
Cocrystal Synthesis of Carbamazepine with Succinic Acid and Its Solid-State Characterization

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Abstract:

Carbamazepine (CBZ) is a widely used antiepileptic drug that suffers from poor aqueous solubility, which limits its oral bioavailability. Pharmaceutical cocrystallization has gained as an effective strategy to improve the physicochemical properties of poorly soluble drugs without altering their therapeutic activity. In the present study, a cocrystal of carbamazepine with succinic acid (SA) was synthesized using the slurry crystallization method. The prepared cocrystal was analyzed using powder X-ray diffraction (PXRD) to confirm the formation of a new crystalline phase.

Keywords: Carbamazepine, Succinic Acid, Cocrystal, Slurry Crystallization

Introduction:

Carbamazepine was first synthesized in 1953 by the Switzerland Chemist Walter Schindler, in the Great Britain and Switzerland introduced to market in 1963. [1].

Carbamazepine is an important anticonvulsant drug with low water solubility. Pharmaceutical cocrystals are crystalline materials composed of an Active Pharmaceutical Ingredient (API) and a co-former bonded through non-covalent interactions. Succinic acid was selected as a co-former due to its hydrogen bonding capability. It is anti convulsant. It works to blockade of presynaptic voltage-gated sodium channels and inhibit release of synaptic glutamate and other neurotransmitter. [2]. Carbamazepine is less soluble in water. It is soluble

in acetone, alcohol, carbontetra chloride, Chloroform, dimethyl-form amide, dioxane and propylene glycol .Molar mass of Carbamazepine is 236.12g/mol.The Melting point of Carbamazepine is 206-210⁰C.Boiling point of around 378.73⁰C .[3].

Carbamazepinepre dominantly its pharmacological action by blocking a sodium (Na⁺) channel in the nervous system. As a result, the formation of action potential scanbesuppressed and high frequency neuronal firing is reduced [2,4]. Traction with voltage-controlled calcium(Ca²⁺) and potassium (K⁺)channels are also thought to inhibit stimulatory effects on nerves [5]. Carbamazepine is now the principal drug used for treating trigeminal neuralgia and nasopharyngeal neuralgia. Idiopathic trigeminal neuralgia is more likely respond to treatment than the symptomatic from of diseases, such as in multiple sclerosis [6]. Beyond its primary indications, carbamazepine is widely prescribed for the management of epilepsy and trigeminal neuralgia. Furthermore, several off-label applications have been reported, including the treatment of postherpetic pain syndrome, neurogenic diabetes insipidus, bipolar disorder, alcohol withdrawal symptoms, and cocaine dependence. [7].

Cocrystalsaremulti-componentcrystalsbasedonhydrogenbondinginteractionsratherthanon the exchange of hydrogen ions to create salt [8,9]. Co crystals are composed of two or more constituents that work together to create a unique crystalline structure with an exclusive set of features. Cocrystal development and study has gained a lot of attention for its potential to alter physicochemical qualities while keeping therapeutic effectiveness. To create a single-phase molecule in a specific ratio, two or more molecules, such as conformer and medication, are combined in a cocrystal.One important advantage of creatinga co-crystalis that, depending on the situation, the bioaccessibility of a pharmaceutical molecule can be improved. [10,11].

Method : Co-crystal preparation:

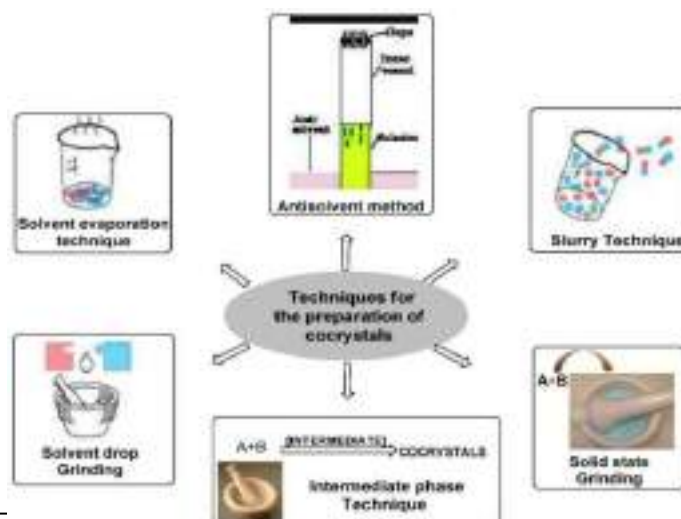
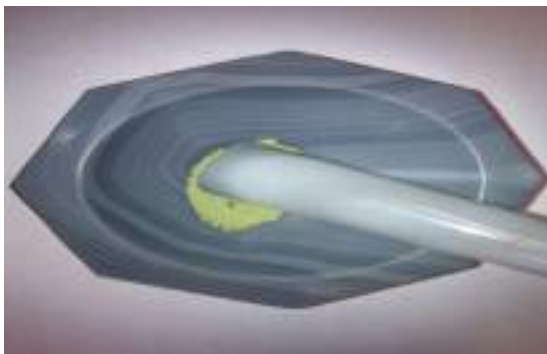


Fig1 : Methods of Cocystal preparation**Materials and methods:**

The carbamazepine used for the synthesis of cocystal with the using various conformer i.e., succinic acid, cinnamic acid, with the help of solvent assisted grinding.[12].

**Fig2 : Mortar and Pestle****Cocrystal of Carbamazepine and succinic acid:**

Cocrystal were synthesized using API and conformer. When API and conformer are grinded uniformly hydrogen bonding which is detected by characterization. IUPAC Name of succinic acid Butene 1,4-dioic acid and chemical formula is $C_4H_6O_4$. Meltingpoint of succinic is $184^{\circ}C$.

**Fig 3 :1:1Co-crystal preparation of Carbamazepine and Succinic acid.**



Fig4: Succinic acid and Carbamazepine placed on mortar pestle.

Approximately 0.296 g (0.002 moles) of succinic acid and 0.472 g (0.002 moles) of carbamazepine were accurately weighed. Both components were transferred to a mortar and pestle, as illustrated in the corresponding figure. The solid mixture was gently ground in a continuous and uniform manner for about 20–25 minutes. During the grinding process, ethanol was added dropwise at regular intervals to facilitate solvent-assisted grinding, ensuring that excess solvent was avoided. Computational analysis using Mercury software was employed to predict possible hydrogen bonding interactions between succinic acid and carbamazepine; however, the actual formation of these interactions may or may not occur, as depicted in the figure. Upon completion of the grinding process, the total yield of the prepared cocrystal was found to be 0.74 g. The melting point of the obtained cocrystal was determined to be 158 °C.

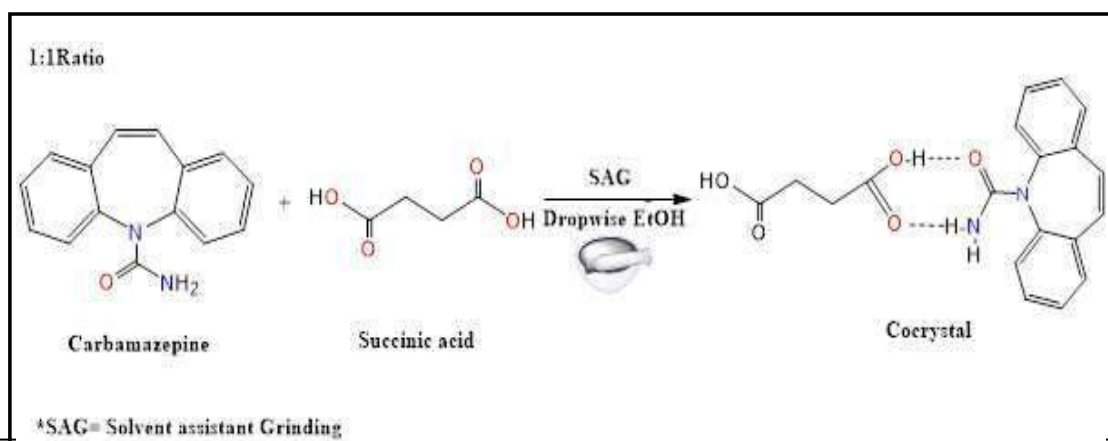


Fig5: Formation of hydrogen bonding between Succinic Acid and Carbamazepine

Results and Discussion:

Crystallographic Analysis:

The Cambridge Structural Database (CSD) accessed through the Conquest software (Conquest version 3.7; CCDC version 2.0.0) shows that the crystal structures of the title molecules (Scheme 1) were reported by Sylwia Pawlędzio, Damian Trzybiński, Krzysztof Woźniak [13]. The crystal structure and crystallographic details are explained here. crystallographic information file code yf3179sup1. The space group of the molecule is observed P2₁/c. The unit cell volume of the given compound is 2076.91 Å³. [14].

Crystal Data	Compound Code
Formula	C ₁₅ H ₁₂ N ₂ O, C ₇ H ₄ N ₂ O ₆
Molecular weight	236.27
a(Å)	10.7545(3)
b(Å)	6.47168(18)
c(Å)	30.0313(9)
$\alpha(^{\circ})$	90
$\beta(^{\circ})$	96.456(3)
$\gamma(^{\circ})$	90
Z'	1
Z	4
Crystal system	Monoclinic
Density (gcm ⁻³)	1.46
Space group	P2 ₁ /c
Cell volume	2076.91

Table1-Cell parameter and crystallographic details of compounds

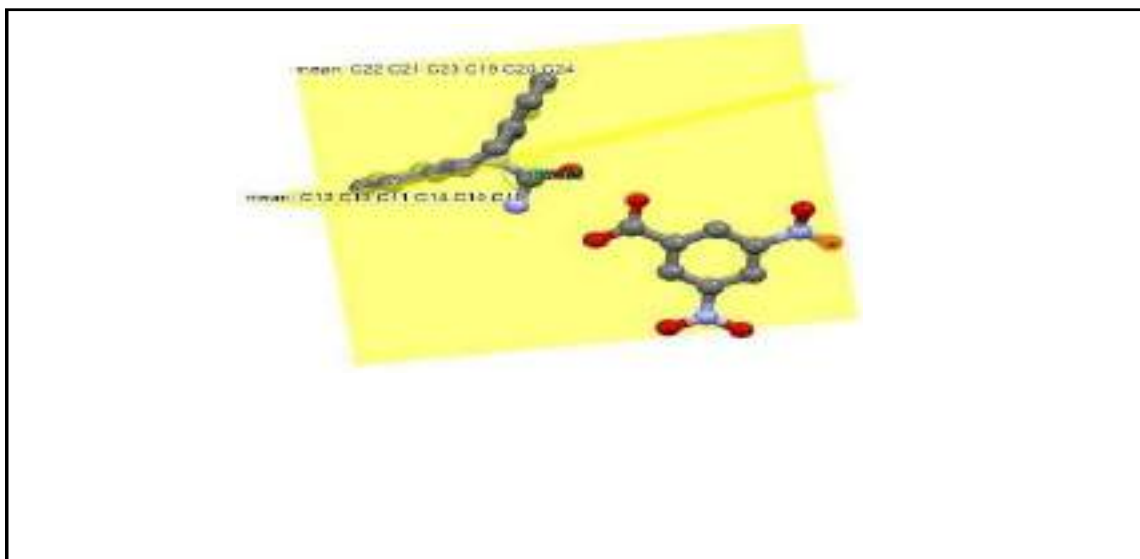


Figure 6 : Tetrahedral angle between two different phenyl rings of synthesized compounds.

In the crystal lattice, the strong hydrogen bonds are prepared and responsible for the well packing. The N18-H18A...O₂₇ (3.026Å, 95.07°) hydrogen bond form strong in the crystal. There are two intermolecular hydrogen bonding presents in the compound as shown in the figure below. The hydrogen bonding details and its analysis are listed in the table no. 2. [15].

D-X...A	D-X(Å)	X...A(Å)	D...A(Å)	<D-X...A(°)
N ₁₈ -H _{18A} ...O ₃₂	0.867	2.041	2.894	167.48
N ₁₈ -H _{18B} ...O ₂₇	0.862	2.261	3.026	147.91
C ₁₆ -O ₁₇ ...H ₃₃	1.256	1.663	3.400	12.44

Table 2: Prominent hydrogen bonding interactions present in the compound

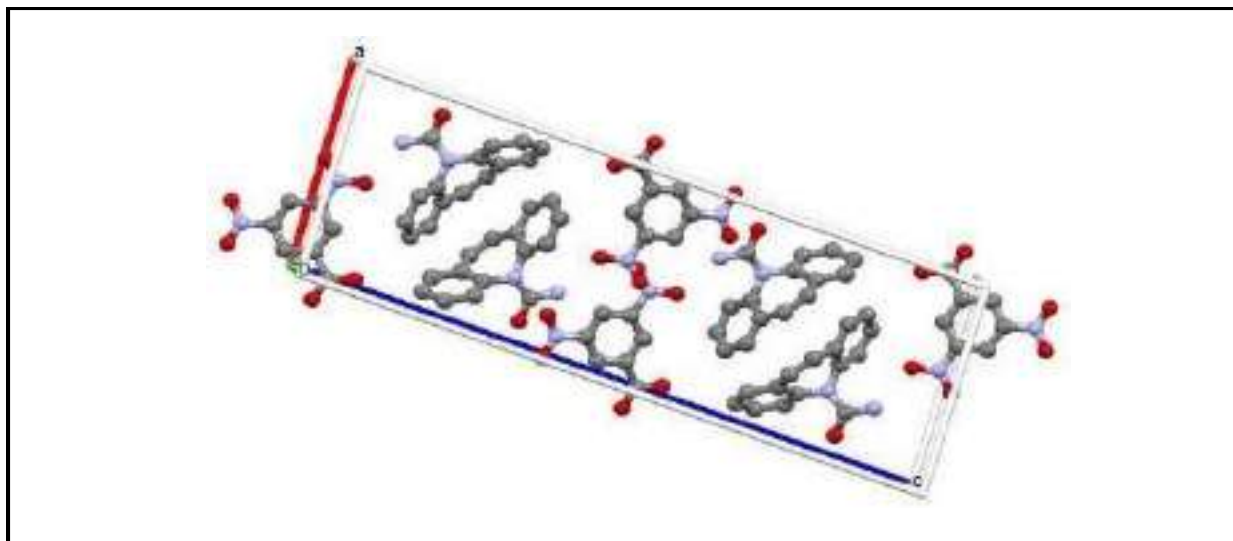


Fig7 : Mono clinic crystal system in Carbamazepine

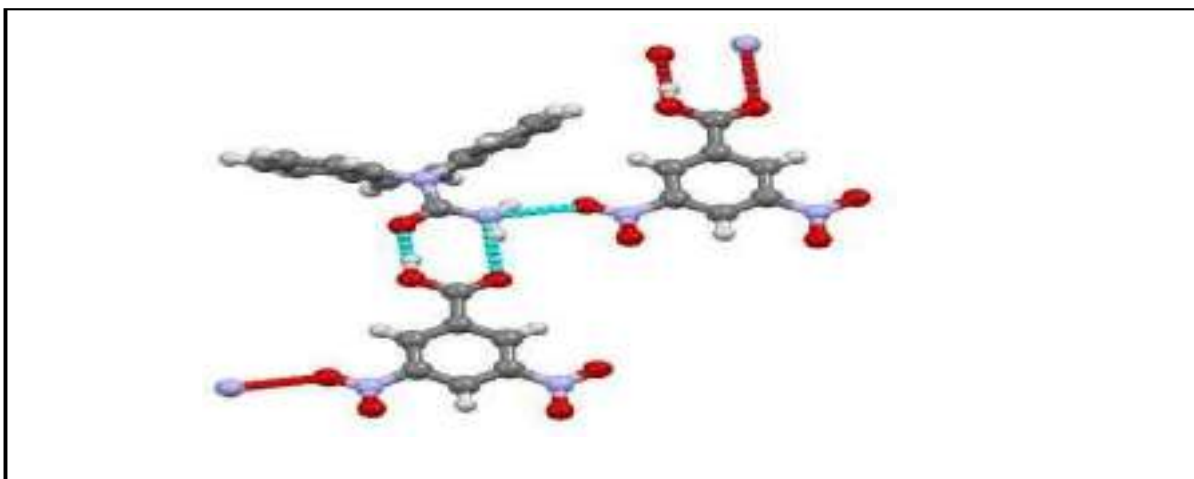


Fig8 : Hydrogen bond sand crystal structure in title compound

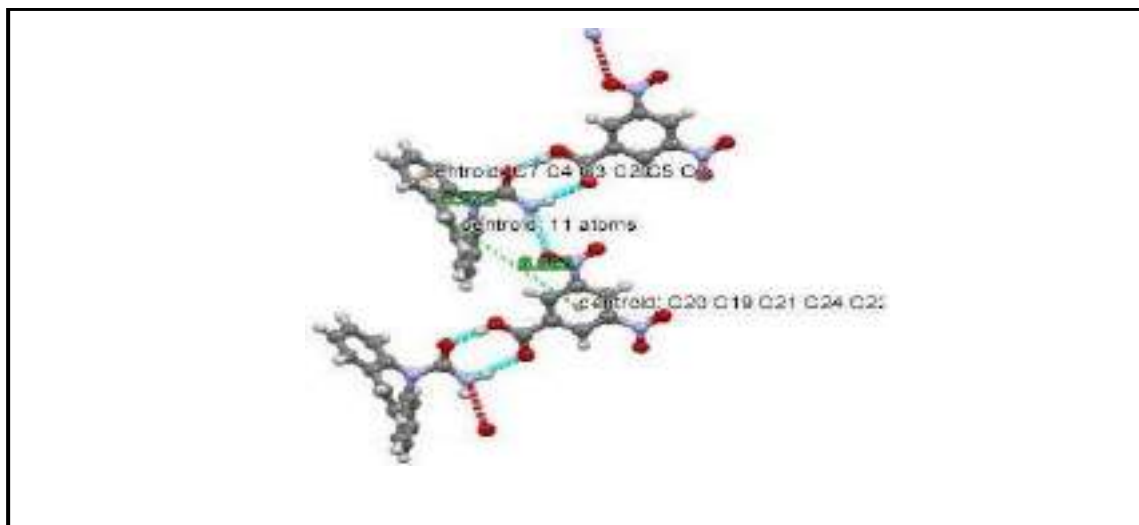


Figure 9 : The pi-pi interactions shown in the crystal lattice.

Simulated powder pattern image:

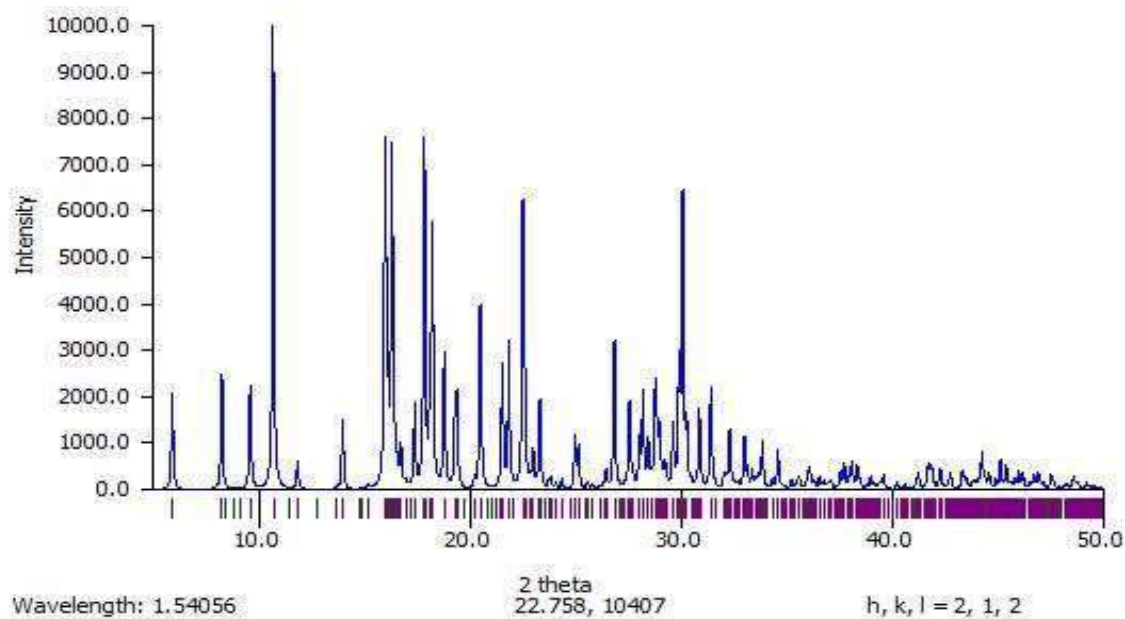


Fig10 : Simulated powder X-ray pattern for the title compound obtained from single-crystal x-ray diffraction technique.

The Simulated Powder X-ray pattern for the title compound was obtained from single-crystal x-ray diffraction technique and analysis using Mercury software.[16] The plot of diffraction intensity against 2 theta for the wavelength 1.54056 is shown in figure 10. The sharp peak indicate that substance is crystalline in nature.[17,18].

Conclusion:

The supra molecular study of surface analysis of pharmacologically active Carbamazepine compound was analyzed using mercury software. It was observed that the title compound has orthorhombic system in the crystal packing. The peak observed in powder pattern clearly showsthat the compound is highly crystalline in nature.

Future research will look at the FTIR and PXRD data of the produced cocrystals to seeif hydrogen bonds are created between the Carbamazepine and the coformers.

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