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FORMULATION AND CHARACTERIZATION OF CARBAMAZEPINE NANOCRYSTALS BY ANTISOLVENT PRECIPITATION METHOD

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ABSTRACT

Nanocrystals of any drug are pure solid drug particles with a mean diameter in nanometer range. The aim of this study was to develop nanocrystals of a hydrophobic drug. carbamazepine, by addition of solvent to an antisolvent to achieve solubility enhancement. The developed nanocrystals were characterized for particle size, solubility, solid nanocrystals were characterized for DSC and XRD. These are considerable increase was found in the solubility of the nanocrystals as compared to pure drug. The nanocrystal development by antisolvent precipitation procedure using ethanol as solvent, water as antisolvent, it's a very promising and effective method to increase the dissolution rate of carbamazepine.

KEYWORDS-*Carbamazepine, Nanocrystals, Antisolvent Precipitation Method.*

INTRODUCTION

A nanocrystal is a material particle having at least one dimension smaller than 100 nanometers, based on quantum dots (a nano-particle) and composed of atoms in either a single or poly-crystalline arrangement. When embedded in solids nanocrystals behavior than conventional solids and may form the basis of a special class of solids They can behave as single-domain system (a volume within the system having the throughout) that can help explain the behavior of microscopic samples of a similar material without the complicating presence of grain boundaries and other defects. Semiconductor nanocrystals having dimension smaller than 10 nm are also described as quantum dots. (1) Nanocrystals and their composites can exhibit markedly different properties with respect to bulk phases and hence offer new opportunities. For pharmaceuticals, nanocrystals promise to resolve the issue of poor bioavailability of poorly soluble drugs. The immense surface area of the particles, increased saturation solubility, and the decreased diffusional pathway adjacent to the nanocrystal surface all converge to enhance the bioavailability. The difficulty in exploiting this technology is the technical challenge of generating and stabilizing nanocrystalline products.

Nanocrystals can be prepared by a variety of methods, which in general terms can be categorized as comminution (top down) or controlled precipitation (bottom up). Although the technology is maturing, there are still important issues and limitations. Top-down processes which include milling and high-pressure homogenization usually require long processing times, high energy input, and tend to yield a broad particle size distribution. There is also a concern with regards to contamination of the products from the milling media[2]. With respect to precipitation methods, there are many variants including simple precipitation, spray freezing into a liquid precipitation from a supercritical fluid using an antisolvent, and microfluidics. Precipitation has also been employed in combination with homogenization. The major limitations with precipitation are considered to be uncontrolled particle growth which has resulted in its adoption for only a few selected molecules.[3.] Carbamazepine (CBZ) is a class II antiepileptic drug and has high intestinal permeability. But the bioavailability of CBZ is limited because of its low solubility in water. CBZ exists in at least four anhydrous forms: primitive monoclinic (III), C-cantered monoclinic (IV), trigonal (II), and triclinic (I). Among these, form III is the most stable polymorph under ambient conditions. Herein, we describe a Precipitation technique followed by annealing to produce nanocrystals of CBZ with the most stable form III for continuous pharmaceutical manufacturing. The effects of the solution properties and operating parameters on the morphology, crystallinity, and polymorphism of CBZ nanocrystals are described. The solubility and dissolution rates of the nanocrystals are also reported. (2)

MATERIALS AND METHODS

Material-Carbamazepine, Ethanol, phosphate buffer 6.8 and 7.4, Distilled water.

Method of Preparation of Carbamazepine Nanocrystals

The Nanocrystal of Carbamazepine were prepared using precipitation technique. A known quality of carbamazepine was completely dissolved in solvent (ethanol) which was

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completely water miscible having concentration 10 mg/ml and then sonicated for 30 s. The solution was filtered through a 0.45 μm Whatman filter paper to remove impurities. The carbamazepine nanocrystals formed were filtered and dried at room temperature.

CHARACTERIZATION

1. SOLUBILITY

The solubility of carbamazepine in the solvent–antisolvent system was measured by adding an excess amount of the original carbamazepine into ethanol antisolvent (water and Phosphate buffer pH 6.8) mixture at various concentration. The mixture was shaken continuously at room temperature (25 ºC) for 1 h and then filtered through a Whatman filter paper and analysed spectrometrically at 284 nm using UV spectrometer (UV-3101PC, Shimadzu). [3]

2 PARTICLE SIZE DETERMINATION

The morphology and size of samples were observed using a optical microscope. The particle sizes were analysed by the image Tool program. [5]

3 DIFFERENTIAL SCANNING ELECTRON MICROSCOPY

Differential scanning calorimetric (DSC) measurements were carried out using a DSC (Mettler Toledo, STARe SW 14.00 T6) thermal analyser in a temperature range of 25–350 ºC at a heating rate of 10 ºC/min in nitrogen gas. The melting point and heat of fusion were calculated using the DSC software. [14]

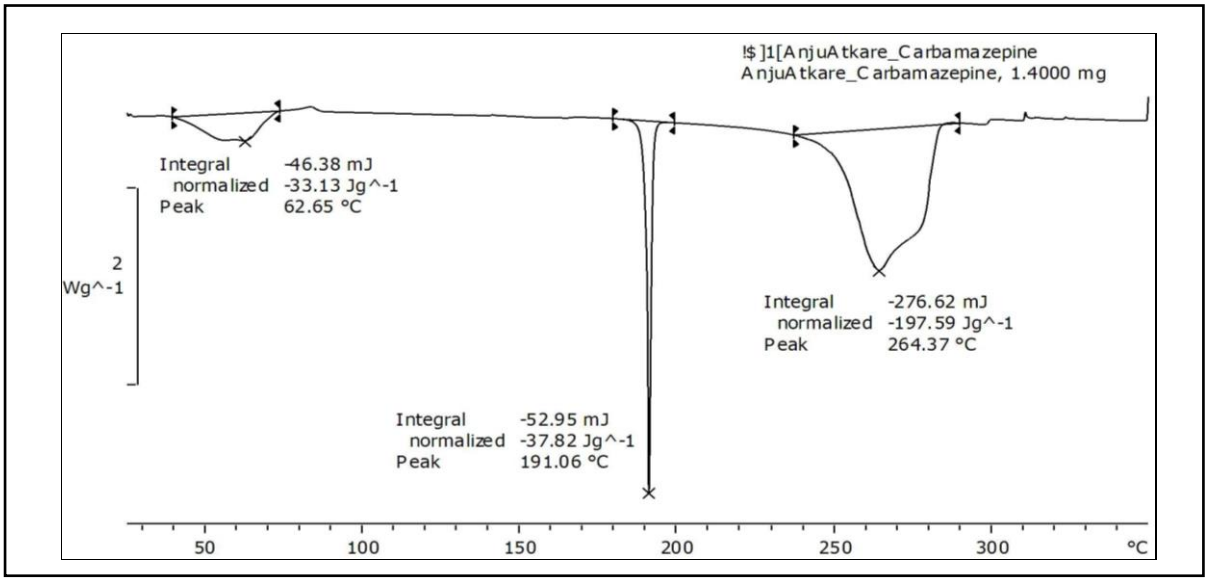
4 X-RAY DIFFERACTION STUDY

X-ray diffraction (XRD) study was conducted using (PANalytical, Netherlands model: PW 3040/60 X'pert) diffractometer to study crystalline nature of pure untreated Lercanidipine API and lyophilized LER - NCs. Samples were characterized by X-Ray diffraction method at room temperature using Cu Kß X-ray radiation source over 2 range from 5° to 80° with a step size of 0.02° and scan rate of 0.04/s. [12]

RESULT AND DISCUSSION

Differential Scanning Electron Microscopy

Thermal analysis of nanocrystals was done through DSC. It was commonly used method within the pharmaceutical industry, which allows the assessment of any change in phase transition from crystalline to amorphous state of drug concurrently preformulation and formulation steps. This approach aid in the assessment of physical properties, compatibility and stability studies of the constituents of pharmaceutical advancements. It was observed from the thermos gram of x drug was implicated in the fig. The single sharp endothermic transition was characterized at a temperature of maximum of 191℃ and these values found to be in acceptable range with the literature value of 190℃-195℃



X-ray Diffraction Studies

The P-XRD patterns of pure carbamazepine showed numerous sharp peaks at 7.213, 9.995which are the characteristics of the crystalline compound and are compared with the P-XRD patterns of nanocrystals. The nanocrystal shows crystal peaks. P-XRD graphs are shown in fig. respectively.

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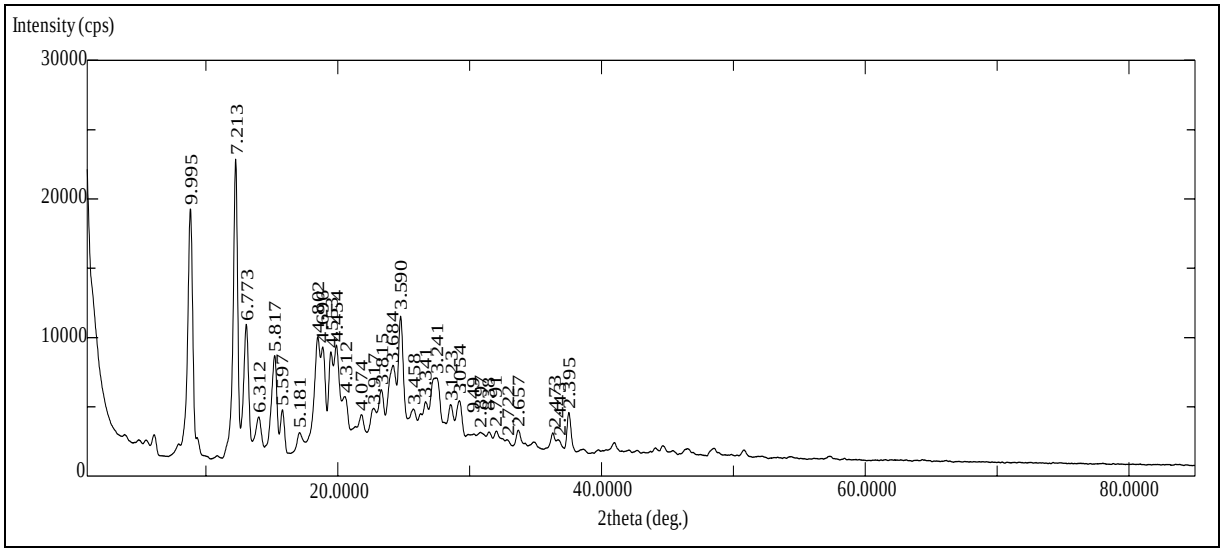

Particle Size

The mean particle size of carbamazepine nanoparticles was found to be smaller than 130 nm. Particle size plays an important role in the drug delivery to the brain as nanoparticles with smaller size can easily cross the barrier comparable to the particles with size more than 500nm. Also decrease in the particle size leads to increase in the surface area particularly effective surface area, which leads to increase in solubility of the hydrophobic drug. So, the nanoparticles size range was found to be satisfactory and was according to the specifications. (15)

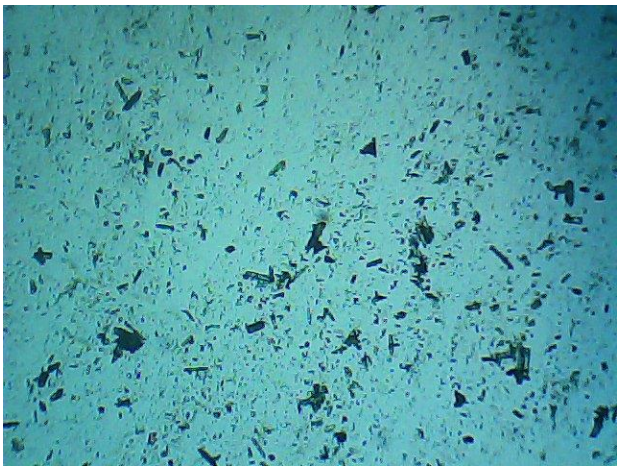

Fig. Particle size

Solubility Studies

To verify the maximum solubility of the drug in the relevant solvent and to analyse the solubility curve of CBZ as an active moiety, distilled water, ethanol, and buffers at a pH of 6.8 were used. It was found that CBZ solubility in distilled water was 26.4 %; in ethanol it was 17.3%, which is lower than in distilled water. The lowest solubility was found in phosphate buffer due to a significant increase in the surface area of the prepared nanocrystals which increased the CBZ solubility. The complete data of solubility has been shown in below table.

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Solubility of CBZ Nanocrystals

Sr. No	Medium	Pure drug concentration of CBZ (mg/ml)	Nanocrystals concentration of CBZ (nm)	Solubility Enhancement (%)
1	Distilled Water	0.139 ± 0.003	320 ± 52	26.4
2	Ethanol	0.129 ± 0.005	540 ± 44	17.3
3	Phosphate buffer pH 6.8	0.122 ± 0.004	960 ± 92	10.9

CONCLUSION

Now a day's Nanoparticles are used very much because of more bioavailability of drug as compare to conventional formulations almost 3 to 4 folds increment of bioavailability as compare to original so nanoparticles are used very much in pharmaceutical sciences & various faculties of sciences as well. In the present study, nanocrystals were prepared to enhance the solubility of poorly water-soluble drug carbamazepine. The antisolvent precipitation procedure using ethanol as solvent, water as antisolvent. The method is simple and cost effective and uses safe materials. The physiochemically stabled carbamazepine nanocrystals obtained in this method were remarkably showed higher solubility as compared to pure carbamazepine.

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