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Research Article

# Binary or ternary mixture of solid dispersion: Meloxicam case

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## Abstract

The present work was carried out to assess the value of adding water insoluble polymer to meloxicam amorphous solid formulation (ASD). Meloxicam was mixed with polyvinylpyrrolidone (PVP) (1:1 ratio) as a binary mixture and with PVP and ethyl cellulose (1:1:1 ratio) as a ternary mixture. Solvent evaporation method was used to prepare ASD formulations. The differential scanning calorimetry, powder X-Ray diffraction, Cambridge Structural Database and in-vitro dissolution were performed to assess the formulas. The results showed that the addition of insoluble polymer could prevent the recrystallization process during ASD formation. However, the binary mixture showed higher drug release percentage than the ternary mixture. Therefore, a rational amount of insoluble polymer could be considered to control recrystallization and manipulate drug release from ASD formulations.

## Keywords

Cambridge structure database, Meloxicam, Solid dispersion, Solvent evaporation

## Introduction

Drug solubility is still a challenge for many formulators. Hence, many methods have been adapted to increase the solubility such as prodrugs, salt formation, micronization, and amorphous solid formation. The last method showed an increase in the solubility of many drugs such as indomethacin, ketoprofen and griseofulvin (Li et al. 2020; Rahman et al. 2020; Kuhikar et al. 2021). However, recrystallization issue usually arise during amorphous solid formation.(Kissi et al. 2018)

The presence of water soluble polymer is important to enhance drug water solubility (Aejaz et al. 2010; Sawafta et al. 2021). But, it is also consider a source of recrystallization process due to polymer water adsorption (Baird and Taylor 2012; Sheokand et al. 2014). Literatures showed clearly this type of instability occurred with felodipine and ketoconazole with Polyvinylpyrrolidone (PVP) (Rumondor et al. 2009; Rumondor et al. 2011). Conversely, using a water insoluble polymer could enhance the stability of the amorphous solid dispersion (eg., ethyl cellulose with paracetamol amorphous solid dispersion) (Ghaly et al. 1993). The presence of water insoluble polymer is a double edged sword. In spite of improving the stability, they can retard the drug release from the mixture as in dipyridamole and cinnarizine with polyvinylpyrrolidone K30 and hydroxypropyl methylcellulose K100 (Baghel et al. 2018). Literatures showed an increased attention to use both water soluble and insoluble polymers together with the drug as a ternary mixture to increase both solubility and stability (Ohara et al. 2005; Alagdar et al. 2017; Liu et al. 2020). Nevertheless, PVP and ethyl cellulose polymers were not assessed yet.

Meloxicam (MEL) is a class II drug of the biopharmaceutical classification system (low aqueous solubility and

high permeability) (Hîrjău et al. 2020). It has an analgesic effect due its selectivity on inhibition COX-2 receptor (Fogle et al. 2021). It has a low molecular weight (351.4) and pKa values of 1.1 (hydroxyl group) and 4.2 (thiazole group) (Bednarczyk 2021; Zou et al. 2021). There were many methods used to enhance meloxicam water solubility such as micronization method, complexation with cyclodextrin, microemulsion and solid dispersion (Chiou et al. 2007; Shende et al. 2015; Ismail et al. 2021). As mentioned earlier, the binary mixture has many obstacles; hence, this work is designed to assess the effect of insoluble polymer (ethyl cellulose) addition to binary mixture of water soluble polymer (PVP) and meloxicam in amorphous solid dispersion preparation.

# Materials and methods

## Materials

Meloxicam was kindly donated form Al-Furat factory, Baghdad-Iraq, ethyl cellulose from Provizer pharma India, sodium lauryl sulphate (SLS) form Fluka chemical. Buchs, sodium dihydrogen orthophosphate dihydrate, di-sodium hydrogen orthophosphate dihydrate and methanol form Thomas baker, India. Polyvinylpyrrolidone K30 (PVP) was purchased from HiMedia Laboratories (India).

## Preparation of physical mixture and solid dispersion formulations

Physical mixtures were prepared by mixing meloxicam with PVP (1:1) and with PVP:ethyl cellulose (1:1:1). The mixtures were triturated by hand using a mortar and pestle for 5 minutes at room temperature. Solid dispersion formulations were prepared by the solvent evaporation method. The required amount of drug and carrier in 1:1 ratios is weighed and blended in a porcelain dish. Then, the mixtures were dissolved in methanol. Afterward, the solvent was removed under reduced pressure for 20 min at 70 °C using a rotary vacuum evaporator. The obtained solid dispersions were pulverized in a mortar and sieved, then stored in a desiccator to be utilized for further characterizations.

## Probability of H-bond formation

To assess the probability of bond formation between all materials, the H-bond in crystal structure was evaluated using Cambridge Structural Database (CSD) (Version 5.42, CCDC, Cambridge, UK). ConQuest was used to form the queries (version 3 CSDC, Cambridge, UK).

## Differential scanning calorimetry (DSC)

All samples were examined by DSC 60 (Shimadzu, Japan). The samples were sealed in an aluminum pans (5–6 mg) and subject to heat (35 °C to 400 °C) at rate of 10 °C/min under an argon atmosphere.

## Powder X-ray diffraction (PXRD)

The X-ray diffraction was measured using a powder X-ray diffractometer. The operating conditions were: current 30 mA, voltage 40 kV, and 1/min scanning speed with a range of 10–90° (2θ). The Degree of Crystallinity was calculated using Origin Lab software.

## In-vitro release

Dissolution experiments for all formulations which equivalent to 15mg meloxicam (meloxicam powder, physical mixtures, binary and ternary mixtures) were performed using Cosmolab Type II dissolution apparatus, India, at 37 °C (100 rpm). The dissolution media was 900 mL water with SLS (0.2%) to ensure sink condition. At predetermined time intervals, 5 mL of samples were withdrawn and analyzed using UV-spectrophotometer ($\lambda_{max}$ = 363 nm). The same volume (maintained at 37 °C) was added to the dissolution media to maintain constant volume and sink condition. Model dependent and independent methods were used to compare meloxicam dissolution profiles. The model-dependent approaches included the zero order, the first order, the Hixson-Crowell, the Higuchi and the Weibull models. While the model independent approaches included Fit factors (difference factor $f_1$, and the similarity factor $f_2$), dissolution efficiency % (DE%), mean dissolution time (MDT). The results were compared using one-way analysis of variance (ANOVA) when applicable (SPSS Statistics 22).

# Results and discussion

## Prediction of H-bond formation

Stabilization of amorphous solid dispersions (ASD) is largely depend on specific drug-polymer interaction (Van Duong and Van den Mooter 2016). It is well known that H-bonding has a significant role in stabilizing ASD by preventing drug-drug or polymer-polymer intramolecular interaction (Janssens and Van den Mooter 2010; Van Duong and Van den Mooter 2016; Pugliese et al. 2021). The results revealed (Figs 1–3) good probabilities of H-bond formation between meloxicam and PVP, meloxicam and ethyl cellulose and PVP and ethylcellulose. Hence, the stability of ASD is highly anticipated. Consequently, these combinations can be selected for further assessment by DSC and XRPD to confirm the formation of the solid dispersion and its stability.

## DSC

Fig. 4 shows the differential scanning calorimetry thermogram of meloxicam powder (as received) and meloxicam after solvent evaporation. It is clearly seen that the melting point of meloxicam as received is about 259 °C which similar to solvent evaporated meloxicam. This value was dissimilar from another report due to the

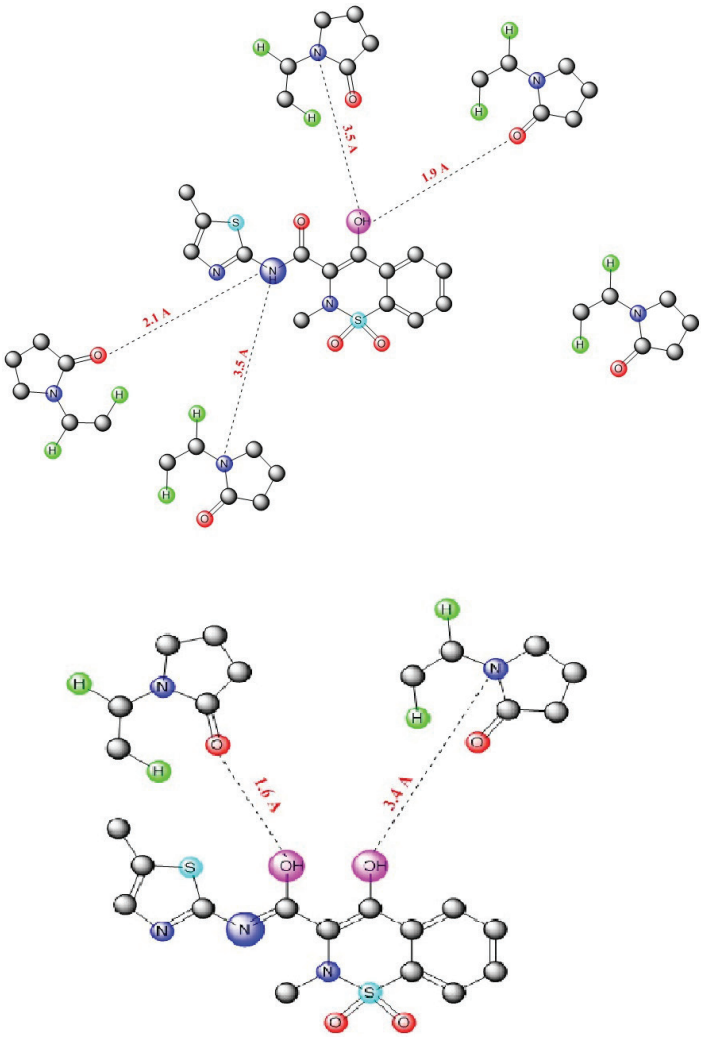


**Figure 1.** Probabilities of H-bond formation between meloxicam and polyvinylpyrrolidone (PVP) and the resonance probabilities.

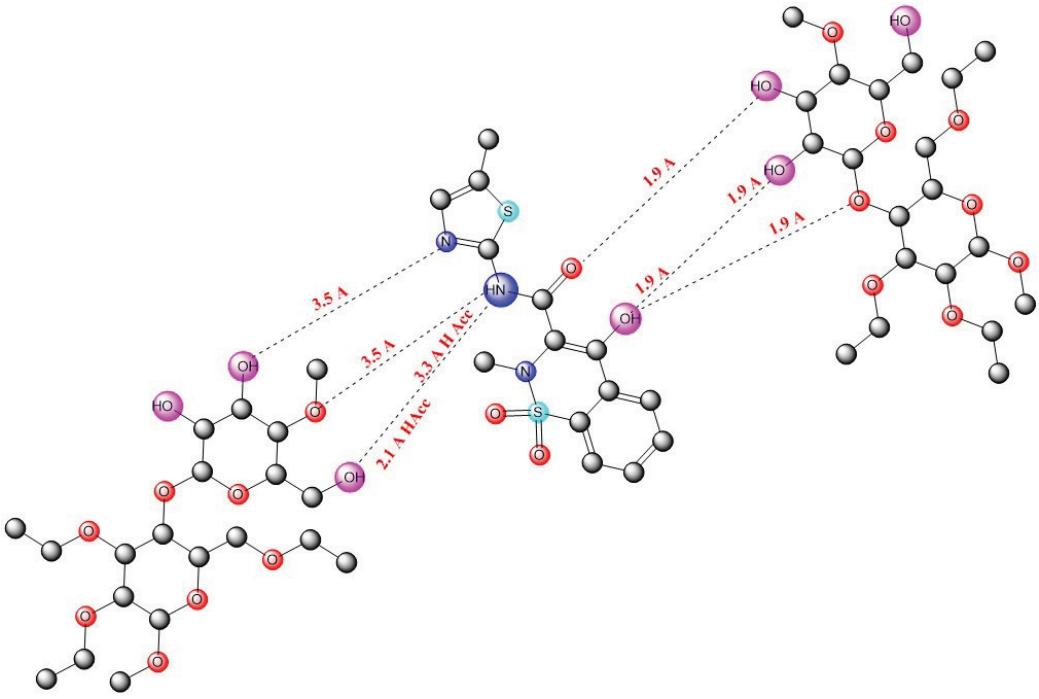


**Figure 2.** Probabilities of H-bond formation between meloxicam and ethyl cellulose.

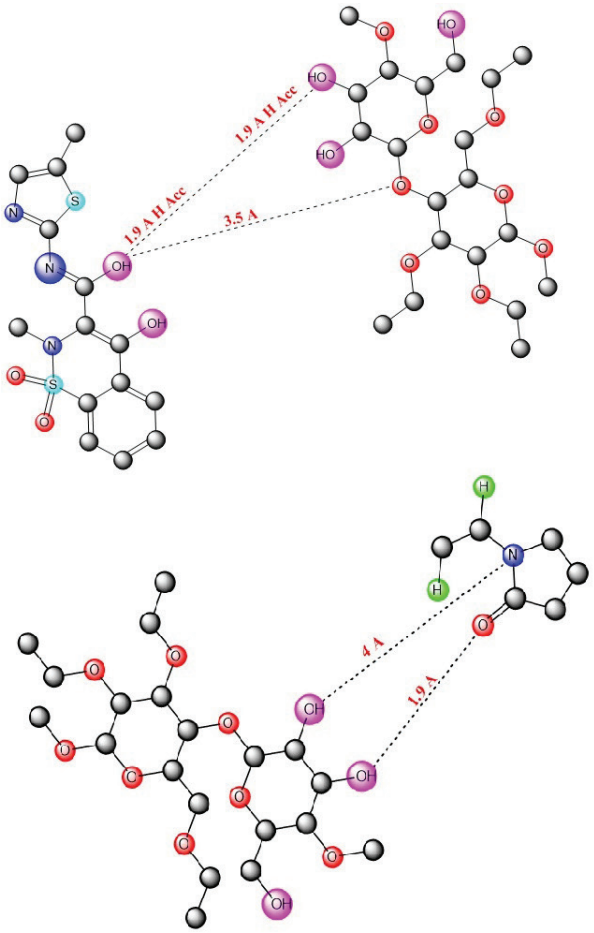


**Figure 3.** Probabilities of H-bond formation between polyvinylpyrrolidone (PVP) and ethyl cellulose and resonance probabilities.

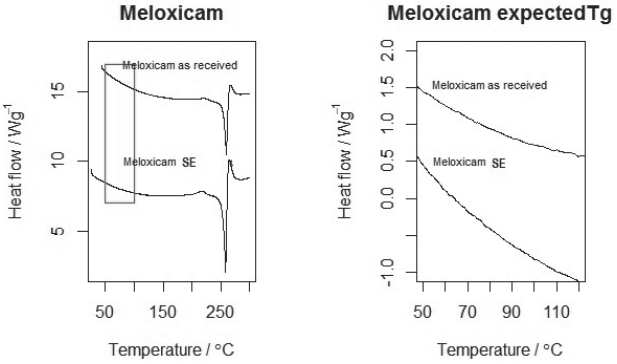


**Figure 4.** Differential scanning calorimetry patterns of meloxicam before and after solvent evaporation (SE). $T_g$: glass transition temperature.

decomposition of meloxicam on melting (Ki and Choi 2007). The melting point of meloxicam showed an exothermic peak after melting around 264 °C and 266 °C respectively which reflect its decomposition (Pomázi et al. 2011). Moreover, there is no glass transition temperature (Tg) for meloxicam after solvent evaporation process. This indicated that meloxicam still in a crystalline form (Hancock and Zografi 1994; Megarry et al. 2014; Liu et al. 2018).

On the other hand, the physical mixture of meloxicam and PVP (Fig. 5) showed a melting peak around 84.9 °C in addition to the original melting point of meloxicam which is shifted downward to 231 °C with a sharp decline in the enthalpy. In addition, the thermogram showed no melting peak around 84.9 °C for a solvent evaporated mixture. This indicated water evaporation process of PVP polymer (El-Maradny et al. 2008; Noolkar et al. 2013). Meloxicam melting point peak showed significant reduction in the enthalpy (229.4 °C) with an exothermic peak around 258 °C. Furthermore, this mixture showed a Tg at 170 °C. The reduction in the enthalpy and the presence of Tg indicated that the mixture was in amorphous state (Li et al. 2016; Hameed 2017).

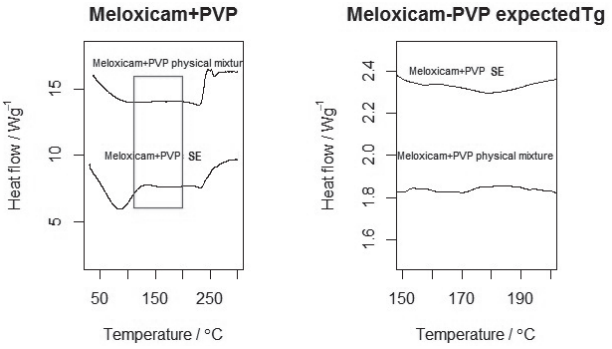


**Figure 5.** Differential scanning calorimetry patterns of meloxicam and polyvinylpyrrolidone (PVP) before and after solvent evaporation. $T_g$: glass transition temperature.

Moreover, Fig. 6 shows the thermogram of the physical mixture of meloxicam with PVP and ethylcellulose and after solvent evaporation process. It's clearly seen that the melting point peak of meloxicam was shifted to 252 °C with a distinct reduction in the enthalpy. Then again, the solvent evaporated mixture revealed Tg around 151.2 °C and a melting point peak at about 222 °C with sharp reduction in the enthalpy. The results suggested the formation of amorphous solid dispersion. These results were consistent with previous report (Setyawan et al. 2019). Moreover, these results suggested that the addition of water insoluble polymer (ethylcellulose) could prevent the recrystallization process (Hameed 2017).

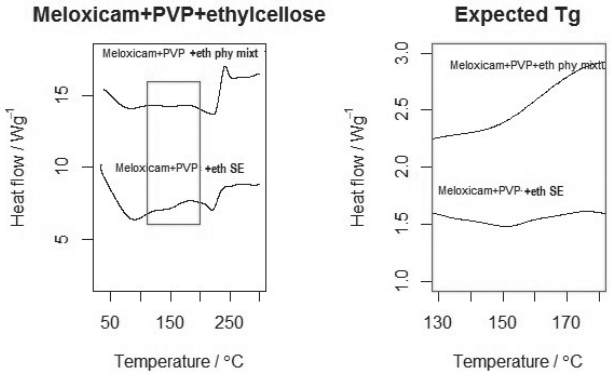


**Figure 6.** Differential scanning calorimetry patterns of meloxicam and polyvinylpyrrolidone (PVP)-ethyl cellulose before and after solvent evaporation. $T_g$: glass transition temperature.

## XRPD

The DSC results revealed the amorphous formation of the binary and ternary mix. However, it did not confirm the stability of the formulations. The recrystallization process can be assessed quantitatively by calculation the Degree of Crystallinity (DC). Fig. 7 showed the XRPD of different formulas. The meloxicam powder showed sharp Braggs peaks which indicated a crystalline nature of meloxicam (Degree of Crystallinity (DC) = 36.41). After solvent evaporation process, this Braggs peaks unchanged except changing in the intensity (DC = 35.10) which might indicate a changing in the polymorphic type due to solvent effect (Bauer 2008).

The physical mixture of meloxicam and PVP showed a reduction in the intensity of Braggs peaks due to the dilution effect of the polymer (Ngo et al. 2018). However, the DC increased to 40.01. After solvent evaporation, there is an increase in the crystallinity of the mixture (DC = 42.46). The ternary mixture showed a further reduction in the Braggs peaks before and after solvent evaporation that might indicate a further reduction in the crystallinity of the mixture (DC = 35.68 (physical mixture), DC = 38.12 (after solvent evaporation)).

The overall results suggested that the ternary mixture had better stability than the binary mixture. Moreover, the results consistent with the previous report (Albadarin et al. 2017). In the present study, ethyl cellulose, a water insoluble polymer, had an important role in protection ASD from recrystallization process which results in a stable mixture. However, more work is needed to assess the effect of polymer concentration on the degree of crystallinity as shown in previous literature (Poralan et al. 2015).

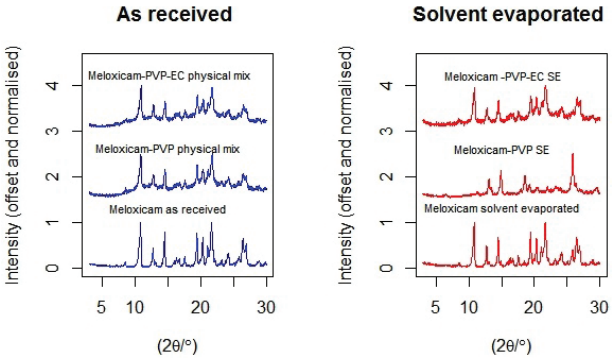


**Figure 7.** Powder X-ray diffraction patterns of meloxicam, polyvinylpyrrolidone (PVP) and ethyl cellulose (EC) before and after solvent evaporation.

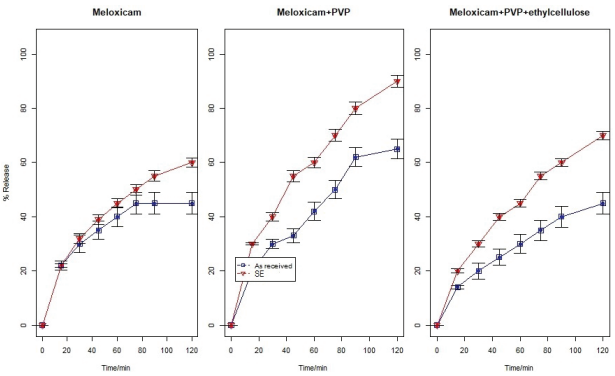


**Figure 8.** The release profile of meloxicam as received, mixed with polyvinylpyrrolidone (PVP) and ethyl cellulose before and after solvent evaporation (n = 3). Blue color line: as received powder or physical mixture; Red line color: after solvent evaporation (SE) process.

## Dissolution study

Fig. 8 shows the release of meloxicam powder (as received), meloxicam-PVP and meloxicam PVP-ethyl cellulose before and after solvent evaporation process. The figure revealed that meloxicam alone showed not more than 40% release although there was an increase in the release rate to about 60% for solvent evaporated meloxicam. This may be due to the changing in polymorphic state of the drug. Previous report showed that changing in the carbamazepine polymorphic state cause a change in the dissolution rate (Schrode et al. 2017).

The release rate of the physical mixture of meloxicam with PVP was increased from 40% to about 60% due to the presence of PVP which is water soluble polymer. After solvent evaporation, the release rate increased to about 90% which is consistent with the previous report (Fini et al. 2008). The ternary mix of meloxicam-PVP-ethyl cellulose release rate remains the same as meloxicam powder and this percent increased after solvent evaporation process to about 70%. Although the release rate is higher than meloxicam powder, it was lower than the release rate of the binary mixture due to the presence of ethyl cellulose.

The dissolution profiles corresponding to binary and ternary mixtures showed Hixon-Crowell model with the higher determination coefficients ($r^2$) and smallest AIC values (Table 1). This model describes the release according to the changes in the surface area and diameter of the particles. Moreover, the MDT showed insignificant difference between binary and ternary mixture ($P > 0.05$). However, the DE% showed higher values ($P < 0.05$) for binary mix-

**Table 1.** Models fit for meloxicam formulations.

| Model | Statistics | Formulations | | | | | |
|---|---|---|---|---|---|---|---|
| | | I | II | III | IV | V | VI |
| Zero order | r2 | 0.816 | 0.968 | 0.995 | 0.962 | 0.985 | 0.982 |
| | k | 0.223 | 0.453 | 0.330 | 0.353 | 0.607 | 0.480 |
| | AIC | 35.33 | 31.84 | 14.92 | 29.57 | 30.71 | 28.39 |
| | MSC | 1.12 | 2.86 | 4.62 | 2.70 | 3.60 | 3.46 |
| First order | r2 | 0.861 | 0.979 | 0.996 | 0.986 | 0.988 | 0.996 |
| | k | 0.004 | 0.008 | 0.004 | 0.007 | 0.017 | 0.010 |
| | AIC | 33.33 | 28.96 | 10.69 | 22.78 | 27.80 | 18.87 |
| | MSC | 1.41 | 3.28 | 4.94 | 3.72 | 3.89 | 4.82 |
| Hixon-Crowell | r2 | 0.847 | 0.980 | 0.9943 | 0.999 | 0.994 | 0.996 |
| | k | 0.001 | 0.002 | 0.001 | 0.632 | 0.004 | 0.003 |
| | AIC | 34.04 | 28.44 | 13.06 | 8.99 | 23.03 | 17.40 |
| | MSC | 1.306 | 3.35 | 4.59 | 5.69 | 4.61 | 5.03 |
| Higuchi | r2 | 0.888 | 0.965 | 0.993 | 0.992 | 0.994 | 0.995 |
| | k | 4.275 | 6.098 | 4.150 | 5.64 | 8.315 | 6.863 |
| | AIC | 32.00 | 32.50 | 15.32 | 18.63 | 23.82 | 19.53 |
| | MSC | 1.62 | 2.77 | 4.36 | 4.31 | 4.53 | 4.73 |
| Weilbull | r2 | 0.966 | 0.9818 | 0.996 | 0.977 | 0.995 | 0.996 |
| | β | 0.284 | 1.279 | 0.903 | 0.002 | 1.660 | 1.144 |
| | AIC | 25.51 | 29.89 | 13.54 | 25.95 | 24.26 | 19.57 |
| | MSC | 2.54 | 3.15 | 4.77 | 3.22 | 4.43 | 4.72 |

**Table 2.** Mean dissolution time and dissolution efficiency of different formulations.

| Variables | Formulations | | | | | |
|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI |
| Mean dissolution time (MDT)* | 25.47±0.84† | 37.36±1.01† | 42.02±2.22‡ | 44.65±0.70‡ | 43.85±1.89‡ | 45.52±1.70‡ |
| Dissolution efficiency (DE) | 0.36±0.02† | 0.41±0.01*‡ | 0.59±0.01‡ | 0.46±0.16† | 0.42±0.01*† | 0.29±0.02† |

ture (Table 2). Previous literatures showed that the type of the polymer and its amount will affect the DE% (Fouad et al. 2021). Fit factors of the solvent evaporated formulations [$f_1$(22.27±1.03) and $f_2$ (42.04±0.93)] showed significant difference between the binary and ternary mixture release. As a result, the addition of ethyl cellulose did not change mechanistic model or MDT. Nonetheless, the amount of the polymer had a crucial role in the overall dissolution efficiency.

I meloxicam powder; II solvent evaporated meloxicam powder; III physical mixture of meloxicam-PVP; IV solvent evaporated meloxicam-PVP mixture; V physical mixture of meloxicam-PVP- ethyl cellulose; VI solvent evaporated of meloxicam-PVP- ethyl cellulose mixture; red color bold font indicate model fit.

I meloxicam powder; II solvent evaporated meloxicam powder; III physical mixture of meloxicam-PVP; IV solvent evaporated meloxicam-PVP mixture; V physical mixture of meloxicam-PVP- ethyl cellulose; VI solvent evaporated of meloxicam-PVP- ethyl cellulose mixture; † significant differences between formulations ($P < 0.05$); ‡ insignificant differences between formulations ($P > 0.05$); * insignificant difference between two formulations ($P > 0.05$).

## Conclusion

Ternary mixture from hydrophilic and hydrophobic polymer can be used in a proper ratio to ensure both solubility and stability of amorphous solid dispersion formulation. The miscibility between the polymer mixtures is important to avoid phase separation in pharmaceutical pre-formulation which can be easily detected by CSDB through H-bond formation. From this study, the results acquired from DSC, XRPD analysis confirmed the conversion of meloxicam from crystalline to amorphous state. Moreover, the dissolution profile was greatly enhanced compared to meloxicam powder. Consequently, it was concluded that the addition of insoluble polymer could prevent the recrystallization process during ASD formation with an acceptable dissolution properties.

## Conflict of interests

The author reports no conflicts of interest in this work.

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