STRUCTURE OF INTERMOLECULAR DRUG-POLYMER INTERACTIONS: ACETAMINOPHEN−PVP K30 COMPLEX

[1]NUR BALQISH EZLYN IBRAHIM, [2]FAIZANI MOHD-NOOR, [3]SITI MAISARAH AZIZ

[1,3]UniSZA Science and Medicine Foundation Centre, Universiti Sultan Zainal Abidin, Gong Badak Campus, 21300 Kuala Nerus. Terengganu, Malaysia
[2]Department of Physics, Faculty of Science, Universiti Teknologi Malaysia, 81310 Skudai, Johor, Malaysia
Email: [1]sl4520@putra.unisza.edu.my, [2]faizani@utm.my, [3]smaisarahaziz@unisza.edu.my

Abstract - Structural and physicochemical interactions in the co-amorphous system of acetaminophen (APAP) and polyvinylpyrrolidone (PVP K30) were examined to enhance the stability and amorphous characteristics of APAP. Samples with varying APAP to PVP weight ratios were prepared using the melt-quenching technique and analysed via X-ray diffraction (XRD) and Fourier-transform infrared (FTIR) spectroscopy. XRD patterns demonstrated the crystalline nature of pure APAP, which gradually decreasedwith increasing PVP content, resulting in an amorphous state at a 20:80 (APAP:PVP) ratio. FTIR analysis identified significant spectral shiftsand band broadening in key vibrational regions, indicating hydrogen bonding between APAP and PVP. These interactions disrupted the crystalline lattice of APAP, inhibited recrystallization, and stabilized the amorphous phase. The results highlight the function of PVP as an amorphous stabilizer through intermolecular interactions with APAP, providing insights for designing stable amorphous pharmaceutical formulations.

Keywords - FTIR spectroscopy; DFT calculation; co-amorphous system; acetaminophen; PVP K30; melt-quenched.

INTRODUCTION

Preparing drugs in their amorphous form presents significant challenges due to their metastable nature, which makes pure amorphous compounds prone to crystallization.[1,2]This issue is particularly prominent for active pharmaceutical ingredients (APIs) with low glass transition temperatures, as it possesses a very unstable amorphous phase and tend to crystallize even at room temperature.[3,4]Polymer-based amorphous formulations have consistently demonstrated efficacy in improving the physical stability of the amorphous systems. Polymers contribute to this stabilization by forming molecular-level interactions, such as hydrogen bonding, which prevent the arrangement of molecules into a crystalline structure.[5] Acetaminophen (APAP) well known due its wide accessibility and status as one of the most widely consumed drugs known to be common analgesics and antipyretics in the pharmaceutical industry.[6]Despite its extensive use, formulating APAP in an amorphous state is a significant challenge. Its low glass transition temperature (21.5^{o}C)and inherent molecular properties make it highly prone to recrystallization, which compromises its stability.[3]These inherent limitations in the APAP makes it a relevant subject for exploring new ways to stabilize amorphous materials and address issues with crystallization.
Polyvinylpyrrolidone K30 (PVP K30), a biocompatible polymer, is frequently used to stabilize amorphous systems due to its ability to form hydrogen bonds with active pharmaceutical ingredients (APIs) like acetaminophen (APAP),since both are organic compounds and have weaker hydrogen bonds.[3,7,8,9,10]PVP K30 has potential to creates strong intermolecular bonds that slow down molecular movement and increase the energy barrier for crystallization, enhancing stability.[11,12]For instance, studies on co-amorphous system involving myricetin have shown that PVP K30 helps maintain the amorphous state through hydrogen bonding and other molecular interactions.[13]

The amorphous structure, characterized by higher internal energy, increased Gibbs free energy, and greater thermodynamic instability compared to its crystalline form, influences the material's phase behavior, thermal stability, and molecular dynamics. The challenge in amorphous material research lies in unraveling the precise mechanisms governing phase transitions and understanding the role of intermolecular forces in maintaining stability. The lack of long-range order in amorphous systems further complicates the characterization of their structural and dynamic properties. A comprehensive approach is essential to address these challenges, combining experimental techniques like X-ray diffraction (XRD) and Fourier-transform infrared (FTIR) spectroscopy with theoretical modelling, like density functional theory (DFT).This approach not only enables deeper insights into the physical principles governing amorphous systems but also sheds light on the structural and dynamic interplay betweenAPAP and PVP K30, offering a pathway to improved stability of amorphous pharmaceutical formulations. Unlike previous studies, this work uniquely investigates the structural properties and intermolecular interactions within the APAP-PVP K30 system induced by the melt-quenching technique.[9,14,15,16]

II. DETAILS EXPERIMENTAL

2.1. Materials and Procedures

Amorphous samples were prepared using acetaminophen purchased from Sigma-Aldrich and PVP K30 polymer from Inno Lab Engineering Sdn

Bhd.Preparation of the samples was done by using the melt-quenching technique via the co-amorphous route. Lab-grade crystalline powders of pure substances are weighted according to the correct nominal composition. For the binary system (BCAS), the nominal compositions utilized in this study were $x(C_8H_9NO_2)$ - $(100-x)(C_8H_9NO)n$, where x = 0, 20, 40, 60, 80 and 100 mol %. The mixture powder was melted in an alumina crucible at a melting temperature (190°C) for 20 minutes. The melt will then be quickly quenched by pouring the melt on the metal plate at ambient temperature (25°C) and powdered for analysis.

2.2. Amorphicity Determination

The degree of amorphicity in the samples was evaluated using X-ray diffraction (XRD) analysis. XRD patterns were obtained using a Rigaku Smartlab X-Ray Diffractometer equipped with a Cu Kα radiation (λ = 1.5406 Å) source. The samples were scanned over a 2θ range of 5°– 50° and a scan rate of 3°/min.

2.2. Vibrational Analysis

Intermolecular interaction between components in a co-amorphous system was evaluated using attenuated total internal reflection (ATR) A Perkin Elmer System 2000 FT-IR spectrometer. The samples, approximately 0.02 mg in powder form, were thoroughly mixed and ground with 2 mg of potassium bromide (KBr) using an agate mortar. The resulting mixture was transferred into a 13 mm diameter barrel. Transparent disc pellets were then formed by compressing the homogeneous powder mixture for five minutes under a pressure of 10 tons per square inch using a hydraulic press. Finally, the pellet was placed in the spectrometer for spectrum analysis. The spectra were collected as the average of 64 scans acquired in the spectral range from 600 to 4000 cm^{-1} for FTIR analysis at room temperature.

DFT calculation was conducted to confirm the vibration of the hetero-molecular network. The electronic structure was calculated using the Density Functional Theory technique using the Gaussian16 package, Becke, 3-parameter, Lee-Yang-Parr (B3LYP) functional at the ground state with the 6-31G' basis set for the mixtures and individual components, respectively.

III. RESULTS AND DISCUSSION

3.1. FTIR Analysis and DFT Calculation

Samples of acetaminophen (APAP), PVP K30 and their mixture were prepared and characterised using Fourier Transform Infrared (FTIR) Spectroscopy and calculated using DFT B3LYP/6-31G' basis set. Individual components were used as references in the analysis by comparing them with the mixture, to validate and understand the molecular interactions and functional groups present in BCAS. The infrared bands observed in Fig.1for acetaminophen[17,18]and PVP K30 [12,19,20,21]were consistent with the data previously reported in the literature allowing for a thorough analysis of the molecular vibrations in the binary system.

The vibrational frequencies of molecular bonds are affected by their surroundings. Changes in the environment, such as transitioning from crystalline to amorphous, cause frequency shifts and peak broadening, indicating successful environmental modification. [22]In vibrational analysis, hydrogen bonding shifts the vibrational frequencies of the involved functional groups. A shift to lower wavenumbers indicates a stronger bond, while a shift to higher wavenumbers suggests a weaker bond than in the pure phase.[1,23,24]Since APAP contains both hydrogen bond donor and acceptor groups, it is anticipated to interact with polymers possessing either of these functionalities.[14]

The infrared spectra in the range of 3200 to 3400 cm^{-1}, specifically at 3321.18 cm^{-1} in this study, correspond to the N-H stretching vibration, a characteristic feature of the amide group in pure acetaminophen (APAP). In the x=20 sample, this N-H peak becomes broader, indicating extensive hydrogen bonding with the C=O group of PVP K30, theoretically calculated at 3394.07 cm^{-1}. Furthermore, the N-H bending vibration in APAP shifts slightly from 1562 cm^{-1} to 1563.79 cm^{-1} in the x=20 sample, interacting with the C=O vibration of PVP at 1644.22 cm^{-1}.

Similarly, the C=O stretching vibration, initially observed at 1650.81 cm^{-1} in pure APAP and 1644.22 cm^{-1} in pure PVP K30, exhibits broadening and a slight shift to 1644.29 cm^{-1} in the mixture for x=20. Following that, a significant reduction in peak intensity and a shift are observed, likely due to intermolecular interactions involving the CH_2 (bending) of PVP K30 with C=O group of APAP, at 1562 cm^{-1} and 2953.61 cm^{-1}, where this peak is theoretically calculated at 1536.64 cm^{-1} and 3061.94 cm^{-1}, respectively. The x=20 sample mixture shows the broadest peak intensities compared to other mixtures, signifying its amorphous state and a higher degree of hydrogen bond formation between the molecules.

Hydrogen bonding typically depends on concentration levels.[8] which can be observed to the BCAS samples with x=20 produce different results compare to another ratio. PVP K30 contains carbonyl (C=O) groups capable of forming hydrogen bonds with the hydroxyl (-OH) and amine (-NH) groups of acetaminophen. These hydrogen bonds stabilize acetaminophen molecules in a disordered configuration, reducing the tendency to recrystallize,

as well as CH group of PVP interact with C=O of APAP,facilitating the dispersion of APAP into the PVP matrix and contributing to its stabilization in the amorphous state. Moreover, the peak associated with APAP molecules remain intact in the infrared spectra of BCAS for x=40,60 and 80, indicating the presence of a dominant APAP component in these compositions.

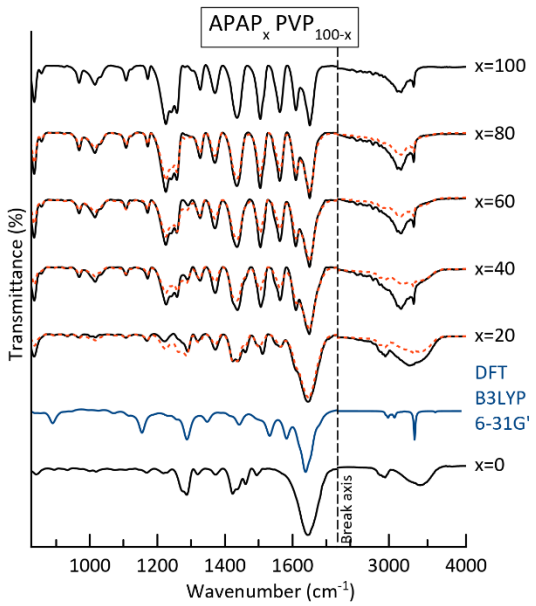


Fig.1. Normalized and corrected FTIR spectra of pure acetaminophen, PVP K30, and the BCAS at varying compositions (mol%), based on DFT calculations (B3LYP 6-31G').The red dotted line represents the simulated pattern of the mixture

The FTIR spectra of APAP-PVP mixture revealed significant spectral deviations from the simulated spectra (red dotted line), particularly in the fingerprint region, confirming the presence of intermolecular interactionswithin drug-polymer matrix.[25,26]DFT-calculated vibrational frequencies further supported experimental assignments and validated the role of specific functional groups in molecular interactions. This phenomenon has been previously documented, with studies attributing the broadening of infrared frequencies to changes in crystal structure caused by molecular disorder, indicating an amorphous state.[22,25,26,27] These conclusions are further supported by X-ray diffraction (XRD) spectra (Fig. 4.), which confirm a loss of hydrogen bonding interactions due to increased molecular disorder.

In this work, the complex exhibited up to 168 normal modes, while the individual components demonstrated 54 modes for APAP and 51 modes for PVP, respectively. These results align with prior studies.[28,29,30]

The structural properties of APAP and PVP K30, revealed through their HOMO and LUMO distributions, highlight their distinct reactivities. The HOMO in acetaminophen was localised on the oxygen and nitrogen atoms and around the benzene ring reflecting their electronegativity.[28,29] The presence of the hydroxyl group increases the electron density on the benzene ring, making it morereactive towards electrophilic attack. The LUMO in acetaminophen was localised on the carbonyl group making it a potential site for nucleophilic attack. The negative charge density on the HOMO suggests acetaminophen can act as a hydrogen bond acceptor.[31]In contrast, for PVP K30, the HOMO was delocalized around the C=O group in the pyrrolidone ring and the ethyl group, identifying regions prone to electron donation. Meanwhile, the LUMO was localized around the carbonyl group of the pyrrolidone ring, indicating regions likely to participate in electron acceptance. In a prior study, the HOMO of PVP K30 was found on the oxygen atom of the C=O group, suggesting potential sites for nucleophilic activity, while the LUMO was distributed across the molecule, excluding the C=O site.[30]The interaction of molecules in BCAS was determined by considering the nature of the reacting molecules of individual components. The binding energy of isolated and interacting molecules of PVP K30 and APAP shows that the HOMO-LUMO energy gap is higher for isolated molecules than for interacting ones (Table 1). The reduction of the energy band gap for interacting molecules shows a formation of new electronic states due to orbital hybridization between the two materials.[30]When multiple materials come together in one system, their atomic orbitals with similar energy levels can slightly overlap.[32]

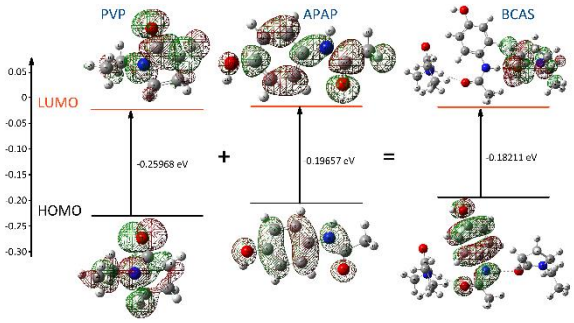


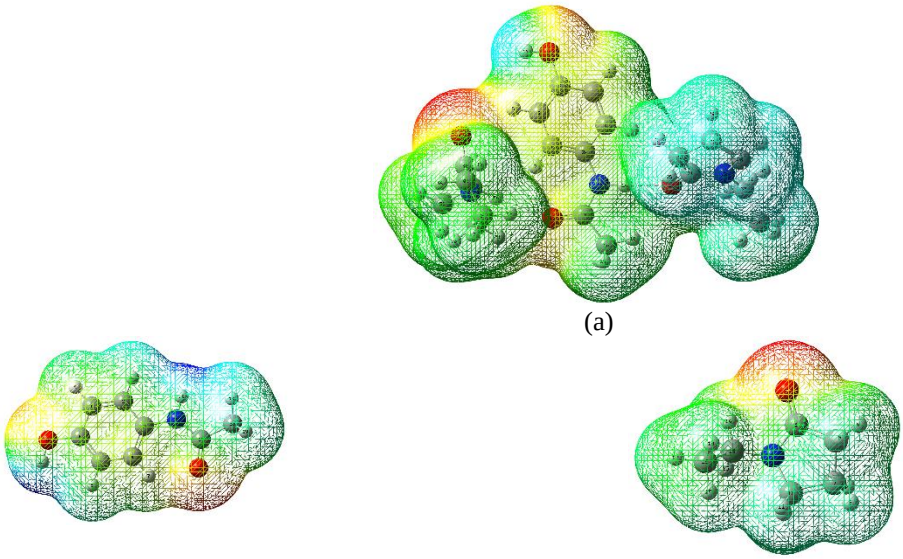
Fig.2. Optimized molecular structure, HOMO and LUMO orbital levels and energy gap of APAP, PVP K30 and BCAS calculated with DFT at the B3LYP/6-31G' level using Gaussian16 package

The PVP K30 has a higher energy gap than the APAP due to its structural and stability properties.[30]However, incorporating PVP K30 into APAP reduces the energy bandgap of the mixture. In a co-amorphous system, molecular orbital overlap between different components enhances electronic delocalization, thereby lowering the energy required for electron transitions from the HOMO to the LUMO.[33]A smaller energy HOMO-LUMO gap generally indicates greater reactivity indicating successful forming an amorphous state. This

reduction also influences the physicochemical properties of the co-amorphous system. Next, the dipole moment values for interacting molecules were higher than the isolated molecule indicating strong polarity. Strong polarity contributes to its ability to form hydrogen bonding and significantly impacts the physical properties of substances. An increased dipole moment for interacting molecules shows that the presence of hydrogen bonding enhances the overall dipole moment of the system.[34]The interacting molecule exhibits the lowest chemical hardness, indicating a high tendency to react. This characteristic makes the most unstable and highly reactive molecule compared to isolated molecules, which aligns with the amorphous nature.Furthermore, the decrease in the electronegativity in the interacting molecules indicate a lower tendency to attract electrons, as part of their electron density is delocalized or shifted toward the interaction sites.Electronegativity significantly impacts co-amorphous systems by enhancing stability through charge balancing.[35]

The molecular electrostatic potential (MEP) is a valuable tool for predicting chemical reactivity. The MEP analysis of the individual components reveals that the oxygen atoms in the carbonyl (C=O) groups of PVP K30 and APAP have high electron densities. The MEP surface of the APAP-PVP complex demonstrates electron transfer between molecules, specifically from the C=O group of PVP K30 to the amide (N-H) group of APAP, and from the C=O group of APAP to the CH_2 group of PVP K30, resulting in changes in electron density.

Regions with high electron density (negative potential) are observed in the carbonyl groups of APAP and PVP in the complex, particularly in areas containing oxygen. Conversely, regions of low electron density (positive to near-zero potential) across the interacting molecules, highlight the role of PVP K30 in stabilizing the structure through hydrogen bonding, thereby reducing the system's overall electrostatic potential.



(a) (b) (c)

Fig.3. Molecular Electrostatic Potential (MEP) of (a) the BCAS, (b) Acetaminophen and (c) PVP K30

These findings are supported by observed increases and decreases in electrostatic potential at the bonding sites on the MEP surface. This phenomenon aligns with a prior study, where the MEP surface displayed zero potential (green) on MEP surface withinco-amorphous system.[36]

Molecule name	Equations	APAP	PVP K30	BCAS
Basis Set		6-31G’	6-31G’	6-31G’
E_{HOMO}		-0.20618	-0.23174	-0.18603
E_{LUMO}		-0.00961	0.02794	-0.00392
$E_{HOMO-LUMO}$		-0.19657	-0.25968	-0.18211
Chemical hardness (η)	$\eta = (E_{LUMO} - E_{HOMO})/2$	0.098285	0.12984	0.091055
Chemical potential (μ)	$\mu = (E_{HOMO} + E_{LUMO})/2$	-0.107895	-0.1019	-0.094975
Electronegativity(χ)	$\chi = -(E_{HOMO} + E_{LUMO})/2$	0.107895	0.1019	0.094975
Electrophilicity index	$\omega = \mu^2/2\eta$	0.059222	0.03999	0.049531
Dipole moment		2.2850937	4.1550342	9.8308948

Table 1:Electronic properties for isolated and interacting molecules

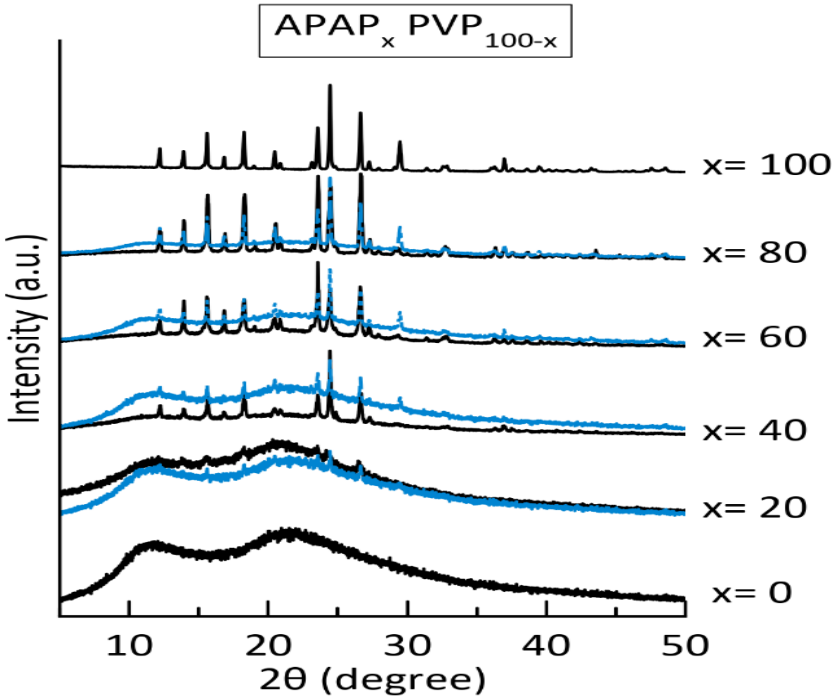


Fig.4. XRD patterns of APAP:PVP K30 mixtures at varying compositions (x = 0–100). The decrease in peak intensity with increasing PVP concentration highlights the transition from crystalline to amorphous structure, with the x = 20 sample exhibiting the most prominent amorphous characteristics.The blue line represents the simulated pattern of the mixture.

The XRD pattern of pure acetaminophen (x = 100) shows sharp, well-defined peaks, confirming its crystalline structure. As the proportion of PVP K30 increases (x = 100 to 20), the peaks become less intense and broader, indicating disruption of acetaminophen's crystalline lattice. At x = 20, a broad halo peaks, signifying an amorphous structure. The pattern for pure PVP K30 (x = 0) also shows a broad hump, reflecting its amorphous nature. This demonstrates that PVP K30 effectively prevents the recrystallization of acetaminophen, thereby stabilizing it in the amorphous state at specific ratios.

IV. CONCLUSIONS

The study demonstrated the role of PVP K30 in stabilizing the amorphous state of acetaminophen. XRD analysis confirmed the transformation of crystalline APAP into an amorphous form as PVP content increased, with amorphization observed at a 20:80 ratio. FTIR spectroscopy further validated this transition by detecting intermolecular hydrogen bonding between the functional groups of APAP and PVP, which disrupted APAP's crystalline lattice and prevented recrystallization. The findings support the potential of PVP K30 as an amorphous stabilizer, enabling the development of stable amorphous drug formulations.However, further investigation into alternative stabilizers, processing techniques, or environmental factors influencing long-term stability could provide deeper insights into optimizing co-amorphous systems for pharmaceutical and material applications.

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