was diluted 0.1N HCl upto 50 mL mark in a volumetric flask resulting in 50 µg/mL concentration and was referred as primary standard solution. From the above primary standard solution following working standard solutions are prepared 2, 4, 6, 8, 10, 12, 14, 16 µg/mL by diluting the primary standard solution with appropriate amount of methanol -0.1N HCl. The working standard solutions were then measured at 284 nm using a double beam UV-visible spectrophotometer. The plot of absorbance v/s concentration was plotted.

### Fourier Transform Infrared Spectroscopy (FTIR)

IR spectroscopy[7] is one of the important analytical techniques for chemical identification. The drug polymer interaction was studied by using FTIR spectroscopy. The spectra were recorded for pure drug using the Shimadzu (Model No- IR Prestige 21). The scanning range was 4000–400 $cm^{-1}$.

### Method of Preparation of Nanosuspension

Nanosuspensions were prepared by co-solvent technique.[8] This involves mixing of two different solutions. First the drug is dissolved in an organic solvent (PEG-200) miscible with water. Polymer quantities are dissolved in the aqueous phase in which the drug is almost insoluble. Then the organic phase is mixed with the aqueous phase to a final volume under continuous stirring at 300 rpm for 2 minutes. The different batches of formulation are shown in Table 1.

### Saturation Solubility

The 1.5 mL of prepared nanosuspension[9] was filled in 2 mL centrifugation tube and centrifuged after 24 hours, using sigma centrifuge at 25000 rpm for 30 minutes. Concentration of CZ in the supernatant was measured spectrophotometrically using UV-visible spectrophotometer (ELICO) at 284 nm after suitable dilution with 0.1 N HCl. Saturation solubility of plain drug was also measured in the similar manner.

### Drug Content

The dispersed systems[10] of were assayed spectrophotometrically for the drug content at the wavelength of 284 nm with proper dilution of formulations taking 0.1N HCl as blank.

### Partcle Size Analysis and Zeta Potential

Particle size analysis[11] studies are carried out to find out the diameter of the particles present in the suspension and zeta potential studies are used to know the overall stability of the suspension. Both particle size and zeta potential analysis were done by using a Zetasizer (Malvern instruments, Model No ZEN 3500, Nano ZS).

### *In vitro* Drug Release Study

*In vitro* dissolution test was carried out by using USP type II (paddle) apparatus. The nanosuspension[12] is kept in 900 ml of dissolution fluid of 0.1N HCl and maintained at 37 ± 0.5ºC with 100 rpm of stirrer. In specified time intervals an aliquot of 5 mL sample of the solution was withdrawn through 0.45 µm cellulose acetate filter from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. After appropriate dilution the samples were analyzed for the drug using UV-visible Spectrophotometer at 284 nm for 0.1N HCl.

### Stability Study

Stability studies[13] for nanosuspensions were conducted at two different storage conditions, viz., room temperature and refrigerated conditions (2–8ºC) for 3 months. Three batches, each of nanosuspensions were used for each storage condition. At periodic time intervals, the samples were withdrawn and analyzed for particle size and drug content.

## RESULTS AND DISCUSSION

The wavelength of maximum absorbance ($\lambda_{max}$) of CZ was obtained at 284 nm for 0.1N HCl. The calibration curve was found to be linear in the range of 2–16 µg/mL and straight line equation was obtained having regression coefficient value of 0.998. The values of absorbance to corresponding concentration in 0.1 N HCl for CZ was presented in Table 2, and calibration curve was presented in Figure 1. The FTIR spectra of CZ and optimized formulation are shown in Figures 2 and 3. The characteristic peaks of the pure compound and nanosuspension were found that the polymers indicating the absence of any interaction with the drug.

Saturation solubility of optimized batch of nanosuspension and pure drug was found to be 1.16 ± 0.12 and 0.45 ± 0.05 mg/mL, respectively it indicates that saturation

**Table 1:** Composition of different batches of formulations

| *Batches* | *CZ (mg)* | *PVP K30 (mg)* | *Pluronic F 68 (mg)* | *HPMC K100M (mg)* | *PEG 200 (mL)* | *Water (mL)* |
|---|---|---|---|---|---|---|
| F1 | 200 | 10 | 25 | 40 | 10 | 40 |
| F2 | 200 | 20 | 25 | 30 | 10 | 40 |
| F3 | 200 | 30 | 25 | 20 | 10 | 40 |

solubility of nanosuspension was increased several times than that of pure drug. This improvement in saturation solubility is due to reduction in particle size and subsequent increase in surface area. All the values of saturation solubility, drug content, particle size and zeta potential are shown in Table 3. The percentage of drug content varied in formulations from 96.32 ± 1.41 and 99.91 ± 1.4 %. All are in the acceptable limits. Particle size distribution of the optimized batch (Figure 4) and mean Particle size of optimized batch was found to be 996.5 ± 10 nm. The particle size of a nanosuspension for oral use is around 200 to 1000 nm. It is observed that optimized formulation fulfilled the requirements of a nanosuspension. In general, zeta potential value of ± 20 mV is sufficient for stability of nanosuspension stabilized by steric stabilizer Pluronic. Zeta potential of the optimized batch was found to be -19.5 mV which complies with requirement of zeta potential. The drug release study of different formulations of CZ was shown in Table 4. In case of nanosuspensions, the drug release was more compared to pure drug within 15 minutes. Among developed formulations the optimized (F3) formulation showing 97.46 ± 2.49% within 15 minutes.

**Table 2:** Absorbance values to corresponding concentration of CZ in 0.1 N HCl

| *Concentration (µg/mL)* | *Absorbance (S.D)[a]* |
|---|---|
| 0 | 0 |
| 2 | 0.1250.035 |
| 4 | 0.2280.042 |
| 6 | 0.3450.018 |
| 8 | 0.4520.023 |
| 10 | 0.555 0.027 |
| 12 | 0.672 0.078 |
| 14 | 0.787 0.093 |
| 16 | 0.936 0.096 |

**N.B.-**All values are expressed in meanS.D ([a]n=3), Where is mean

In the case of F3 formulation stored at room temperature, the particle size increased form 996.5 to 998.6 nm in 90 d. But, under refrigerated storage conditions, there was a nominal increase from 996.5 to 999.8 nm indicating better stability under these conditions. The results showed that temperature

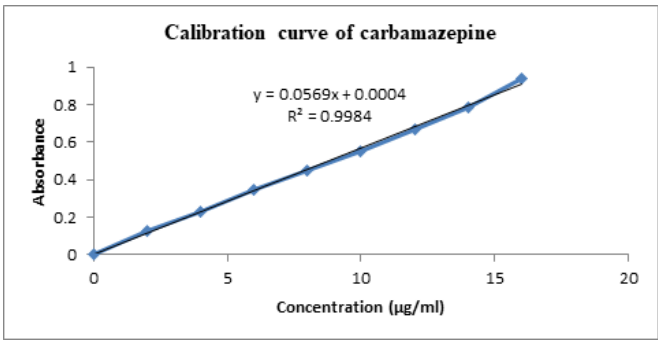


**Figure 1:** Calibration curve of carbamazepine 0.1 N HCl at $\lambda_{max}$ 284 nm

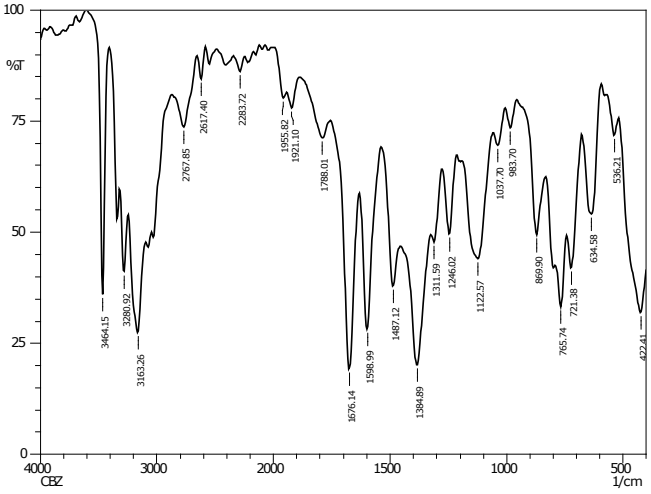


**Figure 2:** FTIR study of carbamazepine

**Table 3:** Evaluation parameters of developed batches and drug

| *Batches* | *Solubility (mg/ml, ± SD)* | *Drug content (%, ± SD)* | *Particle size (nm ± SD)* | *Zeta potential (mv, ± SD)* |
|---|---|---|---|---|
| CZ | 0.45 ± 0.05 | 100 | ……. | ……. |
| F1 | 0.66 ± 0.38 | 96.32 ± 1.41 | 1712.1 ± 11 | -38.3 ± 2.58 |
| F2 | 0.97 ± 0.25 | 97.64 ± 0.98 | 1123.4 ± 19 | - 35.4 ± 3.52 |
| F3 | 1.16 ± 0.12 | 99.91 ± 1.4 | 996.5 ± 10 | - 19.5 ± 1.59 |

**Table 4:** %CDR of developed nanosuspensions and pure drug

| *Time (min.)* | *Pure Drug* | *F1* | *F2* | *F3* |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 5 | 28.82 ± 1.14 | 78.82 ± 3.14 | 83.87 ± 2.12 | 85.01 ± 2.11 |
| 10 | 44.66 ± 1.18 | 84.72 ± 3.12 | 86.15 ± 1.94 | 89.38 ± 1.12 |
| 15 | 54.46 ± 2.45 | 92.46 ± 2.43 | 93.41 ± 2.41 | 97.46 ± 2.49 |
| 20 | 55.72 ± 2.38 | 91.72 ± 2.33 | 90.72 ± 2.86 | 96.71 ± 2.37 |
| 25 | 53.14 ± 2.67 | 89.14 ± 2.63 | 88.05 ± 2.97 | 95.14 ± 2.65 |
| 30 | 52.24 ± 2.42 | 85.24 ± 2.48 | 87.94 ± 1.48 | 95.44 ± 2.48 |

**N.B.** Mean ± SD, n=3

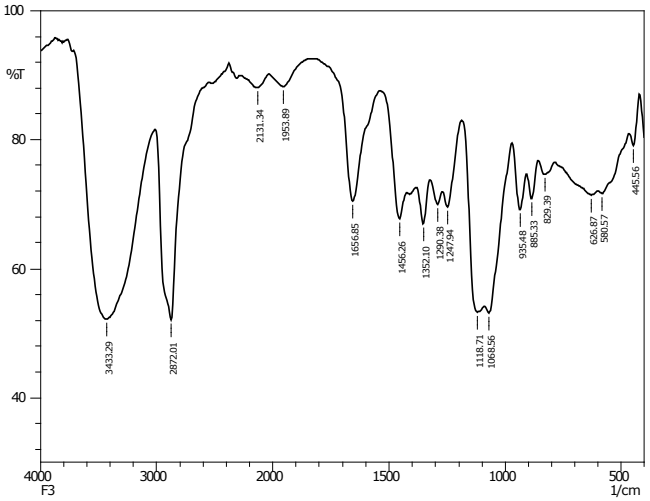


**Figure 3:** FTIR study of formulation F3

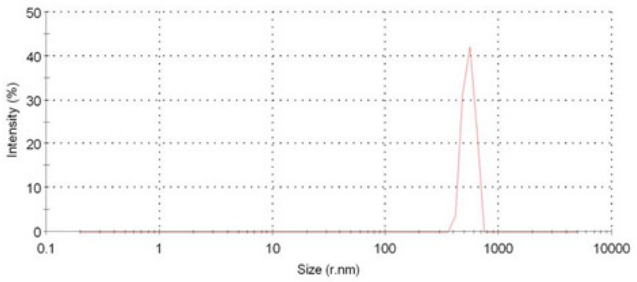


**Figure 4:** Particle size analysis of optimized formulation(F3)

has an influence on aggregation of nanoparticles and at room temperature aggregation was higher compared to refrigerator condition for liquid nanosuspension. The drug content of the formulation was not varied significantly.

## CONCLUSION

The preparation of nanosuspension of was achieved through the screening of several polymer types and polymer mixtures and the use of cosolvent technique with PEG-200 and water. These dispersions were found to be stable for more than 90 days. Particle size analysis and Zeta potential analysis showed that the particle size of the produced nanosuspensions is within the acceptable limits and the nanosuspension is stable. *In vitro* drug release study shows that above 90% of the drug is released between 15 minutes from the formulation.

## ACKNOWLEDGEMENTS

The author would like to express their gratitude to the College of Pharmaceutical Sciences (Affiliated to BPUT), Puri and School of pharmacy, Arka Jain University, Jharkhand for providing necessary facilities to carry out this work.

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