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№ 6321

Synthesis and Characterization of Captopril Co-Crystals with Two Amino Acids

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August 17, 2021

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***Abstract* :**

The study reports a DSC investigation of solid–liquid equilibria in captopril-Arginine and captopril proline binary system revealing a simple eutectic behavior (one TE) for captopril-Arginine binary systme . The eutectic temperature and temperatures of liquidus were determined 370.15 ± 2.0 K and eutectic composition was estimated at X1 = 0.9 mol. Further, assessed eutectic and liquidus temperatures together with the data for pure components And for Phase diagram studies the second binary system have revealed the formation of congruent melting type phase diagram TC = 424.74°K and molar fraction of 80% X=0.8 and (two TE) different eutectics, A first eutectic X=0.6 and second eutectic at X= 0.9 of CAP fraction.

Keywords: co-crystals, L-arginine, L-proline captopril, DSC, phase diagrams

I. INTRODUCTION

In the last few years, a large number of drugs have been discovered with low aqueous solubility. Among these recently discovered drugs, about 60-70% of the compounds are related to the BCS Class II (low solubility/high permeability) and IV (low solubility/low permeability).[1] Many active pharmaceutical ingredients (APIs) have not been developed in formulations due to low aqueous solubility, which causes low bioavailability of drug. developed so, the co-crystallization of drug substances offers a great opportunity for the development of new drug products with superior physicochemical such as melting point, stability, solubility, dissolution, bioavailability, permeability

Differential scanning calorimetry (DSC) finds many applications in the field of pharmaceutical research and development . Among them the polymorphs stability investigation, examination of drug components compatibility and cocrystals formation or solid–liquid equilibria studies represent typical examples. Recently, a number of papers dealing with DSC investigation of pharmaceutically relevant systems have been published, e.g. [2][3]. The obtained results, most often liquidus temperatures, invariant points (eutectic or peritectic) temperatures and relevant enthalpies can be further used for the construction of phase diagrams as well as for the assessment of thermodynamic data of individual phases and components within the systems under study.

A. Captopril (CAP) :

The benefits of captopril in hypertension and heart failure result primarily from suppressing the renin-angiotensin-aldosterone system (RAAS)[4]. As an angiotensin-converting enzyme (ACE) inhibitor, it inhibits ACE, which converts angiotensin I to angiotensin II. Angiotensin II binds to AT1 receptors on smooth muscles to produce vasoconstriction of precapillary arterioles and postcapillary venules, inhibits the reuptake of norepinephrine, and release of catechol amines from the adrenal medulla, which all increases blood pressure. .

B. Amino acids L-proline (PRO) and L-arginine (ARG)

Proline plays important roles in protein synthesis and structure, metabolism (particularly the synthesis of arginine, polyamines, and glutamate via pyrroline-5- carboxylate), and nutrition, as well as wound healing, antioxidative reactions, and immune responses, Proline contain an α-imino group and, therefore, it's α-imino acids. However, it's referred to as AA in biochemistry [5]

Arginine its very essential amino acids involved in many biological process such as wound healing, tissue repaired, nitric oxide production etc [6]

C. Co-crystals

As a new crystal engineering strategy, co-crystals have opened a new avenue to modify the physicochemical properties of pharmaceutical solids. Co-crystals are defined as "solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts".[7] Non-covalent interactions such as hydrogen bonds (the main interaction), π-π interactions, halogen bonding, and van der Waals forces are responsible for the formation of cocrystals.When components of a co-crystal

are a drug and a pharmaceutically acceptable excipient (co-former) the resultant molecular complex is called a pharmaceutical co-crystal. The co-formers usually are water-soluble molecules such as saccharin, caffeine, nicotinamide, and amino acids[8]. The availability of numerous coformers makes it possible to prepare several co-crystals for each drug and select the most appropriate one. Co-crystals can modify properties of drugs without any impact on the intrinsic pharmacological activity of the molecule. Co-crystallization has been studied to optimize physicochemical properties of drugs such as mechanical properties, stability, solubility, permeability and bioavailability.[9]

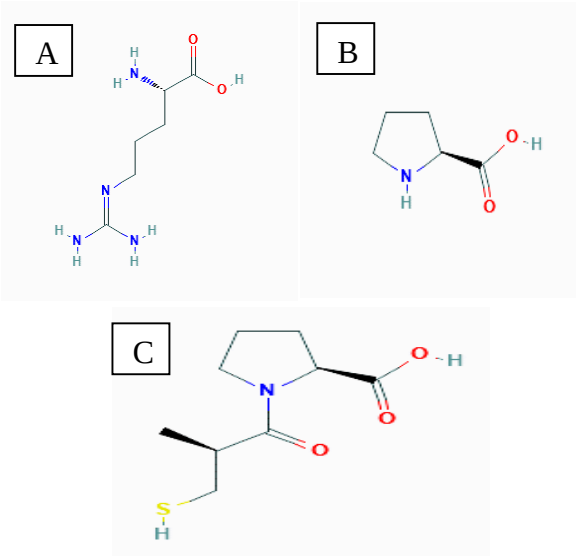

Figure 1: Chemical structures of drug captopril (C) and co-formers L-proline (B) and L-Arginine (A)

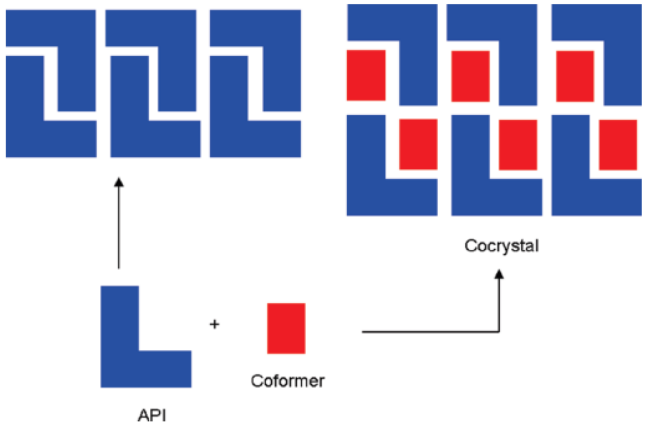

Figure 2: A co-crystal is a stoichiometric molecular complex of a molecule (blue) with a co-former (red) assembled via non-covalent interactions[1]

The aim of present research work was to prepare co-crystals of captopril with two amino acid as co-formers l-proline and l-arginine. the physical nature of binary mixture and prepares co-crystals were characterized by differential scanning calorimetry (DSC), the investigation was report for solid–liquid equilibria of binary mixtures, captopril with , l-arginine and l-proline, resulting in a temperature-composition phase diagrams with eutectic equilibrium. Eutectic mole fractions , temperatures, enthalpies and co-crystal formation,.

II. Experimental

- Captopril (CAP), C9H15NO3S (purity C 99 %), with molecular mass 217.29 g mol^{-1} and L-proline (PRO),C5H9NO2 (purity ⩾ 98 %) with molecular mass 119.12 g mol^{-1} and L-Arginine monohydro-chloride (C6H14N4O2 • HCl) (purity ⩾ 98 %) with molecular mass 210.66 g mol^{-1} were commercially available (Sigma-Aldrich) and used without further purification.
- For binary mixtures, certain amounts of powder components were weighted (KERN ABS accarcy 0.001 g) and mixed in a mortar using a spatula. the preparation was with different ratios like 1:1, 1:2, 1:3 (molar fraction X1 and X2) using “green process”, liquid assisted grinding for 30 min and solvent evaporation method for 3 days respectively to overcome low aqueous solubility
- Heat-flux DSC calorimeter 131 DSC (SETARAM with SETSOFT 2000) was used for the measurements. Samples of approx. 1-2 mg (SARTORIUS, accuracy 0.0015mg) were heated in unsealed aluminium pans 30µl at a rate of 2 K min-1 in a dynamic azote atmosphere with a purge flow rate of approx. 50 cm^3 min-1.
- Pure substances and all the fraction of Binary mixtures was heated in the same range of temperature 25–250 °C at a rate of 2 K min^{-1}
- Registered DSC scans on heating (see selected samples in Fig. 3,4 and 6) were interpreted as follows: the melting temperatures of pure substances as well as the eutectic temperatures were assessed as extrapolated onset temperatures, liquidus temperatures as temperatures of relevant peaks maxima. Pure indium was used for the calorimeter calibration. The sensitivity S = 1.172 µV mW^{-1} and the temperature correction Δt = texp - tref = -0.45 °C were determined at the melting temperature of indium (t_{fus} = 156.6 C).

III. Results and Discussion

A. DSC study of pure substances

- For pure CAP we evaluated t_{fus} = 105.27 °C and . It is associated with the endothermic heat effect ΔH_{fus} = 27.00 kJ mol^{-1} (ΔH_{fus} = 124.232 J g^{-1}) from DSC scans during the heating is shown as an example in Fig. 3. Fusion data of CAP are frequently quoted in the literature, the melting temperature and ΔH fus is in quite good agreement with the published in [11][12] which is t_{fus} = 105.15 C and ΔH_{fus} = 27.7 kJ mol^{-1} and tfus = 105.15 C for the paper[12], and for the tow amino acid for PRO we evaluated t_{fus} = 223.066 °C and for ARG we evaluated tfus = 226.886 °C and for

enthalpy ΔH_{fus} = 30.435 kJ mol^{-1} (ΔH_{fus} = 264.64 J g^{-1}) and ΔH_{fus} = 39.705 kJ mol^{-1} (ΔHfus = 188.482 J g^{-1}) from DSC scans during the heating. this values has been observed by [13][14].

- Small deviations were noted between the different experimental data of the melting temperatures of ARG This can be attributed to the difference in the used heating rates, as well as to the difference that can be found in the methods used to calculate the different melting temperatures (by considering the onset or the melting peak maximum).

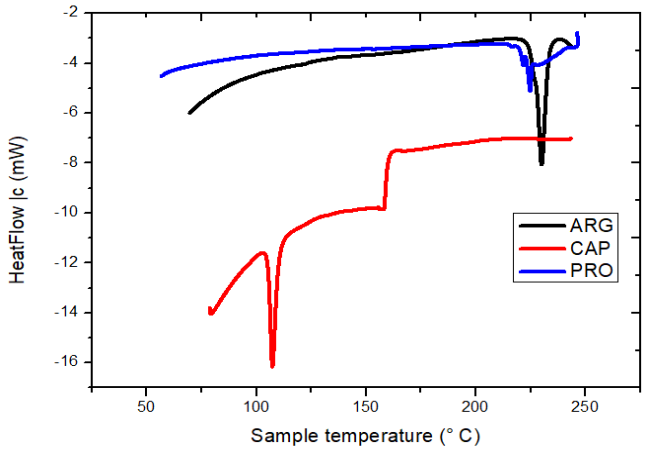

Figure 3 : DSC signal during the heating of the pure components POR, ARG and CAP

B. DSC study of CAP–ARG mixtures:

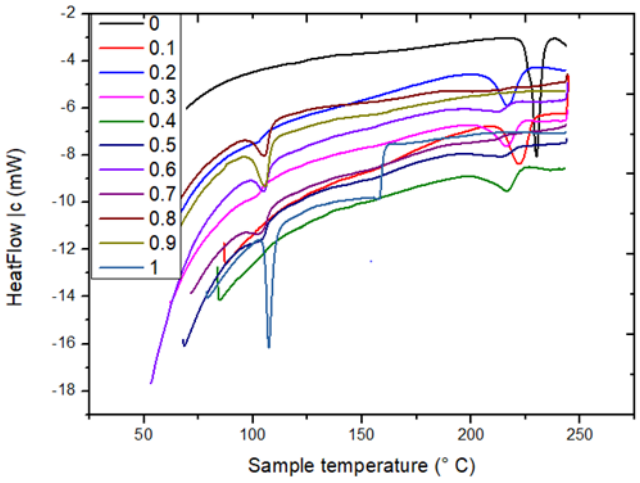

Figure 4: DSC-curves (2 K min−1) of the studied systems CAP (1) + ARG (2)

- Fig 4: showed the experimental results of the investigated systems. In each binary mixture, two melting DSC peaks were observed. The first one, at a lower temperature, was attributable to the melting of eutectic, whilst the second, at a higher temperature, corresponded to the melting of the major component. Moreover, the maximum temperature in fusion peak is taken as the melting temperature and the enthalpy of fusion is calculated by the area bound between the curve and the base line. It is obvious that the area of the eutectic peak in a DSC thermogram depends on the amount of the sample and the enthalpy of its melting, tures corresponding to the eutectic equilibrium (T_E) obtained from the DSC experiments (Fig. 5) were 370.15 ± 2.0 K for the system CAP + ARG .the eutectic composition was estimated at X1 = 0.9 mol fraction of CAP and that the shift of the eutectic equilibrium for this composition was accompanied by an enthalpy change of 92.643 ± 2.0 J g^{-1}.

- mechanical behaviour of CAP have being studied before with MT (metoprolol Tartrate), the DSC measurements are performed for the pure components by [15] In particular, CAP melts at 378.71 ± 0.39 K with an enthalpy change (ΔH) of 26.68 ± 0.12 kJmol^{-1} and The experimental phase diagram showed a simple eutectic behavior with the eutectic point at temperature 332 K and X1= 0.7 mol fraction of CAP eutectic mixture[15].

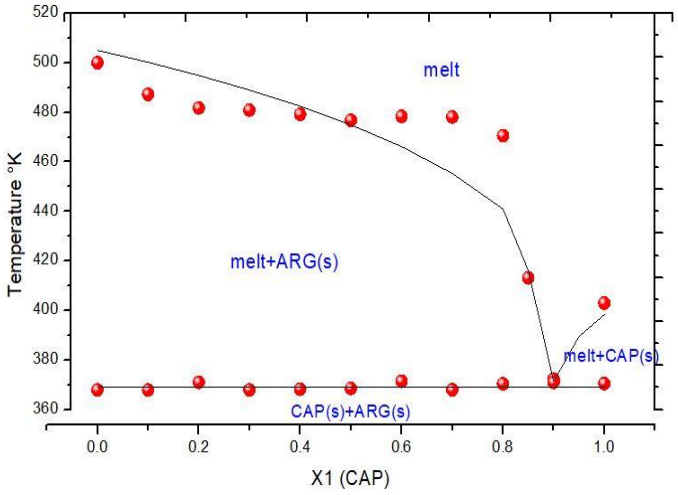

Figure 5: Phase diagram of the system CAP–ARG

C. DSC study of CAP–PRO mixtures:

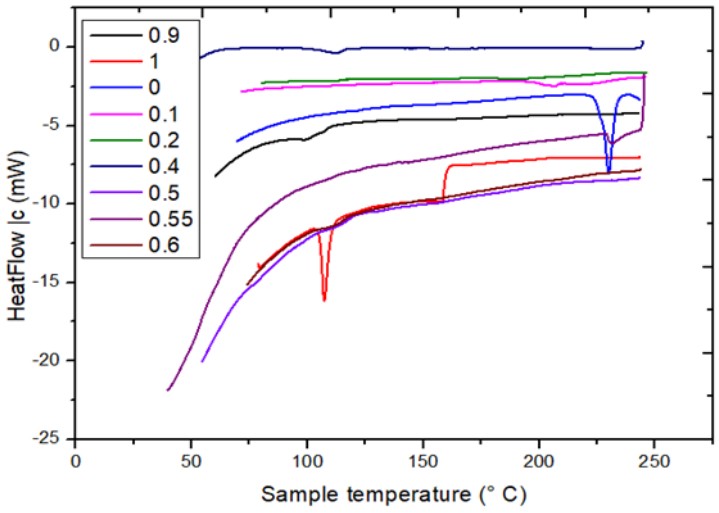

Fig. 1. Figure 6: DSC-curves (2 K min−1) of the studied systems CAP (1) + PRO (2)

- The diagram in Fig 5 shows a single eutectic composition at X=0.9 molar fraction of CAP and a eutectic melting temperature of 370.15 ± 2.0 °K, which, as expected, is lower than the melting temperature of both components.
- For the co-crystal forming in the second system CAP-PRO Fig 7 the situation is different. The binary diagram now shows three different crystalline phases. The diagram is therefore also characterized by two different eutectics. A first eutectic which occurs between CAP (captopril) and the co-crystal is found for a (overall) ratio of 60% X = 0.6 molar fraction of CAP and is characterized by a eutectic melting temperature of 377.81°K, which is below the melting temperature of the pure co-crystal phase, the pure co-crystal is found for a ratio of 78-80% (X = 0.78-0.8) molar fraction of CAP with TC = 424.74°K, A second eutectic is found between the co-crystal and PRO (L-proline) characterized by 10% of L-proline with molar fraction of X= 0.9 of CAP and shows a eutectic melting temperature of 364.58 °K. the Binary phase diagrams of combinations that are capable of co-crystal formation are shown in Fig. 7 Of the two such combinations known, one is characterized by a so-called incongruent melting point[16], while the other involves an congruent melting point, our study followed the congruent melting point type TC (melting point of co-crystal)

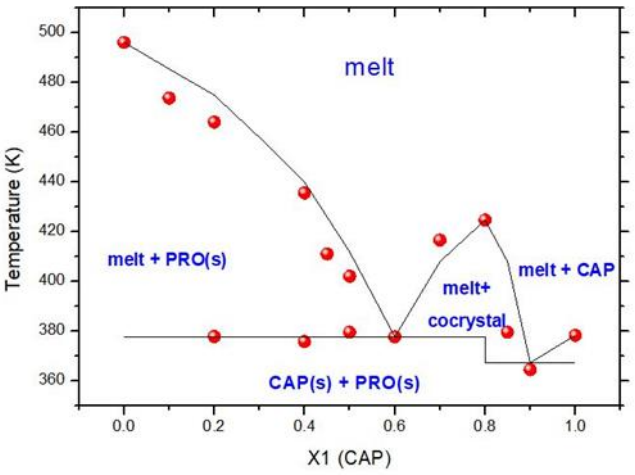

Figure 7: Phase diagram of the system CAP–PRO

IV. Conclusion

Pharmaceutical co-crystals possess a high potential for API physical and biopharmaceutical property enhancement, and therefore constitute a field of study that is currently experiencing rapid development, in this contribution, we tried to grow a co-crystal using a binary mixture of captopril with arginine at first and proline at last so in The tow binary system captopril-arginine and captopril-proline was studied by DSC and the relevant solid–liquid phase diagram was calculate and draw using ORIGIN software for pure substances and thermodynamic description of the melt based on the eutectic and liquidus temperatures obtained in this study. Temperatures and enthalpies of melting of pure substances $t_{fus.CAP}$ = 105.27 °C = 378.42 °K and . It is associated with the endothermic heat effect $\Delta H_{fus.CAP}$ = 27.00 kJ mol^{-1} ($\Delta H_{fus.CAP}$ = 124.232 J g^{-1}) and for the tow amino acid for PRO we evaluated tfus.PRO = 223.066 °C =496.216°K and for ARG we evaluated t_{fusARG} = 226.886 °C = 493.88 and for enthalpy ΔHfus.PRO = 30.435 kJ mol-1 (ΔHfus.PRO = 264.64 J g-1) and $\Delta H_{fus.ARG}$ = 39.705 kJ mol-1 (ΔHfus ARG = 188.482 J g-1) are in good agreement with the previously published values. The first binary system is simple eutectic type and the acquired values t_{eut} = 370.15 ± 2.0 K and $X_{CAP,eut}$ = 0.9 Molar fraction of CAP. And for Phase diagram studies the second binary system have revealed the formation of congruent melting type phase diagram T_C = 424.74°K and molar fraction of 80% X=0.8 and two different eutectics, A first eutectic X=0.6 and second eutectic at X= 0.9 of CAP fraction.

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