Improving Stability of Effervescent Products by Co-crystal Formation: A Novel Application of Crystal Engineered Citric Acid

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ABSTRACT: The major concern of the physical and chemical instability of the effervescent products during manufacturing and storage is addressed through the co-crystallization strategy. Citric acid (**CA**) and sodium bicarbonate (**SBC**) are the essential components of effervescent products. **CA** is hygroscopic and led to uncontrollable autocatalytic chain reaction with **SBC** in presence of small amount of moisture causing product instability. The acid…amide dimer bond and layered structure of citric acid-nicotinamide co-crystal restricts interaction of moisture with **CA**, making it non-hygroscopic and improves stability of effervescent products. The

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comparative study of effervescent products containing **CA** in its free form and as a co-crystal suggests significant advantage of use of co-crystal in effervescent products. This finding is supported by the mechanistic understanding developed through GAB and Y&N models obtained from moisture sorption data along with the computational investigations into moisture interactions with different crystal surfaces.

Effervescent products, such as vitamin C Fizz tablets, are designed to provide a clear solution or uniform dispersion when added to water along with effervescence. Effervescent products are widely used in pharmaceutical, nutraceutical, food, agriculture, detergent and cleaning sectors. A typical effervescent product contains at least two components; an alkaline agent and an acidic agent, which react with each other in the presence of water, producing carbon dioxide (CO_2) as a by-product, this leads to the disintegration of the tablet and cause effervescence.[1,2,3] Typical alkaline agents are sodium carbonate and sodium bicarbonate (**SBC**), whilst typical acidic agents are citric acid (**CA**), tartaric acid, malic acid and maleic acid. There are many challenges in the manufacturing, performance and storage of effervescent products due to its hygroscopic nature and moisture induced instability. [4,5] It is important that, we understand the interactions of moisture with the effervescent material and can then address the instability issue.[6] This interaction depends on the affinity of the solid for moisture bonding, strength of bonding, functional groups present at the solid surface and exposed surface area. [7]

CA, which is widely accepted as a food ingredient, is an acidic agent of choice in most of the effervescent products along with **SBC** as an alkaline agent. The presence of moisture or small amount of water initiates reaction between **CA** and **SBC**, which in turn releases more water.

Once started, this autocatalytic reaction is difficult to control during manufacturing or storage (Scheme 1). [5]

$$C_6H_8O_7 + 3\,NaHCO_3 \xrightarrow{\text{In presence of moisture/water}} Na_3C_6H_5O_7 + 3\,CO_2\uparrow + 3\,H_2O$$

Citric acid, Sodium bicarbonate → Sodium citrate, Carbon dioxide

Scheme 1. Effervescence reaction between **CA** and **SBC**

To address this challenge, currently effervescent product manufacturing is undertaken at controlled hygrothermal conditions, maintaining less than 20 % relative humidity (% RH) at 25 °C. [8] However, this increases the carbon footprint of the process and makes the manufacturing process expensive as there is a huge cost involved in achieving and maintaining low humidity. In addition, highly moisture impervious packaging materials and desiccants are required to ensure storage stability which adds to the overall product cost.[9] Despite these stringent controls, studies have shown that there is still at least an 8 - 10 % loss of CO_2, during processing and storage. Processing under low humidity conditions affects the quality of the tablets. A high compression force is required for the tableting; this leads to dust generation which is the main cause of occupational hazards for the working staff. Currently, there is not a single approach available to manufacture stable effervescent products under ambient manufacturing conditions i.e. at 45 %RH at 25 °C. These critical issues associated with the manufacturing and storage of the effervescent products has motivated us to provide the solution to address the above mentioned challenges.

Herein, we explore co-crystallization as a means of improving the stability of an effervescent product, during the manufacturing process and storage. Our initial investigation was focused on

finding the most moisture sensitive/hygroscopic component of the effervescent products. To determine the interaction of CA and SBC with the moisture we conducted dynamic vapor sorption measurements. The vapor sorption isotherms of CA and SBC at 25 °C were obtained by equilibrating the samples between 0 % RH to 90 % RH using DVS intrinsic instrument (Make - Surface Measurement Systems, UK). The experimental details of DVS study is provided in Supporting Information, SI 1.

It was observed that **CA** starts absorbing moisture at 80 %RH and absorbs 31 % moisture as RH increases to 90 % (see Figure SI 2 in Supporting Information), whereas **SBC** absorbed only 0.32 % moisture between 10% - 90 %RH (see Figure SI 3 in Supporting Information). This study confirmed that **SBC** is not hygroscopic, but **CA** is highly hygroscopic in nature, most probably as a result of the carboxylic groups present. During sorption cycle of the DVS, **CA** forms hydrogen bonds with water above 80 % RH and solid **CA** turns into a liquid form showing deliquescent nature. During desorption cycle the CA in the liquid form transforms back to a solid but it is **CA** monohydrate rather than CA anhydrous. This was confirmed by differential scanning calorimetry (DSC) (see Figure SI 4 in Supporting Information).

The **CA:SBC** effervescent mixture (1:1.5 weight ratio) when subjected to DVS investigation the reaction between **CA** and **SBC** starts when only 0.5 % moisture was absorbed at 45 % RH. The reaction is evidenced by continuous weight loss due to CO_2 release (Figure 1).
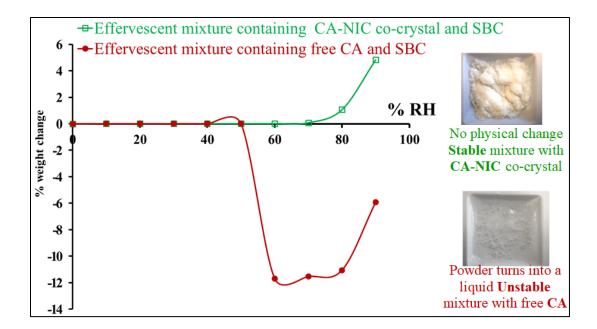
Figure 1. Comparative DVS study for a) effervescent mixture containing free **CA** and b) effervescent mixture containing **CA-NIC** co-crystal and images showing physical state of material by the end of 90 %RH.

The deliquescent nature of **CA** and initiation of autocatalytic reaction between **CA** and **SBC** after such a low moisture uptake is mainly responsible for the instability of the effervescent products. Hence, we proposed to change deliquescent nature of **CA** by transforming it into a co-crystal form. Tailoring of physicochemical properties by co-crystallization, mainly deliquescence will overcome the stability issue in effervescent products. [10]

A co-crystal is a multicomponent crystalline entity, which contains at least two molecular or ionic components, which are held together in the same crystalline lattice either by hydrogen bonds, halogen bonds or π-π interactions.[11,12,13] Co-crystals have emerged as a new solid form that can tailor the physicochemical properties of crystalline Active Pharmaceutical Ingredients (API).[14] A number of potential applications for co-crystals have been demonstrated, including

improving drug dissolution rate, tailoring compressional properties, tuning color and taste of molecules and improving photo-stability.[15-20] Previous work has shown that the formation of co-crystals can reduce the hygroscopicity of a number of active pharmaceutical ingredients including caffeine, oxiracetam, ibuprofen and dapagliflozin.[21-24] However, this is the first attempt where we demonstrate co-crystallization of an excipient to control acid-base reaction to improve stability of the product.

Nicotinamide (**NIC**) was selected as a coformer molecule as it is a 'Generally Recognized as Safe' (GRAS) molecule and widely accepted in the formulations of nutraceutical supplements. The DVS study for **NIC** showed only 0.31% moisture absorption by the end of exposure to 90% RH at 25 °C (see Figure SI 3 in Supporting Information). Apart from this, co-crystal of CA with NIC (CA-NIC, 1:2 molar ratio) is reported in the literature along with detailed information about its crystal structure parameter.[25] This makes NIC as an ideal co-former for CA to study the effect of co-crystallization on the stability of effervescent products. The co-crystal was synthesized by liquid assisted grinding (LAG) using ethanol as a solvent. The formation of the pure co-crystal phase was confirmed through PXRD (see Figure SI 5 in Supporting Information) and DSC analysis (see Figure SI 6 in Supporting Information). The details of PXRD and DSC experiments are provided in Supporting Information, SI 1. The obtained PXRD pattern matches the simulated pattern of the known co-crystal of **CA-NIC**. The DSC thermogram of the sample showed e a single melting endotherm at 127 °C indicating formation of phase pure CA-NIC co-crystals.

The CA-NIC co-crystal obtained from the LAG experiment was also evaluated for moisture uptake performance using DVS. The co-crystal shows only 0.23 % moisture uptake at 90 %RH (see Figure SI 2 in Supporting Information) which is significantly lower than pure **CA**. At the end of the desorption cycle of DVS experiment, **CA-NIC** co-crystal was also found to remain in

the solid form and did not show any hydrate formation as confirmed by DSC (see Figure SI 4 in Supporting Information). This suggests the hygroscopic property of **CA** has been successfully tailored through co-crystallization. However, at 50 %RH, the **CA-NIC** co-crystal showed 0.04 % moisture uptake compared to the 0.01% moisture uptake by **CA**. This is not significantly higher moisture uptake by **CA-NIC** co-crystal. This higher moisture uptake was attributed to the higher surface area of **CA-NIC** co-crystal (1.16 m^2g^{-1}) than **CA** (0.145 m^2g^{-1}), means co-crystal has 8 times higher surface area than **CA**. The Brunauer–Emmett–Teller (BET) surface areas for **CA-NIC** co-crystal and **CA** were calculated from the DVS data using DVS-Intrinsic analysis software (version 5.1.0.8).

The DVS study involving an effervescent mixture consists of **CA-NIC** co-crystal and **SBC** in 1:1.5 weight ratio (co-crystal equivalent to required amount of **CA** was weighed) showed 4.5% moisture uptake by the end of exposure to 90% RH during DVS analysis without any weight loss (Figure 1). This indicates that no interaction took place between **CA** from **CA-NIC** co-crystal and **SBC** to release CO_2 to show the weight loss. This improvement in the stability is likely due to the interaction of the carboxylic functional groups of **CA** with **NIC** in the co-crystal, making them unavailable, or making it unfavorable, to react with **SBC** in the presence of small amount of moisture. Thus, the co-crystal showed improved stability of an effervescent mixture in presence of small amount of moisture.

To test the advantage of **CA-NIC** co-crystal against **CA** in effervescent products, we manufactured magnesium oxide effervescent tablets under the standard hygrothermal manufacturing conditions (i.e. at 25 °C and 45 %RH). Two batches of magnesium oxide effervescent tablets were produced; one batch with acidic component in the form of co-crystal i.e. **CA-NIC** co-crystal and another with **CA** as the acidic component of the effervescent product

(formulation details are provided in Supporting Information SI 1). Tablets from these two batches were subjected to stress stability by exposing the tablets in an open beaker to 40°C at 75 %RH. At the end of 24 hrs it was observed that tablets containing plain **CA** shows collapsed structure resulting in instability whereas tablets containing **CA-NIC** co-crystal were stable for at least 30 days retaining their strength and effervescence performance (Figure 2). This clearly shows manufacturing and storage stability advantage of **CA-NIC** co-crystal over **CA** in the effervescent products. The co-crystallization of **CA** with **NIC** has created a solid phase of **CA** that is less hydroscopic at high relative humidity; the stability of this phase in the effervescent mixture reactivity needs to be investigated.
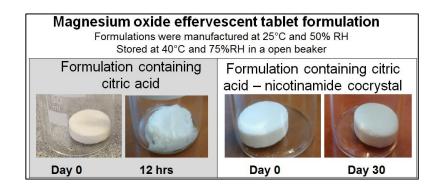

Figure 2. Comparative stability of magnesium oxide effervescent tablet containing free **CA** and **CA-NIC** co-crystal as part of effervescent mixtures

It is well known that rather than the total amount of moisture adsorbed, the amount of free moisture is critical for the physical and chemical stability of the moisture sensitive materials.[26] The amount of moisture adsorbed depends on the affinity of water molecules to the surface, relative humidity, temperature and exposing surface area.[27] To understand difference in the distribution of moisture in **CA** and **CA-NIC** co-crystal, we fitted the moisture isotherm to the

Guggenheim-Anderson-de Boer (GAB) and Young and Nelson (Y&N) models. These models provide information on the interaction of water molecules at the interface as well as the strength of the interaction.[28, 29, 30] Upon adsorption onto the dry surface of the material; water molecules form a monomolecular layer which is then subjected to surface binding and diffusional forces. Once, a layer of water molecules adhere to the surface and diffusional force exceeds the binding forces; the adsorbed moisture is transferred into the material. In case of multilayer water adsorption water goes into pores and capillary spaces and lead to solute dissolution. [31, 32] The theoretical details of the GAB and Y & N models are provided in the Supporting Information SI 7. Both the GAB and Y&N models suggest that **CA** has a lower capacity to hold the water as a monolayer in comparison to **CA**-NIC (Table 1).

Table 1. Water interaction with **CA** and **CA-NIC** co-crystals calculated by GAB and Y&N equation using moisture sorption data from DVS study

Parameters	CA		CA-NIC co-crystal	
	GAB	Y&N	GAB	Y&N
Sorption constant§ (J mol^{-1})	1.2439	5.3206	0.9656	2.918
Moisture capacity of monomolecular layer (mol g^{-1})	1.87×10^{-6}	8.94×10^{-12}	1.80×10^{-5}	1.79×10^{-5}
The amount of moisture internally absorbed or "bulk" moisture (mol g^{-1})	---	5.35×10^{-2}	---	8.59×10^{-8}
Model fitting, correlation coefficient (r^2)	0.954	0.701*	0.988	0.900

Note: §Strength of interaction of water vapor with the sample
*Correlation coefficient is tested by t-test and it is <5%. This poor correlation is attributed to conversion of citric acid into citric acid monohydrate during DVS study.

This might be attributed to a higher surface area **CA-NIC** co-crystal than the **CA** as discussed before. In addition, as **CA** is deliquescent in nature, it shows adsorption of water molecules to the surface in a semi-organized manner and capillary condensation below the deliquescence point thus showing lower monolayer water capacity. The sorption constant shows strength of interaction of water vapor with the crystal surface and is calculated by GAB and Y&N equation. It is observed that the sorption constant for CA is higher than **CA-NIC** co-crystal.

The difference is probably due to the different functional groups present on the crystal surfaces. Predicted morphologies for **CA** and **CA-NIC** were generated to identify the nature of the dominant crystal faces and the available functional groups. The crystal structures used for the computational predictions and methodology is provided in the Supporting information SI 1. For **CA** the (100) and (002) faces are dominant, which display carboxylic acid groups (Figure 3).
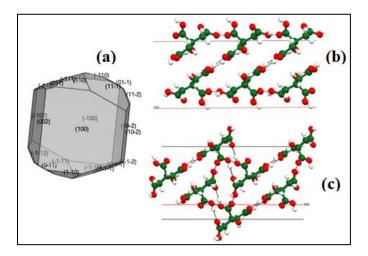

Figure 3. (a) Predicted morphology for **CA**- perpendicular view of **CA** crystal surface, (b) **CA** (100) face and (c) **CA** (002) face.

Whereas, the dominant (001) and (010) faces for **CA-NIC** (Figure 4) cut through the amide…amide and acid…amide dimers of the complex.
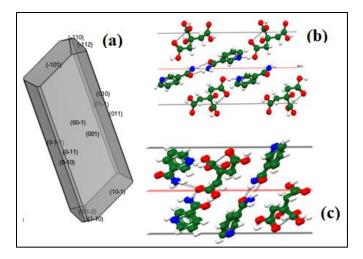
Figure 4. (a) Predicted morphology for CA-NIC-perpendicular view of CA-NIC crystal surface, (b) CA-NIC (010) face and (c) CA-NIC (001) face.

Thus, the higher sorption constant for **CA** is attributed to the presence of three carboxylic groups which act as potential hydrogen bonding sites. The lower sorption constant for **CA-NIC** shows a loose and physical adsorption of water molecules with the hydrophilic groups present at the surface. The moisture distribution obtained from the Y&N equation suggests that **CA** has significantly higher (5.35×10^{-2} mol g^{-1}) absorbed moisture in the bulk of the material compared to **CA-NIC** co-crystal (8.59×10^{-8} mol g^{-1}).

A computational investigation into the ability of different crystal and co-crystal surfaces to interact with water was undertaken with a view to understanding the experimental results. The difference in absorbance of these surfaces to a water molecule was investigated through optimization of a water molecule onto each surface using the differential evolution global optimizer (Table 2).

Table 2. Optimized Interaction Energy for water with selected crystal surfaces

System	Face	Lowest Energy (KJ.mol-1)
CA	(100)	-54.40
CA	(002)	-38.28
CA-NIC co-crystal	(001)	-22.72
CA-NIC co-crystal	(010)	-47.01

Three surfaces [**CA** (100), (002) and **CA-NIC** co-crystal (010) faces] display bridging of the water molecule over carboxylic acid groups on the surface (Figure 5 (a) (b) and (c)) with stronger bonding. In contrast the (001) face of the **CA-NIC** binds water weakly to the nicotinamide amide group (Figure 5 (d)). The total interaction energy was stronger with **CA** compared to the **CA-NIC** co-crystal. This suggests that a **CA-NIC** will bind water selectively on one face, while **CA** binds water upon multiple crystal faces. Thus, the larger level of **CA** hygroscopicity may be due to a larger number of potential hydrogen bonding sites.
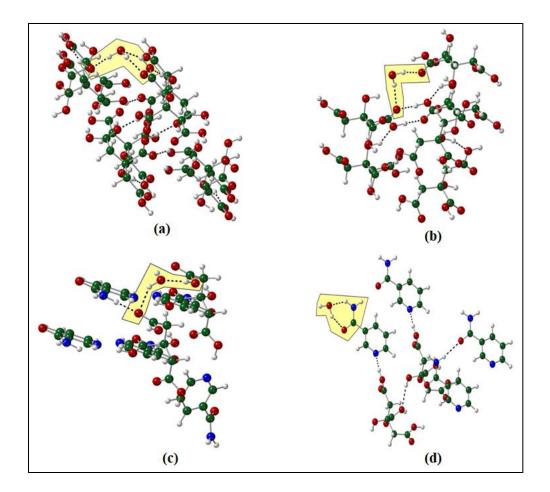
Figure 5. (a) Optimized location of a water molecule onto (100) surface of CA, (b) Optimized location of a water molecule onto (002) surface of CA, (c) Optimized location of a water molecule onto (010) surface of CA-NIC co-crystal and (d) Optimized location of water molecule onto (001) surface of CA-NIC co-crystal. Representative water interaction is highlighted by yellow box.

The co-crystal structure shows that one molecule of **CA** is connected through hydrogen bonding to NIC forming a layered structure (Figure 6).
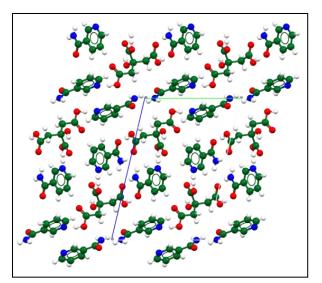
Figure 6. Crystal packing of **CA**-NIC co-crystal, viewed along the a-axis.

Thus, it can be concluded that penetration of water molecules inside the bulk of **CA-NIC** is prevented by the **NIC** molecules which are present on the surface of the co-crystal. From the computational modelling and the DVS data it was concluded that the formation of **CA-NIC** makes **CA** less interactive with water molecules and so provides better storage stability in effervescent products by preventing interaction of **CA** with **SBC** in a limited amount of moisture.

In summary, we have successfully demonstrated application of co-crystallization to tailor the hygroscopic nature of the **CA** by blocking the water interaction sites. This tailored **CA** has shown its potential in the manufacturing of stabilized effervescent product at ambient condition which will significantly lower down the production and packaging cost along with reduction in carbon footprint.

ASSOCIATED CONTENT

Supporting Information

The details of materials, methods, co-crystal preparation, its characterization along with moisture uptake study using dynamic vapor sorption analyzer and computational experiments are given in the supporting information. In addition to this relevant PXRD, Differential Scanning Calorimetry, DVS models (GAB and Y & N), moisture sorption curves and computational data is also provided in the supporting information.

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Author Contributions

All authors have contributed equally.

ABBREVIATIONS

CA, Citric acid; SBC, Sodium bicarbonate; NIC, Nicotinamide; CO_2, Carbon dioxide; %RH, Percent relative humidity; DVS, Dynamic Vapour Sorption; GAB, Guggenheim-Anderson-de Boer; Y & N, Young and Nelson.

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