Global Scientific JOURNALS

GSJ: Volume 9, Issue 7, July 2021, Online: ISSN 2320-9186
www.globalscientificjournal.com

AN ANALYTICAL APPROACH ABOUT COCRYSTALS OF LEVETIRACETUM AND OXALIC ACID THROUGH H^1 NMR AND C^{13} NMR

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Abstract

A new cocrystal of Levetiracetum and oxalic acid has been formed by using a technique which is based on hydrogen bonded Synthon illustrate by notation $(F^2)_4(8)$. Several Techniques were used to explain the new bonding formed between Levetiracetum and oxalic acid along with traditional crystallization method. New Solid formation have been detected and explain with various NMR techniques, which revealed synthon $(F^2)_4(8)$.

CH: 1 INTRODUCTION

From last couple of years the preparation of cocrystals in the pharmaceutical industry has gained much intention to obtain polymorphs, salts and solvates of an active pharmaceutical ingredient (API).[1-3] Due to the higher solubility or increased degree of crystalinity organic salts are generally preferred crystals form of Active pharmaceutical ingredient (API). The probable number of suitable organic salts is limited to the counter ions specified by the food and drug association (FDA) as GRAS (generally regarded as safe). A recently suggested alternative to the common inorganic salts is the preparation of cocrystals or organic salts, some of which have been shown to improve beneficial utility while reducing side effects. The highly biologically active drug substances which developed over the past few decades are almost insoluble in aqueous media. There are about 30% of drugs which are successfully gone through preliminary

biological tests, fail to pass clinical trials because of adverse characteristics (adsorption, distribution, metabolism, excretion).[4] The procedure of drug development is quite time-consuming and adds much to the cost of the final product. In this connection a requirement arises to develop scientific foundations for the creation of soluble forms of drugs. This problem can be solved by searching for regularities in the change in the physicochemical properties of compounds that exist as crystals and pass into solution. The available theoretical and experimental evidence on correlation between the crystal structure, physicochemical properties, and pharmacological activity of compounds opens up the possibility not only for targeted structural modification of known drug, aimed at improving their properties, specifically solubility, but also supports in the search for principally new biologically active compounds.[5] The standard dosage which has to give to the patient regularly is the solid state form of active pharmaceutical ingredients (e.g., tablets, capsules etc.). APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug.[6] Most APIs and their salts are purified and isolated by crystallization from a relevant solvent during the final step in the synthetic process.[7,8]

A discussion paper has also been published by the European Medicines Agency (EMA) about the use of cocrystals in medicinal product which states that co crystals are a versatile tool that can be used to obtain more suitable solid-state properties. It is defined cocrystals as homogeneous crystalline structures constituted by two or more components in a definitive stoichiometric relation 1:1 where the arrangement in the crystalline lattice is not based on ionic bonds and requires that the formation of the cocrystal is confirmed by means of suitable

analytical technique.[9] Cocrystal field also place some or all of the following requirements on the solid forms in question:

1. All components are organic species (ruling out inorganic or organometallics).

2. None of the components are charged (otherwise classified as salts).

3. None of the components are water (otherwise classified as hydrates).

4. None of the components are solvents (otherwise classified as solvates).

5. There is a directional interaction between the different components.

Salts have been the preferred crystals form of API that exhibit poor aqueous solubility. There are number of potential advantages of cocrystal engineering and cocrystalization of the API over salt formation. Firstly all types of API including acidic, basic and non-ionizable molecule may potentially employ with the pharmaceutical compound through crystallization. Secondly, the scope of cocrystallisation has been increased potentially over salt formation due to presence of a large number of pharmaceutically acceptable cocrystal formers.[10] When cocrystallisation process takes place between two incongruently soluble components, the component that has lower solubility will precipitate, form a solid mixture of cocrystal and cocrystal component, moreover, it also has a possibility that cocrystal failed to formed.[11-12] Just like any crystallization process, cocrystal formation using this method involves three steps of the process; super saturation, nucleation and crystal growth, where a super saturation step is a rate-limiting step for nucleation and crystal growth step.

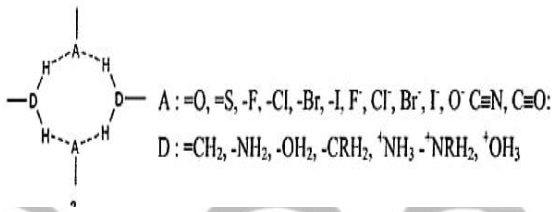
In this paper, the main technique use for the preparation of cocrystals is solvent evaporation method. A solvent evaporation method is the most common method for cocrystal formation, where drug and coformer at stoichiometry ratio solved in a specific solvent, stirred in constant condition to facilitate molecular interaction between drug and conformer, then solvent

allowed to evaporate. Nonionic attraction between the components is developed during cocrystal formation. Mainly attraction is hydrogen bonding. The Cambridge Structural Database (CSD), provides a repository of 3,55,000 small molecule organic and organometallic crystal structures. The existence of each structure in the database may be considered as testament to the practicalities of that structure's own crystallization, or more precisely, each database entry adds to a collective a posteriori understanding of the kinetics and thermodynamics of similar crystal formation. Related molecular and structural properties may be subjected to statistical analysis such that this latent information in the CSD may be revealed. The work presented here focuses on hydrogen bonds, which play a dominant role in the supramolecular arrangement within a crystal structure. Knowledge of such interactions is vital in crystal engineering.[13] Our interest in the rational design and synthesis of molecular crystals with controlled dimensionality prompted us to explore a new class of hydrogen-bonded salt. Hydrogen bond would also assemble into two-dimensional networks as a consequence of equal numbers of donor and acceptor hydrogen bonding sites. Columbic forces between the oppositely charged ions would further enhance network formation. We were particularly interested in determining whether the strength of hydrogen bonding operative in such networks could be exploited to overcome the tendency for materials to crystallize in centrosymmetric space groups.[14]

In the CSD, there are 918 hits for structures utilizing the $(F^2)_4$ (8) synthon (Scheme 1) in which the donor is the amino group (NH_2) and the acceptor is the carbonyl group (C=O). These are broken down into specific functional groups like (C=O)O, N(C=O), N(C=O)N, (C=O)OH, C(C=O)C, C(C= O)H, $-NH_3^+$,$-C(NH_2)$, NH_4^+, and $-N(NH_2)$. This survey clearly indicates that the highest incidence of participation in the $(F^2)_4$ (8) synthon is for carboxylate acceptors and ammonium cation donors.[22] In the work presented here we attempted to cocrystallize molecules

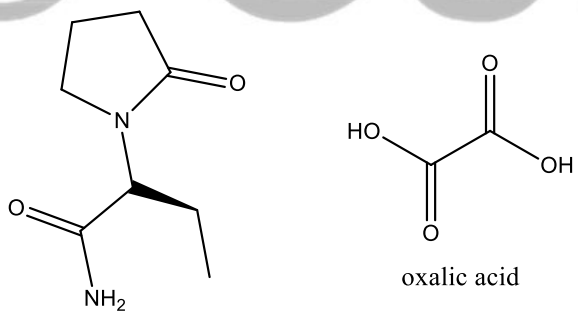
with amino group (-NH_2) that will participate as donors (D) and molecules with carbonyl group (COO) that will participate as an acceptor (A). A CSD survey revealed 918 hits for structures with these particular donors and acceptors that utilize the $(F^2)_4$ (8) synthon. The CSD search also indicated a statistical preference for the ionized species NH_3^+ and COO^- in the formation of the desired $(F^2)_4$ (8) synthon. The combined species increase the stabilization energy of the synthon by approximately an order of magnitude over that of the neutral species.[15-16]

Scheme 1. Possible Acceptors (A) and Donors (D) for the $(F^2)_4$ (8) synthon



Acceptors and Donors are arranged during the hydrogen bond formation in $(F^2)_4$ (8).

Scheme 2. Levetiracetum (Anticonvulsant Drug) and Oxalic Acid



Levitricetum oxalic acid

CH: 2 Experimental Designs

Cocrystals of Levetiracetum and oxalic acid are obtained by using two different solvents water and ethanol with equimolar ratio.

Traditional crystallization method

Solvent evaporation method is the traditional method to prepare the cocrystals at room temperature by using 2 different solvent water and ethanol.

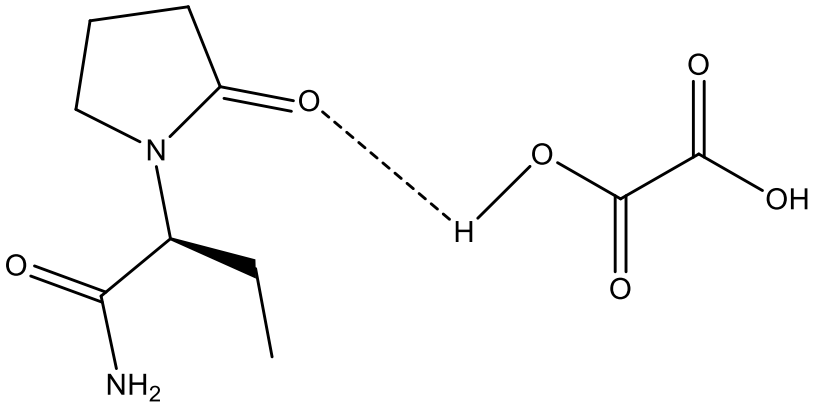
Materials

Levitricetam (transform pharmaceutical) and oxalic acid dihydrate were used for the preparation of the cocrystals from aqueous solution of distilled water.

Procedure

Levetiracetum and oxalic acid were dissolved in a 1:1 molar ratio in water and also second solvent ethanol. Upon slow evaporation at room temperature, colorless crystals appeared after 4 days in both solvents.

Scheme 3. Hydrogen Bonding between Levetiracetum and Oxalic Acid



Levitricetum

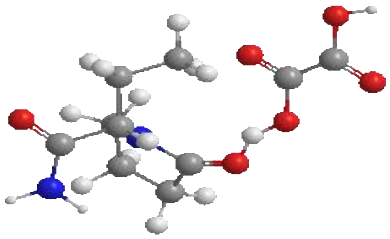


Figure 1. 3D Form Structure

CH: 3 Results and Discussion

NMR Data for the Material

NMR data for both API and conformer was obtained by using NMR technique which shows some peak graph in the figure.1

Proton NMR for material

Several new peaks are obtained in sample which gives the conformation of new hydrogen bonding. These peaks are obtained at 0.9ppm, 1.6ppm, 1.8ppm, 2.8ppm and 2.9ppm, 3.6ppm, 7.2ppm, and 11ppm.

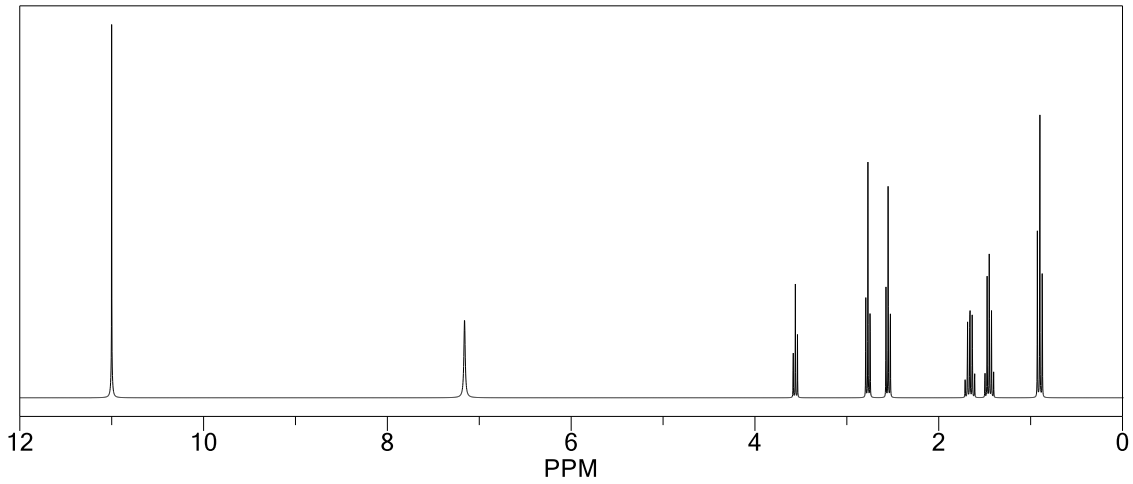


Figure 2. Representative Data of Proton NMR of Levetiracetum and Oxalic acid

Carbon-13 NMR Data

The peaks obtained at 9ppm, 19ppm, 23ppm, 31 ppm, 43 ppm, 58 ppm, 160 ppm, 172 ppm, 179 ppm confirming the linkage of conformers.

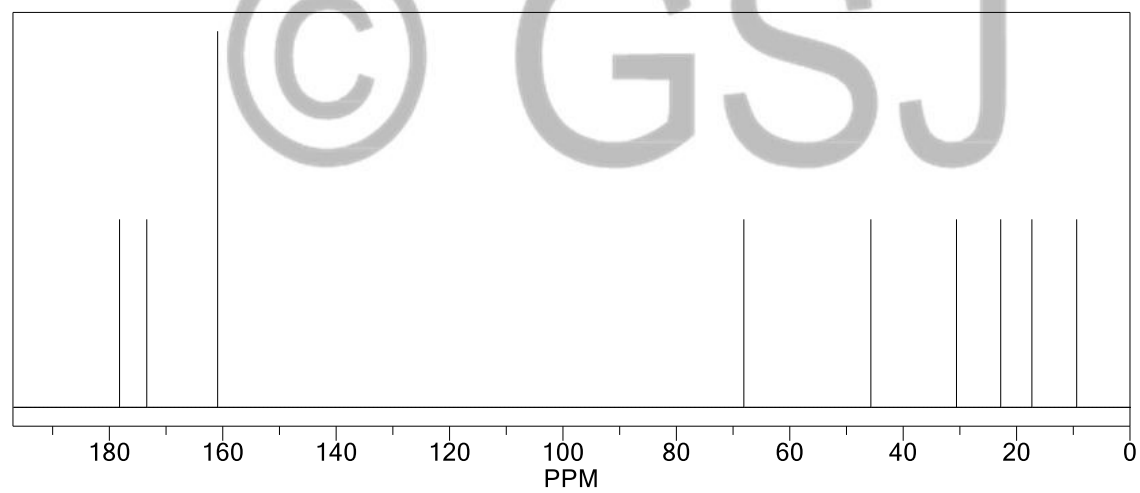


Figure 2. Representative Data of Carbon-13 NMR data for the Levetiracetum and Oxalic acid

Acknowledgement

This work is supported by Punjab Group of Colleges (Chawinda Campus). We are thankful to Dr. Muhammad Jawad Saif (HEC Recognize Supervisor) in NMR measurements (Figure 2 and Figure 3) and also thankful to Prof. Yasir Ali for their technical assistance.

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