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Enhancing Solubility and Dissolution of Caffeine Through Solid Dispersions with Polyvinylpyrrolidone K-30: A Comparative Study of Drug-to-Polymer Ratios

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ABSTRACT: Despite its inherently high aqueous solubility, caffeine demonstrates inconsistent oral bioavailability due to formulation and processing-related limitations. This study aimed to improve the solubility and dissolution rate of caffeine by formulating solid dispersions using polyvinylpyrrolidone K-30 (PVP K-30) via the solvent evaporation method. Solid dispersions were prepared at drug-to-polymer ratios of 1:1, 1:2, and 2:1, and characterized using hot-stage microscopy (HSM), Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) analysis. Solubility and dissolution testing were conducted in phosphate buffer (pH 6.8). The results showed that the 1:2 ratio formulation yielded the most significant improvement, with solubility reaching 22.3 mg/mL and a dissolution rate of 97.6% within 30 minutes, representing a substantial enhancement compared to pure caffeine. FTIR and DSC indicated the presence of hydrogen bonding and the absence of caffeine melting peak, while PXRD confirmed amorphization. These findings suggest that solid dispersion with PVP K-30 is a viable strategy for overcoming the bioavailability challenges of caffeine and similar compounds, warranting further investigation into in vivo performance and long-term stability.

Keywords: Caffeine; Solid dispersion; Polyvinylpyrrolidone K-30; Dissolution rate; Solvent evaporation method

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INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience and patient compliance. However, poor aqueous solubility can hinder drug absorption and reduce therapeutic efficacy, particularly in BCS Class II and IV drugs (Haritha et al., 2024; Malkawi et al., 2022). Various formulation strategies, including nanotechnology, lipid-based systems, and solid dispersion techniques, have been employed to enhance solubility and bioavailability (Attia et al., 2021; Divate et al., 2021; Mustapha et al., 2016).

Solid dispersion is a well-established method that involves dispersing drugs into hydrophilic polymer matrices to improve wettability, reduce crystallinity, and enhance dissolution rates (Khatri & Chhetri, 2020; Velupula et al., 2021). Polyvinylpyrrolidone K-30 (PVP K-30) is widely used as a carrier due to its high solubilizing capacity, good stability, and compatibility with various active pharmaceutical ingredients (Borawake et al., 2021).

Although caffeine is a BCS Class I compound with high solubility and permeability (Estari et al., 2021), inconsistencies in its bioavailability have been reported. Factors such as CYP1A2 polymorphism, metabolic rate variability, and dietary interactions contribute to this variability. While these biological and metabolic factors are beyond the scope of the present study, improving the physicochemical properties of caffeine—particularly its dissolution rate—through formulation strategies like solid dispersions may help mitigate their overall impact by ensuring rapid and consistent drug release (Mohanty et al., 2022).

Given these factors, recent studies have re-examined caffeine's formulation potential, especially in the context of improving its physicochemical stability and dissolution performance (Hines et al., 2019). One notable strategy is the application of solid dispersion technology to caffeine, particularly when enhancing dissolution kinetics, maintaining the amorphous state, or stabilizing under various storage and physiological conditions is desired. Although caffeine's solubility is generally sufficient, converting it into a solid dispersion matrix using hydrophilic carriers can still provide benefits beyond solubility enhancement. For BCS I compounds, such as caffeine, solid dispersion approaches can be leveraged to maintain an amorphous state, ensure consistent dissolution profiles under varying physiological conditions, and improve storage stability. While Elmubarak et al. (2021) demonstrated similar benefits in furosemide (a BCS IV drug), primarily to address both solubility and permeability limitations. The present study differs in that caffeine has high solubility and permeability, and the focus is on enhancing physicochemical stability and dissolution consistency rather than overcoming permeability barriers.

The development of robust formulation strategies remains crucial for optimizing the performance of active pharmaceutical ingredients, even for compounds with favourable BCS classification. As highlighted by recent advances in solid dispersion technology (Song et al., 2024), this approach offers opportunities not only to enhance dissolution but also to improve stability, modify release behaviour, and ensure consistent in vivo performance under diverse conditions. In the case of caffeine, despite its high solubility, there is still a need for formulations that maintain physicochemical stability, especially in moisture-prone environments, and ensure consistent dissolution profiles. This study addresses this need by formulating caffeine solid dispersions with varying drug-to-polymer ratios to evaluate their impact on solubility and dissolution characteristics.

Therefore, this study aims to formulate and evaluate caffeine solid dispersions using PVP K-30 via solvent evaporation, and to investigate how different drug-to-polymer

ratios affect their solubility and dissolution rate. The findings will provide insight into the applicability of solid dispersion systems for optimizing BCS Class I drugs.

METHODS

Materials

Caffeine (≥99% purity, Kimia Farma, Indonesia), PVP K-30 (Merck, Germany), analytical grade ethanol (Emsure®, Merck), distilled water (Brataco, Indonesia), sodium dihydrogen phosphate (NaH_2PO_4), and disodium hydrogen phosphate (Na_2HPO_4) were used to prepare a phosphate buffer solution at pH 6.8.

Instruments

The instruments used included a rotary evaporator Hei-VAP Value (Heidolph, Germany), UV-Vis spectrophotometer UV-1800 (Shimadzu, Japan), hot stage microscope FP82HT (Mettler Toledo, Switzerland), FTIR spectrophotometer IRAffinity-1S (Shimadzu, Japan), DSC 60 Plus (Shimadzu, Japan), XRD-7000 diffractometer (Shimadzu, Japan), paddle-type dissolution tester (Logan Instruments, USA), vacuum oven (Memmert, Germany), and centrifuge (Hettich EBA 20, Germany).

Preparation of Solid Dispersions

Solid dispersions were prepared using the solvent evaporation method. Caffeine and PVP K-30 were dissolved in ethanol to form homogeneous solutions at drug-to-polymer mass ratios of 1:1, 1:2, and 2:1. These ratios were selected to investigate the influence of polymer concentration on solubility enhancement and to compare both polymer-excess and drug-excess conditions. Ethanol was chosen as the solvent due to its excellent solubilizing capacity for both caffeine and PVP, low boiling point, and safety profile, which facilitates efficient removal during rotary evaporation. The mixtures were stirred thoroughly and subjected to rotary evaporation at 50°C under 200 mbar to remove the solvent. The resulting solid mass was further dried in a vacuum oven at 40°C for 24 hours to ensure complete solvent elimination. The dried dispersions were then pulverized and sieved through a 60-mesh sieve to obtain uniform particle sizes suitable for further evaluation.

Hot Stage Microscopy (HSM)

Hot-stage microscopy was used to assess thermal transitions, including melting and recrystallization events, visually. A thin layer of the solid dispersion was placed on a microscope slide and heated from ambient temperature to 200°C at a rate of 10°C/min under polarized light. The observation of the absence of a distinct melting event, combined with the lack of birefringence, was used to confirm the amorphous state of the drug (Ashton et al., 2017). Each observation was performed in triplicate (n = 3)

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were recorded using the KBr pellet method within the 4000–400 cm^{-1} range. The formation of hydrogen bonds between caffeine and PVP K-30 was inferred based on (1) the shift of N–H or O–H stretching vibrations of caffeine, and (2) the carbonyl stretching frequency (C=O) of PVP, as previously described by Sui et al. (2020). Such spectral shifts or broadening indicate molecular-level interactions and hydrogen bonding, suggesting the formation of a stable solid dispersion system. All measurements were performed in triplicate (n = 3).

Differential Scanning Calorimetry (DSC)

DSC thermograms were obtained by heating ~5 mg of each sample from 30°C to 300°C at 10°C/min in a nitrogen atmosphere. The disappearance of the characteristic melting peak of crystalline caffeine (~238°C) indicated conversion to the amorphous state. The presence of a single glass transition temperature (*Tg*) further confirmed the formation of a homogeneous amorphous solid dispersion, indicating molecular miscibility between caffeine and PVP (Aldeeb et al., 2023; Knopp et al., 2015).

Powder X-Ray Diffraction (PXRD)

PXRD was performed using CuKα radiation, scanning from 5° to 50° 2θ at 2°/min. The crystalline form of pure caffeine displayed sharp diffraction peaks, whereas the solid dispersions showed a broad halo pattern with no sharp peaks, confirming the amorphous nature of the material. This shift from crystalline to amorphous morphology is consistent with previously reported findings (Latunra et al., 2024; Morelo et al., 2019).

Solubility Study

The saturated solubility of pure caffeine and its solid dispersions was determined by adding excess samples to 10 mL of distilled water and then incubating at 37°C for 24 hours under agitation. After centrifugation, the supernatant was filtered and analyzed using UV-Vis spectrophotometry at 273 nm. Solubility values were expressed as mean ± SD (n=3). The method allowed direct assessment of formulation impact on aqueous solubility (Dabhade et al., 2021).

Dissolution Study

Dissolution testing was conducted in 900 mL phosphate buffer (pH 6.8) at 37 ± 0.5°C using a USP II (paddle) apparatus at 50 rpm. The medium was selected to mimic small intestinal conditions, the primary absorption site for caffeine (Pimparade et al., 2015). At predetermined intervals (0, 5, 10, 15, 30, and 60 minutes), 5 mL samples were withdrawn and replaced with fresh buffer. Absorbance was measured at 273 nm. Results were reported as mean ± SD of three replicates (n=3).

Data Analysis

All experimental data were expressed as mean ± standard deviation (SD) from three independent replicates (n = 3). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test to evaluate the effect of different drug-to-polymer ratios on solubility and dissolution profiles. A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

RESULT AND DISCUSSION

Preparation of Solid Dispersions

The preparation of caffeine solid dispersions using the solvent evaporation technique aimed to enhance solubility and dissolution characteristics by forming a molecular dispersion of caffeine within a hydrophilic PVP K-30 matrix. The method employed ethanol as a co-solvent, which is known for its capacity to dissolve both the drug and polymer efficiently, allowing uniform mixing and rapid solvent removal (Elmubarak et al., 2021). The resulting dried powders were fine and homogeneous, consistent with findings by Tran et al. (2019), which emphasized the importance of solvent volatility and evaporation conditions on morphology and molecular dispersion.

Drug-to-polymer ratios (1:1, 1:2, and 2:1) had a significant influence on the properties of the formulations. A higher polymer concentration (1:2) facilitated better

molecular dispersion, consistent with reports by Phadke et al. (2019), which highlight that increased polymer content improves drug stabilisation by providing a matrix that limits molecular mobility, thereby inhibiting crystallization.

Hot Stage Microscopy (HSM)

Figure 1 displays the HSM images of pure caffeine (A), polyvinylpyrrolidone K-30 (PVP K-30) (B), and solid dispersion formulations prepared with drug-to-polymer ratios of 2:1 (C), 1:1 (D), and 1:2 (E). Pure caffeine (Figure 1A) exhibited well-defined, birefringent crystalline structures under polarized light, confirming its highly crystalline nature. In contrast, PVP K-30 (Figure 1B) appeared completely amorphous, as evidenced by the absence of birefringence and the presence of a uniform, non-crystalline morphology. The solid dispersions (Figures 1C–E) showed a progressive morphological transformation with increasing polymer content.

The 2:1 ratio displayed partially crystalline features, while the 1:1 and 1:2 ratios revealed increasingly irregular and diffuse morphologies, characteristic of amorphous systems. These visual transitions, characterized by the loss of birefringence and the absence of distinct melting events during thermal analysis, provide strong support for the conversion of caffeine into an amorphous state within the polymer matrix. The findings are consistent with previous studies that employed HSM to distinguish crystalline from amorphous phases in pharmaceutical dispersions (Ashton et al., 2017; Kumar et al., 2020) and confirm the effectiveness of the solvent evaporation method in achieving molecular dispersion and amorphous stabilization.

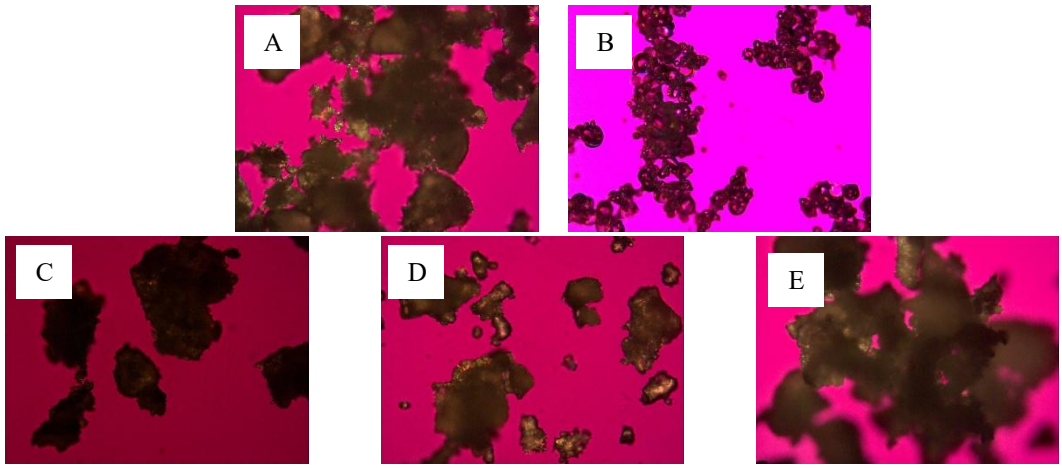

Figure 1. Hot Stage Microscopy (HSM) images of pure caffeine (a), PVP K-30 (b), SD 1:1 (c), SD 1:2 (d), and SD 2:1 (e) at 200× magnification

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra in Figure 2 display distinct differences between pure caffeine, PVP K-30, and their corresponding solid dispersions, particularly in regions indicative of functional groups and molecular interactions. In the spectrum of pure caffeine, characteristic absorption bands were observed around ~3300 cm^{-1} (N–H stretching), ~1700 cm^{-1} (C=O stretching), and ~2900 cm^{-1} (C–H stretching). In the spectra of solid dispersions, these bands shifted or showed reduced intensity, suggesting specific

intermolecular interactions, particularly hydrogen bonding, between the functional groups of caffeine and PVP K-30.

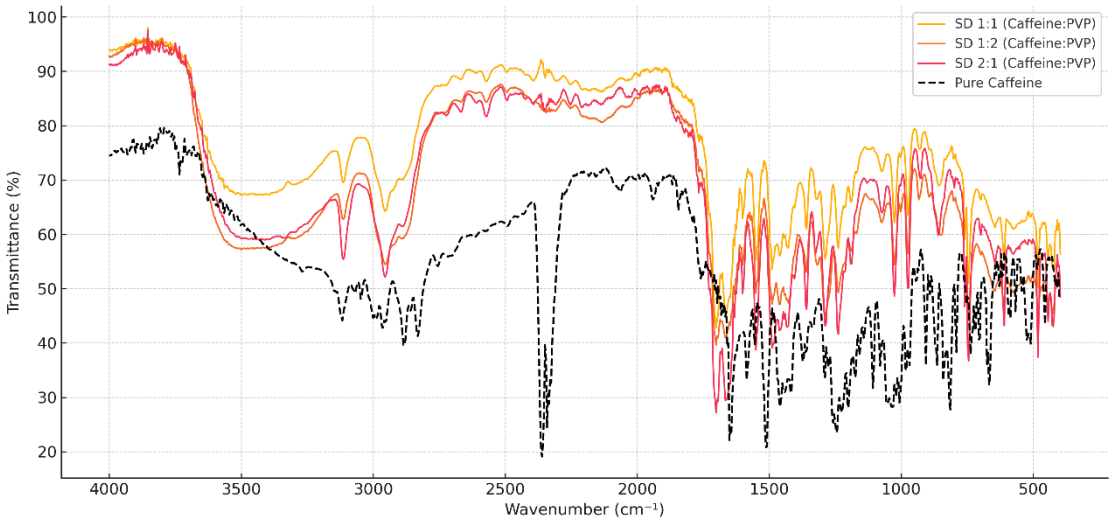

Figure 2. FTIR spectra comparison of pure caffeine and caffeine-PVP K-30 solid dispersions at various drug-to-polymer ratios (1:1, 2:1, and 1:2)

Hydrogen bonding is typically indicated by a broadening or red shift (lower wavenumber) of the N–H and O–H stretching bands due to the formation of interactions with the carbonyl groups (C=O) of PVP. In this case, the observed shift in the N–H band, combined with modifications in the C=O stretching region, supports the hypothesis that the amide group of caffeine forms hydrogen bonds with the carbonyl moiety of PVP. These interactions are well-known to contribute to the stabilization of the amorphous state by reducing molecular mobility and inhibiting recrystallization (Johnson et al., 2017; Sui et al., 2020).

Moreover, alterations in the fingerprint region (~1500–500 cm^{-1}), particularly in the bending and skeletal vibration modes, further indicate changes in the molecular environment, confirming the presence of non-covalent interactions and the successful incorporation of caffeine into the polymeric matrix. These spectral modifications reflect the disruption of the caffeine crystalline lattice and the formation of a more homogeneous amorphous system (Wei et al., 2021). The cumulative evidence from FTIR thus strongly supports the presence of hydrogen bonding, suggesting that such interactions play a critical role in maintaining the drug in a supersaturated, amorphous state within the PVP K-30 carrier.

Differential Scanning Calorimetry (DSC)

The DSC thermograms in Figure 3 provide detailed insight into the thermal transitions and physical states of pure caffeine, PVP K-30, and their solid dispersions. Pure caffeine exhibited a sharp endothermic peak at approximately 235 °C, corresponding to its melting point and confirming its highly crystalline nature. In contrast, PVP K-30 displayed a broad thermal transition without a distinct melting peak, consistent with its amorphous polymer characteristics.

Notably, all solid dispersion formulations showed the complete disappearance of caffeine's melting peak, strongly indicating a transition from crystalline to amorphous

form. Moreover, a single glass transition temperature (*Tg*) in each dispersion suggests that caffeine and PVP K-30 formed a homogeneous molecular mixture rather than a physical blend. The appearance of a single *Tg* is a critical thermal signature of a miscible amorphous system, where the drug is uniformly dispersed at the molecular level within the polymer matrix (Aldeeb et al., 2023; Knopp et al., 2015).

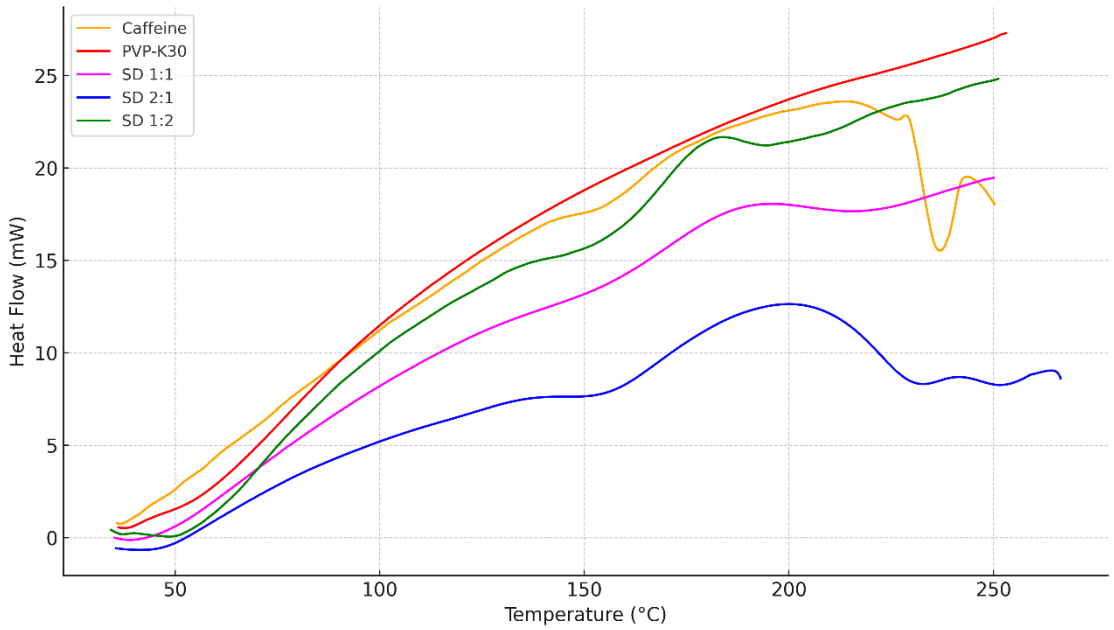

Figure 3. DSC thermograms of pure caffeine, PVP K-30, and their solid dispersions

This molecular miscibility confirms successful amorphization and implies enhanced physical stability, as homogeneous systems are less prone to phase separation or recrystallization. Collectively, the thermal profile reinforces the formation of stable amorphous solid dispersions with potentially improved dissolution performance.

Powder X-Ray Diffraction (PXRD)

The PXRD patterns shown in Figure 4 highlight distinct differences among pure caffeine, PVP K-30, and their solid dispersions. Pure caffeine exhibited sharp and intense diffraction peaks at 2θ = 22.2° and 25.6°, consistent with its crystalline structure. In contrast, PVP K-30 showed a broad halo with no defined peaks, which is characteristic of an amorphous substance. Solid dispersions at all drug-to-polymer ratios exhibited a significant reduction in peak intensity, with the 1:2 formulation showing a complete absence of crystalline peaks, indicating successful amorphization.

A semi-quantitative evaluation of the degree of crystallinity was performed to provide a more objective assessment by comparing the area under the crystalline peaks of the solid dispersions to that of pure caffeine. The calculated relative crystallinity values revealed a substantial decrease: approximately 35% for the 2:1 ratio, 18% for 1:1, and <5% for 1:2, confirming progressive amorphization with increasing polymer content. This finding aligns with previous studies that utilized PXRD to estimate the reduction in crystallinity in solid dispersions (Latunra et al., 2024; Morelo et al., 2019).

The halo pattern and loss of long-range molecular order further support the presence of an amorphous structure. This transformation is crucial for enhancing the thermodynamic activity, solubility, and dissolution rate of poorly soluble or variably bioavailable compounds, such as caffeine.

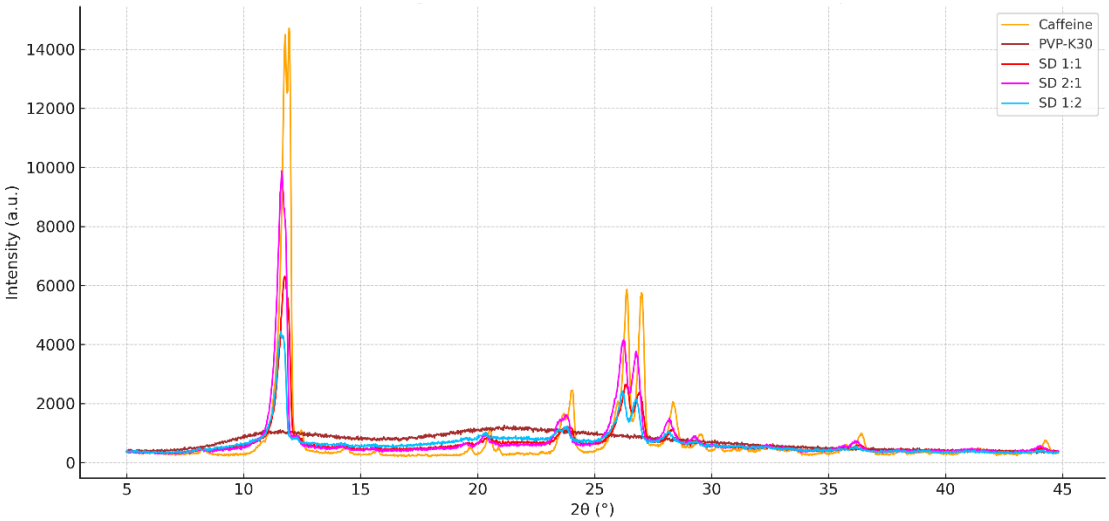

Figure 4. PXRD diffractograms of pure caffeine, PVP K-30, and caffeine-PVP K-30 solid dispersions.

Solubility Study

The solubility of caffeine increased markedly upon formulation into solid dispersions, as summarized in Table 1. Pure caffeine exhibited a solubility of 16.3 ± 0.3 mg/mL, whereas the 1:2 drug-to-polymer formulation demonstrated a significantly higher solubility of 22.3 ± 0.3 mg/mL. The 2:1 and 1:1 formulations also showed improvements (18.8 ± 0.3 mg/mL and 17.7 ± 0.4 mg/mL, respectively). Statistical analysis using one-way ANOVA revealed highly significant differences between all formulations ($p < 0.05$), confirming the impact of increasing polymer content on solubility.

Table 1. Solubility of caffeine and its solid dispersions in phosphate buffer (pH 6.8)

Sample	Solubility (mg/mL)*
Pure Caffeine	16.3 ± 0.3
Solid Dispersion 1:1	17.7 ± 0.4
Solid Dispersion 2:1	18.8 ± 0.3
Solid Dispersion 1:2	22.3 ± 0.3

*Mean±SD, n=3. SD: Standard deviation

These results align with prior findings (Elmubarak et al., 2021), demonstrating that solid dispersion systems enhance solubility by converting the drug to an amorphous state and increasing its wettability. The observed trend confirms that higher ratios of hydrophilic PVP K-30 facilitate better hydration and molecular dispersion in aqueous environments. This supports the mechanism proposed by Phadke et al. (2019), emphasizing that excess polymer provides a stabilizing matrix that prevents recrystallization and enhances solubilization capacity.

Dissolution Study

The dissolution profiles in Figure 5, now presented with error bars (mean ± SD, n = 3), demonstrate a clear enhancement in drug release from caffeine solid dispersions compared to the pure drug. At 30 minutes, pure caffeine achieved only 61.6% release, while the 1:2 solid dispersion reached 97.6%. The 2:1 and 1:1 formulations also exhibited significantly improved release profiles, attaining 95.8% and 89.2%, respectively. These results align with prior studies (Rusdin et al., 2024; Suknuntha et al., 2023), which attributed enhanced dissolution rates to the amorphous nature and polymer interactions in solid dispersions.

The improved dissolution performance of the solid dispersions, particularly the 1:2 ratio, can be attributed to multiple synergistic factors. The transformation of caffeine into an amorphous state increases its free energy and thermodynamic activity, facilitating rapid dissolution in aqueous media (Y. Huang et al., 2019). Additionally, the formation of hydrogen bonds between caffeine and PVP K-30 stabilizes the amorphous form, prevents recrystallization, and maintains supersaturation during dissolution (Johnson et al., 2017; Sui et al., 2020). PVP K-30 also enhances wettability and dispersibility, allowing better penetration of the dissolution medium. These combined mechanisms confirm that solid dispersions, especially at higher polymer ratios, are effective in significantly enhancing the dissolution behavior of caffeine.

These findings are consistent with previous studies involving solid dispersions of caffeine and other BCS Class I drugs, where the amorphous state and drug–polymer interactions significantly enhance dissolution behaviour (Elmubarak et al., 2021; Huang et al., 2019). The superior performance of the 1:2 drug-to-polymer ratio can be attributed to more effective molecular dispersion, increased hydrogen bonding, and greater polymer coverage, which inhibits crystallization and promotes wettability (Johnson et al., 2017; Phadke et al., 2019). Compared to studies on paracetamol and theophylline—both BCS Class I drugs—similar trends have been observed, where polymer-rich formulations yielded better dissolution outcomes due to stronger intermolecular interactions (Kawakami, 2013). However, a limitation of the current study is the absence of long-term stability evaluation under stress conditions, which is essential to confirm the physical robustness of the amorphous state. Furthermore, the in vitro nature of the study does not account for potential pharmacokinetic variability that may occur in vivo. Future research should explore stability profiles under ICH guidelines, conduct in vivo bioavailability studies, and investigate alternative polymers such as HPMC-AS, Soluplus, or Eudragit to further optimize solid dispersion systems for scalable pharmaceutical applications.

CONCLUSION

This study demonstrated that solid dispersions of caffeine with polyvinylpyrrolidone K-30 (PVP K-30) prepared via solvent evaporation effectively improved solubility and dissolution rate. Analytical results from FTIR, DSC, PXRD, and HSM confirmed the transformation of caffeine from crystalline to amorphous form and its stable dispersion within the polymer matrix. The 1:2 drug-to-polymer ratio demonstrated the best performance, achieving a solubility of 22.3 mg/mL and 97.6% dissolution within 30 minutes. These findings support solid dispersion as a practical strategy to enhance the oral delivery of drugs with inconsistent bioavailability. Future research should assess long-term

stability, in vivo bioavailability, and the scalability of the solvent evaporation method for pharmaceutical manufacturing.

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AUTHOR CONTRIBUTION

II: Concepts or ideas; design; definition of intellectual content; literature search; experimental studies; data analysis; manuscript preparation.
RAn: definition of intellectual content; literature search; experimental studies; data analysis.
RAr: Manuscript editing; manuscript review; literature search.

CONFLICT OF INTEREST (If any)

None to declare

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