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Review Article

Zwitterionic co-crystals

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Abstract

Zwitterionic co-crystals family could be basis for very different structural and theoretical examinations as their ability to alter solubility and deliver a wide solubility spectrum is receiving more attention. Many zwitterionic co-crystals crystal structures exhibited carboxylate-hydroxyl supramolecular heterosynthons preference. In addition to examples of zwitterionic co-crystals in the Cambridge Structural Database, L-phenylalanine/fumaric acid, saccharin-piroxicam, gabapentin-oxalic acid, piroxicam- fumaric acid, β-alanine-oxalic acid-water, γ-aminobutyric acid-oxalic acid, 1,1-dicyano-2-(4-hydroxyphenyl)-ethene:L-proline, L-Proline:2,5-dihydroxybenzoic acid, co-crystals of amino acid zwitterions and Li^+ salts, polyphenol with zwitterions (betaine, sarcosine, dimethyl glycine, baclofen, nicotinic acid, isonicotinic acid), and glycine-trimesic acid monohydrate have been reported. The ionization states of the compounds at different pH values need to be examined in order to produce co-crystals. It is hoped that zwitterionic co-crystals have potential scope in drug delivery.

Keywords: Zwitterionic co-crystals, supramolecular synthons, non-covalent interactions

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Co-crystals study has become very significant in the pharmaceutical industry as there is a continuous search for drug compounds which exhibit best possible therapeutic use. Co-crystals are multiple component systems where intermolecular interactions (including hydrogen bonds, van der Waals, and π-π interactions) and favourable geometries lead to a self-assembled supramolecular network. Existing APIs with solubility, stability or processing issues might be improved through crystal engineering of co-crystals, offering a low cost, low risk approach to new drug development. In recent years there has been growing interest in co-crystals as a means of improving the properties of drugs, while leaving the active pharmaceutical ingredients unaltered. Many drugs exist in a zwitterionic form and there have been very few reports of co-crystals formed with zwitterions. No attempt has been made to review this topic. Zwitterionic co-crystals form a family of materials which could be basis for very different structural and theoretical examinations. Examples of zwitterionic co-crystals exist in the Cambridge Structural Database [1-8]. In recent years, the amino acid neurotransmitter γ-aminobutyric acid (GABA) has been widely studied for its significant inhibitory action in the central nervous system. Scientists have described a strategy to design co-crystals of γ-amino butyric acid (GABA, zwitterions form) with the carboxylic group of the oxalic acid and benzoic acid in the form of -CO_2^- using pH as a controlling tool. Two cocrystals namely $(GABA)_2$ oxalate and GABA benzoate were obtained with the active pharmaceutical ingredient GABA (zwitterions form), using pH as a controlling tool [2].

In L-phenylalanine/fumaric acid (1:1) adduct (Fig. 1), $C_9H_{11}NO_2 \cdot C_4H_4O_4$, the amino acid molecules exist as zwitterions and the fumaric acid molecules exist in the unionized state. The asymmetric unit composed of two molecules of each species was observed. The fumaric acid molecules were related to each other through a pseudo-inversion centre and essentially planar. The phenylalanine and fumaric acid molecules formed hydrogen-bonded double layers, linked together by hydrogen bonds [3].

1,1-dicyano-2-(4-hydroxyphenyl)-ethene formed co-crystals with L-proline and hydrogen bonded chains of proline molecules with molecules of 1,1-dicyano-2-(4-hydroxyphenyl)-ethene attached to them were found [4]. The eutectic composition of aqueous mixtures of L and D amino acids was tuned by the addition of achiral dicarboxylic acids that co-crystallized with chiral amino acids [5]. The glycine is present in the zwitterions form in glycine-trimesic acid monohydrate, $H_3N^+CH_2COO^-$ $.C_9H_6O_6.H_2O$ and the three moieties are joined together by a three-dimensional arrangement of hydrogen bonds [6].

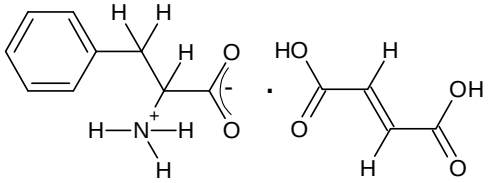


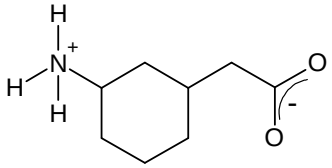
Fig.1. L-phenylalanine/fumaric acid (1:1) adduct

The utility of carboxylates in co-crystal formation has been expanded to include molecules with weakly acidic hydroxyl moieties such as polyphenol and L-ascorbic acid [9,10]. The following neutral co-crystal formers (L-ascorbic acid, hesperetin, quercetin, resveratrol, catechol, protocatechuic acid, ferulic acid, elagic acid, and gallic acid) sustained co-crystals of zwitterions (betaine, sarcosine, dimethyl glycine, baclofen, nicotinic acid, and isonicotinic acid) and their crystal structures revealed that all exhibit carboxylate-hydroxyl supramolecular heterosynthons [11].

L-Proline and 2,5-dihydroxybenzoic acid (1:1) hydrogen bonded zwitterion co-crystal has been reported [12]. Researchers prepared a red coloured co-crystal of acetaminophen (APAP) with 2,4-pyridinedicarboxylic acid (PDA) by screening using the solution-mediated phase transformation technique and its structural analysis revealed that 2,4-pyridinedicarboxylic acid exist in a zwitterionic form in the co-crystal. The components of co-crystal (APAP.PDA) self-assembled as a three-dimensional hydrogen-bonded network and with a pronounced 2D structure. A decreasing π–π^* separation involving the components of the solid was demonstrated [13].

Piroxicam exists as a zwitterions in saccharin-piroxicam co-crystal having N(+)–H…O, N–H…O(2) and C–H…O hydrogen bonds [14]. Piroxicam : fumaric acid co-crystal (4:1) contains one zwitterionic tautomer, one non-ionized tautomer, and one-half of a non-ionized fumaric acid in the asymmetric unit [15].

Gabapentin (1-(aminomethyl)cycloheaxaneacetic acid) is a drug compound which is structurally related to GABA. Gabapentin exists as a zwitterion in the solid state. Co-crystals of an anticonvulsant drug gabapentin with 3-hydroxybenzoic acid (Fig. 2) was found thermodynamically stable **[**16]. Co-crystals of GABA-oxalic acid, gabapentin-oxalic acid and β-alanine-oxalic acid-water were formed at specific pH values. The co-crystal of GABA-oxalic acid has an extensive hydrogen bonding network due to the presence of the NH_3^+ and COOH groups on the GABA molecules and the COO^- groups of the oxalate dianion. Each GABA molecule interacted with three different oxalate dianion molecules and two different neighbouring GABA molecules. The gabapentin molecule was also protonated in this co-crystal with the oxalic acid being in a dianion form. Each NH_3^+ group on the gabapentin molecule has six hydrogen bonding interactions where four interactions were with neighbouring oxalate dianion molecules and the other two were with neighbouring gabapentin molecules. Each gabapentin molecule interacted with three different oxalate dianion molecules and four different neighbouring gabapentin molecules [17].



Gabapentin

Fig. 2. Zwitterion gabapentin

A mathematical model derived the pH dependent solubility profile of a co-crystal with a zwitterionic drug and an acidic coformer which was based on co-crystal dissociation and ionization solution equilibria. Predicted pH dependent co-

crystal solubility and stability were in good agreement with experimental measurements [18].

2-(*p*-Tolylamino)nicotinic acid (TNA) was crystallized in three polymorphic forms. The proton transfer occurred in form III to give a zwitterionic structure of $N–H^{+}\cdots O^{-}$ hydrogen bond. Form III could be obtained only in the presence of pyridine-type coformers. Zwitterionic form III were found to be 2D isostructural. The isolation of zwitterionic TNA as a complex with *m*-nitrobenzoic acid and a TNA salt with *o*-aminopyridine provided a mechanistic rationale for the crystallization of the rare zwitterionic structure of amphoteric TNA molecule [19]. Eight 2:1 co-crystals of amino acid zwitterions and Li^{+} salts were crystallized from hot water to afford cationic networks based on tetrahedral lithium cations [20].

The structure of β-alanine is closely related to the structure of the neurotransmitter GABA, where it simply contains one less carbon atom in the backbone. The crystals obtained at pH 3 were found as co-crystals of β-alanine, oxalic acid and water. A comparison with other β-alanine conformations showed that the molecular conformation of the β-alanine molecule was greatly affected by the presence of the oxalic acid and water molecules within this co-crystal. This would be due to the extensive hydrogen bonding interactions which were present between the three molecules. Further, the β-alanine molecules in this case exist in a cationic form with the carboxyl group being neutral and the amino group positively charged. The oxalic acid molecule exists as a semi-oxalate anion. The co-crystal of β-alanine-oxalic acid-water has an extensive hydrogen bonding network due to the presence of the NH_3^{+} and COOH groups on the β-alanine molecules and the COO- and COOH groups of the semi-oxalate anion as well as the H_2O molecule. Each NH_3^{+} group was involved in four hydrogen bonding interactions, where three of the interactions were with neighbouring oxalate dianion molecules and one of the interactions was with a neighbouring water molecule. Each β-alanine molecule interacted with two different oxalate anion molecules, one different neighbouring β-alanine molecule and one water molecule. Furthermore, for formation of co-crystals, the amino acid needs to have an NH_3^{+} group and the carboxylic acid must be in an anionic form where it is either a semi-carboxylate anion or a carboxylate dianion [17].

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