Development of Novel Paracetamol/Naproxen co-crystals for Improvement in Naproxen Solubility

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Abstract

Co-crystals are new solid forms of drugs that could resolve more than one problem associated with a drug’s formulation like solubility, stability, bioavailability, mechanical and tableting properties. This work aims to prepare multi-drug co-crystals consisting of paracetamol and naproxen to improve the solubility performance.

A preliminary theoretical study for estimating the possible bonding between the co-crystal components (paracetamol and naproxen) was performed using the ChemOffice program. The solvent evaporation method was used to prepare paracetamol/naproxen co-crystal in three different molar ratios. The characterization of the prepared co-crystals was performed by fourier transform infrared spectroscopy, thermogravimetric analysis, differential scanning calorimetry, powder x-ray diffraction, and field emission scanning electron microscopy. In addition, a solubility study was conducted to compare the water solubility of pure paracetamol and naproxen with co-crystals solubility.

The result of the theoretical bonding study revealed a high possibility for bonding between paracetamol and naproxen. The solvent evaporation technique was a successful method for the production of paracetamol/naproxen co-crystals in the three explored molar ratios 1:1, 2:1, and 1:2, which was proved by the different characterizing techniques. The solubility study exhibited an enhancement in naproxen solubility by more than two times in (1:1) and (1:2) paracetamol/naproxen co-crystals in addition to a little increase in paracetamol solubility.

In conclusion, this work succeeded in the formation of new paracetamol/naproxen co-crystals, which can be considered as a new promising technique for the formulation of these two drugs with an obvious enhancement in crystallinity and naproxen solubility. This could be exploited in the preparation of tablets with possible improvement in dissolution and bioavailability. However, further work is needed to prove this assumption.

Keywords: Co-crystal, Powder X-Ray Diffraction, Naproxen, Solubility.
Introduction

The discovery of new active pharmaceutical agents is the cornerstone in the drug industry. However, how to formulate these active pharmaceutical ingredients (APIs) into effective dosage forms is the critical step. The selection of the proper formula that ensures a good drug delivery to the site of action inside the body is controlled by different factors, most of which are related to the drug physical and chemical properties (1). The most important physicochemical property of API is solubility, other properties could be related to lipophilicity, permeation, and $p$Ka (2).

Solubility is a physical property of a compound, it is defined as the amount of solute dissolved in a solvent at a certain temperature (3). About 40% of marketed drugs and about 90% of APIs exhibit poor solubility, which ends up with low oral absorption and therefore a very low bioavailability; consequently a reduction in therapeutic effect (4).

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) that is classified as a Class II drug according to the Biopharmaceutics Classification System (BCS) because of its high membrane permeability and poor aqueous solubility. Naproxen exhibits a variable bioavailability after oral administration due to its low solubility and/or poor dissolution in aqueous media. The key to improve the bioavailability of naproxen and produce a therapeutically effective dosage form is to design it in a more water-soluble form (5). Different techniques were used to increase naproxen solubility including the use of a salt form of naproxen (naproxen sodium) (6), Liquid-pellet formulation, (7) or incorporation of microcrystals naproxen into pulsincap device (5). Some of these techniques improve solubility at a certain pH values only. However, the formulation of naproxen with a suitable hydrophilic co-former in the form of co-crystal could be an alternative technique to ensure that naproxen will have enhanced solubility across all pH ranges (8).

Paracetamol (Acetaminophen) is one of the most commonly used drugs around the world as an analgesic and antipyretic. One of the problems with paracetamol tablet production is its poor compressibility. However, the change in paracetamol crystal structure by co-crystallization showed an enhancement in its mechanical properties. A new compressible form of paracetamol tablet with a good hardness was formulated by Karki and his colleagues using the co-crystal engineering technique of paracetamol with four different co-formers (oxalic acid, naphthalene, theophylline, and phenazine) (9).

Paracetamol combination therapy with an NSAID as a single tablet had exhibited a superior pharmacological activity than NSAIDs alone (10). For instance, the formulation of low-doses of naproxen with paracetamol as a combination therapy to relief arthrosis pain demonstrated a better analgesic effect with a decrease in the incidence of toxicity and side effects which are accompanied with the treatment by high-doses of naproxen alone (11).

Co-crystal is a different solid phase of the compound. It contains two or more materials joined together by non-covalent bonds. The pharmaceutical co-crystal consists of API that binds non-covalently with either active pharmaceutical former and this is known as single-drug co-crystal, or the API is joined with another API and it is called multiple-drug co-crystal (12,13).

The advantages of multi-drug co-crystal over the conventional method of combinational drugs production are the improvement in solubility, dissolution, stability, bioavailability, mechanical characteristics and tableting properties of both or at least one drug component in multi-drug co-crystal. In addition, co-crystal production exhibited other advantages including the simplicity, and low cost of production (14).

The creation of co-crystal was facilitated by using some co-crystal design techniques like studying the possibility of hydrogen bond formation which is the most common non-covalent bond involved in co-crystal production (15). Different methods are used in co-crystal manufacturing. Solvent evaporation is the most common method for co-crystals production (16). It depends on the formation of a clear solution of co-crystal components in a certain solvent, and upon evaporation of the solvent, supersaturation will occur leading to an increase in the co-crystal formed in the mixture. This technique gives a good quality co-crystal suitable for single x-rays diffraction (17).

This study aims to formulate a multi-drug co-crystal between paracetamol and naproxen, using solvent evaporation technique, to enhance the solubility of paracetamol and naproxen.
**Materials and Methods**

**Materials**
Paracetamol and naproxen are gifted from Pioneer drug company/Sulaymaniyah/Iraq. Absolute ethanol and methanol were purchased from Scharlau, Spain.

**Methods**

**Co-crystal design**
A computational method for the prediction of non-covalent bond formation (hydrogen bond and Van der Waals forces) could help in co-crystal design. This computational method is performed by ChemOffice program 2016 in order to predict the possibility of weak bonds formation between paracetamol as acceptor or donor and the selected NSAIDs (naproxen) as donor or acceptor.

**Preparation of co-crystals and physical mixtures:**

The physical mixture was prepared as a control to the co-crystal by simple mixing of the two drug powders in molar ratios (1:1, 2:1, and 1:2) similar to that used in co-crystals preparation.

The solvent evaporation method was used to prepare the multi-drugs co-crystals. The required amount of each drug was placed in a beaker to which 5 ml of ethanol was added, and the solution was stirred at 200-300 rpm using a hot plate magnetic stirrer (AccuplateTM, Labnet international, PC-4200, Mexico) until a clear solution was obtained. The solution was further heated (45-50°C) for 10 minutes, after which the resultant solution was poured into a petri dish and let it to dry at room temperature.

The weight of all physical mixtures and prepared co-crystals with their molar ratios is illustrated in Table 1.

**Table 1. All prepared co-crystals and physical mixtures with their different molar ratios.**

<table>
<thead>
<tr>
<th>Preparation methods</th>
<th>Molar ratios</th>
<th>Number of moles of paracetamol (mol)</th>
<th>The quantity of paracetamol (mg)</th>
<th>Number of moles of naproxen (mol)</th>
<th>The quantity of naproxen (mg)</th>
<th>symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical mixtures</td>
<td>1:1</td>
<td>0.001</td>
<td>151.2</td>
<td>0.001</td>
<td>230.3</td>
<td>C1</td>
</tr>
<tr>
<td></td>
<td>2:1</td>
<td>0.002</td>
<td>302.4</td>
<td>0.001</td>
<td>230.3</td>
<td>C2</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td>0.001</td>
<td>151.2</td>
<td>0.002</td>
<td>460.6</td>
<td>C3</td>
</tr>
<tr>
<td>Solvent evaporation mixtures</td>
<td>1:1</td>
<td>0.0005</td>
<td>75.6</td>
<td>0.0005</td>
<td>115.15</td>
<td>N1</td>
</tr>
<tr>
<td></td>
<td>2:1</td>
<td>0.001</td>
<td>151.2</td>
<td>0.0005</td>
<td>115.15</td>
<td>N2</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td>0.0005</td>
<td>75.6</td>
<td>0.001</td>
<td>230.3</td>
<td>N3</td>
</tr>
</tbody>
</table>

**Co-crystal characterization methods**

**a. Fourier transform infrared spectroscopy (FTIR)**

FTIR spectra were obtained using the BRUKER-FTIR apparatus (Germany) over a range of 4000–500 cm⁻¹. A small amount of the sample was put onto a platinum disk and 10,000–15,000 psi pressure was applied.

**b. Thermo gravimetric analysis (TGA)**

TGA detects the changes that occur in the mass as a function of temperature. The instrument used for TGA measurement was (Mettler Toledo TGA/DSC1, Switzerland). Sample weighing (7-12) mg was placed in an aluminum pan and heated over a temperature range of 30–500°C. The rate of heating was increased by 10 °C/min under a dry nitrogen atmosphere (with a flow rate of 50 mL/min). The analysis of TGA/DSC data was achieved by using the STAR® software system.

**c. Differential scanning calorimetry (DSC)**

Differential scanning calorimetry (DSC) curves were obtained using Shimadzu DSC plus 60 (Japan) apparatus. A sample of 2 to 3 mg was sealed in a flat bottomed aluminum pan and heated at 100 ml/min nitrogen flow rate. The thermal behavior of the sample was evaluated at 10°C/min scanning rate and temperature increased up to 500°C.

**d. Powder x-ray diffraction (PXRD)**

PXRD is measured by diffractometer (DX-2700BH, Haoyuan Instrument Co., Ltd, China) with Cu Kα radiation source at 40 kV and 30 mA and the 20 value ranging from (0°-80°). The scanning rate was 4°/min. The obtained results were analyzed by using the computer program OriginPro 2021b (Learning Edition, Origin Lab, USA).

**e. Field emission scanning electron microscopy (FESEM):**

The morphology of the prepared co-crystal and its physical mixture was observed by using field emission scanning electron microscopy (FESEM) from Zeiss Sigma, Germany 300- HV. The scanned sample was loaded on the aluminum stamp and fixed by using carbon adhesive tape. After that, it was covered with a thin layer of gold and observed at various magnification powers by the a high-resolution field-emission scanning electron microscope.

**Saturation solubility study**

Solubility study was performed by using a shaking water bath (Stuart Scientific, SBS30, UK). Excess amounts of pure paracetamol, naproxen, and the prepared co-crystals were placed in conical flasks and 10 ml distilled water was added to each flask to
obtain a supersaturated solution. These solutions were allowed to stand at 37 ± 1°C for 24 hours in a water bath shaker to achieve a complete saturation (25). After that, each solution was filtered by a 0.45 μm membrane filter, diluted by suitable diluent (15 methanol: 85 water) for paracetamol and absolute methanol for naproxen and analyzed by Shimadzu UV-spectrophotometer. The determination of the content is carried out by simultaneous technique by Ashour et al. 2015 at 242 nm and 331 nm wavelengths for paracetamol and naproxen, respectively (26,27).

Statistical analysis
The values of the solubility study were expressed as a mean ± standard deviation (SD). Statistical analysis was performed by applying a one-way ANOVA test followed by the Tukey test. The difference is considered significant when the P value is ≤ 0.05.

Results and Discussion

Co-crystal design
The co-crystal design was dependent on molecular mechanics to theoretically calculate the strength and energy of bond formation between paracetamol and the selected NSAID (naproxen). Molecular mechanics was used to assuming the total bonding energy between two molecules which came from the summation of different energies required for stretching, bending, stretch-bending, torsional, electrostatic, Van der Waals, and non-Van der Waals attractions (28). In general, the lower total energy required for bonding indicates a more stable and easier bond formation between the two molecules. Theoretical calculation of the total energy of bond formation between (paracetamol-naproxen) was -26.5571 kcal/mole which could be considered as low total energy for bond formation, as demonstrated in Figure (1a). All possible hydrogen bonds between paracetamol and naproxen are illustrated in Figure (1b). In addition to intermolecular hydrogen bonds, other weak interactions like Van der Waals forces may be involved in (paracetamol-naproxen) co-crystal formation.

The results of the molecular mechanics theory indicated a higher possibility for bonding and co-crystal formation between paracetamol and naproxen drugs.

Preparation of co-crystals and physical mixtures
The solvent evaporation technique was used for co-crystals production. Ethanol was used as a solvent since it is non-toxic in low doses, suitable for oral preparations, and evaporates easily. Moreover, both paracetamol and naproxen have a good solubility in it (29).

The products of the solvent evaporation method were white, needle-like structures.

Co-crystal characterization methods

a. Fourier transform infrared spectroscopy (FTIR)
FTIR is a useful tool in confirming the presence of new solid forms like co-crystal. The hydrogen bonding causes a change in stretching frequencies and vibrational bending, leading to the shift of the band to different wavenumbers and increase the width of the band (30). The important
functional groups of paracetamol that could participate in intermolecular bonding in the IR spectrum includes phenolic $\text{O-H}$ stretching at (3315.60) cm$^{-1}$, N–H stretching at (3152.62) cm$^{-1}$, and amide $\text{N-C=O}$ stretching at (1647.24) cm$^{-1}$, as represented in Figure (2). While for naproxen, the IR spectrum includes carboxylic $\text{O-H}$ stretching at (3108.57) cm$^{-1}$, carboxylic acid $\text{HO-C=O}$ stretching at (1717.44) cm$^{-1}$, and methoxy $\text{CH3-O-C}$ stretching at (1167.10) cm$^{-1}$, as illustrated in Figure (3). The C–H stretching whether aromatic or aliphatic in paracetamol was between (2700 and 2800) cm$^{-1}$, in comparison with (2965.94) cm$^{-1}$ in naproxen.

![Figure 2. FTIR spectrum of paracetamol.](image2)

![Figure 3. FTIR spectrum of naproxen.](image3)

Regarding the prepared 1:1 co-crystal mixture (N1), there were significant changes in the IR spectrum from its parent drugs and physical mixture (C1). The appearance of $\text{O-H}$ stretching at wavenumber (between 3350 and 3400) cm$^{-1}$ in the IR spectrum of N1 (Figure 4b) in comparison with (3315.60) cm$^{-1}$ in pure paracetamol could indicate its participation in hydrogen bond formation. In the physical mixture C1 (Figure 4a), the O–H stretching did not appear in the IR spectrum, this may be due to the overlapping with the N–H bands. Also, the shifting in N–H stretching region to (3157.83) cm$^{-1}$ and the peak became sharper with the shifting of methoxy group stretching from (2965.09) cm$^{-1}$ wavenumber to (2941.51) cm$^{-1}$ may indicate the presence of intermolecular bonding. The formation of new band at (1555.20) cm$^{-1}$ could be related to (N–C=O) bending. All of these changes with the increase of the tone between (1900- 2400) cm$^{-1}$ could indicate the formation of a hydrogen bond between paracetamol and naproxen in N1$^{(31)}$. 

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Figure 4. FTIR spectrum of 1:1 paracetamol/naproxen mixtures. a) C1 physical mixture. b) N1 prepared co-crystal mixture.

The 2:1 prepared co-crystal mixture (N2) had changes in IR spectrum in comparison with its physical mixture (C2), as demonstrated in Figure 5 (a and b), there was the shifting of O-H stretching to (3313.06) cm$^{-1}$ and N-H stretching from (3148.34) to (3153.79) cm$^{-1}$. Also, there was the formation of new bands at (3103.49, 2600.99, 1796.36, and 1323.87) cm$^{-1}$ in N2. All of these changes could indicate the presence of intermolecular bonding in N2.
Regarding N3, which represents the (1:2) ratio of paracetamol-naproxen prepared co-crystal mixture, there was a shifting in N-H stretching from 3145.43 cm$^{-1}$ to 3151.49 cm$^{-1}$ and the band became broad and all of the bands had moved to higher absorbing transmittance. The N3 was also different from its physical mixture (C3) by the shifting of the (N-C=O) band from (1675.92) to (1594.78) cm$^{-1}$ and the band became wider. In addition, there was the shifting of (C-O) stretching related to the amide and carboxylic acid in (1499.02) and (1219.99) cm$^{-1}$ wavenumbers to (1458.86) and (1170.29) cm$^{-1}$, respectively, as indicated in Figure 6 (a and b). This could indicate the participation of the carboxylic acid of naproxen with the amide (N-C=O) in paracetamol to form a hydrogen bond.
The interpretation of IR results indicated the presence of bonding between paracetamol and naproxen in all three ratios of the co-crystal mixtures prepared by solvent evaporation method. However, further diagnostic techniques are needed to confirm co-crystals formation.

b. Thermo gravimetric analysis (TGA)

TGA measurements of the pure drugs and the prepared co-crystal mixtures approved that there was no entrapped water inside the materials (no solvate or hydrate form) because there is no mass loss occurred before 200°C.

For paracetamol, the onset of mass loss began at 300°C. The paracetamol loses 50% of its mass by reaching \( \approx 354^\circ C \) and only 10% of the paracetamol mass will remain intact at about 375°C, as shown in Figure (7 a). While in pure naproxen, the initial decomposition temperature (IDT) was \( \approx 237^\circ C \) and the temperature at which 50% of the mass was lost or decomposed (T 50%) was at 300°C, as demonstrated in Figure (7 b).
For the prepared paracetamol-naproxen co-crystals, there were changes in their TGA measurements in comparison with their physical mixtures and parent drugs, like N3 (1:2 paracetamol-naproxen co-crystal mixture) when compared with the physical mixture (C3). In N3, the IDT was 250°C, as in Figure (8 a), in comparison with 240°C for C3. The mass loss in N3 required a higher temperature (310°C) to lose 50% of its mass while in C3, 50% of its mass was lost when the temperature reached 290°C, as demonstrated in Figure (8 b). Differences between the prepared co-crystals and their parent drugs were observed in N1 and N2. The IDT of N1 and N2 were 250°C and 257°C, respectively. While the temperature at which the co-crystal lost 50% of its mass was 365°C for N1 and about 330°C for N2, as demonstrated in Figure 9 (a and b). The TGA of the prepared co-crystals gave an indication about their differences from their parent drugs paracetamol and naproxen, as their decomposition temperature was higher than naproxen and lower than paracetamol. While the physical mixture C3 had, approximately, similar TGA profile to the naproxen alone (Figure 7 b). TGA measurements could exclude the formation of hydrate or solvate solid phase in the prepared mixtures, so this confirms that the products of the solvent evaporation method are co-crystals.
Figure 8. TGA of N3 co-crystal (a) and TGA of (C3) physical mixture (b).

Figure 9. TGA of N1 co-crystal (a) and TGA of N2 co-crystal (b).
c. Differential scanning calorimetry (DSC)

The DSC measurements of paracetamol-naproxen prepared co-crystals were compared with the DSC analysis of pure drugs and their physical mixtures. The pure drug exhibited a single sharp peak around its melting point and a second broad peak appeared at a higher temperature which represented the decomposition of the melted drug, and it matches with the TGA recorded IDT. For paracetamol, the sharp melting peak value was 175.10°C (Figure 10 a), while in naproxen the peak value equals 160.46°C, as illustrated in Figure (10 b). The IDT of paracetamol in the DSC was around 300°C, and for naproxen, the decomposition process was completed before the sample reaching 300°C. In both cases, the DSC results gave a similar decomposition profile to the TGA measurements of paracetamol and naproxen, as in Figure (7 a) and (7 b), respectively.

![Figure 10. DSC of paracetamol (a) and naproxen (b).](image)

The N1, N2, and N3 paracetamol-naproxen co-crystals exhibited a single sharp endothermic peak in the DSC measurement for each mixture. The N1 co-crystal exhibited a peak at 147.41°C (Figure 11 a) while in the N2 and N3 co-crystals the peak was formed at 145.45°C and 151.70°C, respectively as illustrated in Figures (11 b) and (11 c). The DSC analysis of these three co-crystals showed distinctly different thermal profiles from the individual parent drugs and their physical mixture. This could indicate the formation of co-crystals with the three different ratios.

![Figure 11. DSC of N1 (a), N2 (b),](image)
The physical mixture (C1) showed the DSC profile of the eutectic mixture. The eutectic mixture is produced when the components of the mixture start to melt at a lower temperature than the melting points of their starting material (32). C1 physical mixture demonstrates a single sharp peak on DSC thermal analysis at 144.77°C, as indicated in Figure (11 d), which might be attributed to the formation of the eutectic mixture. However, this peak appears at a different temperature from all three prepared co-crystal mixtures (N1, N2, and N3), and this confirms that these three products are co-crystals rather than simple physical mixtures.

**Paracetamol/naproxen co-crystals**

**d. Powder x-ray diffraction (PXRD):**
PXRD is used to confirm the formation of a new solid phase when there is a variation in the XRD patterns from the parent materials. PXRD was measured by diffractometer and the obtained results were analyzed using the computer program OriginPro 2021b. The characteristic peaks of pure paracetamol at 2 theta° of the PXRD pattern (Figure 12) are 12.3°, 15.7°, 18.2°, 20.5°, 23.6°, 24.5°, 26.7°, 32.8°, and 37.0°. On the other hand, naproxen characteristic peaks at 2 theta° (Figure 12) are: 6.8°, 12.8°, 13.6°, 17.0°, 19.2°, 20.2°, 22.8°, 24.0°, 27.5°, 28.0°, 28.7°, and 30.1°.

The (1:1) paracetamol-naproxen co-crystal (N1) exhibited a completely different XRD pattern from their pure drug components. The characteristic peaks at 2 theta° values are 6.6°, 12.4°, 13.5°, 16.6°, 18.8°, 19.7°, 22.1°, 23.2°, 23.7°, 24.1°, 28.2°, 32.2°, 33.4°, 37.3°, 40.4°, and 45.3°, as shown in Figure 13.
Figure 13. X-ray powder diffraction pattern of N1.

The characteristic peaks of the (2:1) paracetamol-naproxen co-crystal (N2) were at the following 2 theta° values: 6.4°, 13.6°, 15.4°, 16.6°, 18.8°, 19.7°, 20.2°, 22.0°, 23.3°, 23.7°, 24.1°, 26.4°, 26.2°, 28.2°, 31.1°, 33.4°, 40.4°, and 45.3°, as illustrated in Figure 14.

Figure 14. X-ray powder diffraction pattern of N2.

The (1:2) paracetamol-naproxen co-crystal (N3) exhibited the following characteristic peaks: 6.6°, 12.5°, 13.6°, 16.7°, 17.9°, 18.8°, 19.7°, 22.3°, 23.8°, 26.4°, 27.2°, 27.7°, 28.4°, 31.1°, 33.5°, 40.5°, and 45.5°, as demonstrated in Figure 15.
Besides the different PXRD characterization peaks of N1, N2, and N3, there were differences in the 2 theta° value that gave the higher intensity peak in comparison with paracetamol and naproxen. In N1 the higher intensity was equal to 3423, which is correspondent with the 2 theta° value of 12.4°, while in N2 and N3 the highest intensities were 3362 (2 theta°= 22°) and 5710 (2 theta°=12.5°), respectively.

These different XRD patterns indicate the presence of different solid phases in N1, N2, and N3 in comparison with their pure drugs. This is in accordance with the work of Abbas et al (33), who applied a similar PXRD explanation in confirming the formation of naproxen/nicotinamide co-crystal.

The PXRD results confirmed the previous conclusions obtained from FTIR, TGA, and DSC data, which indicated the formation of paracetamol-naproxen co-crystals when prepared by using the solvent evaporation method in the three ratios 1:1 (N1), 2:1 (N2), and 1:2 (N3).

e.Field emission scanning electron microscopy (FESEM)

The FESEM was used to indicate the differences in the morphology and surface shape between the co-crystal and its physical mixture. The N1 co-crystal FESEM image had been displayed as an example to confirm the difference between the prepared co-crystal (Figure 16, upper row) and its physical mixture C1 (Figure 16, lower row). Both FESEM images at 1 micrometer and 2 micrometers scale manifested a high crystallinity of N1 co-crystal with the improvement that occurred in the shape of co-crystal when compared with C1. These morphological changes may lead to the enhancement of the flowability and improvement in poor tableting properties (24).
Saturation solubility study

Saturated solubility study was conducted to compare the solubility of N1 (1:1), N2 (2:1) and N3 (1:2) paracetamol-naproxen co-crystals with the saturated solubility of their parent drugs (paracetamol and naproxen). Paracetamol water solubility as a pure powder was found to be $(13.104 \pm 0.952)$ mg/ml at $37 \pm 1^\circ C$ and this result was close to the paracetamol solubility recorded in literature which is around 17 mg/ml (34). The three co-crystals (N1, N2, and N3) showed a higher saturated solubility of paracetamol when compared with the solubility of pure paracetamol, as demonstrated in Figure 17. However, all those increases in saturated solubility of the paracetamol component of the three co-crystals are considered statistically non-significant (p-value is more than 0.05).

In general, naproxen solubility in water is very low. Pure naproxen saturated solubility was found to be $(189.129 \pm 12.548)$ µg/ml at $37 \pm 1^\circ C$ and this result is comparable to the recorded solubility in the scientific literature (35). All three co-crystals N1, N2, and N3 exhibited a significant enhancement in naproxen water solubility in comparison with water solubility of pure naproxen, as demonstrated in Figure 18.
The highest solubility was observed in N3 (1:2) paracetamol-naproxen co-crystal with (450.398±1.205) µg/ml. N1 (1:1) paracetamol-naproxen co-crystal demonstrated the second-highest solubility (421.989±1.206) µg/ml, while N2 (2:1) paracetamol-naproxen co-crystal had the lowest solubility (293.295±16.877) µg/ml. The increase in saturated solubility in all the three co-crystals (N1, N2, and N3) is considered statistically significant (p-value ≤ 0.05).

The increase in paracetamol and naproxen solubility, when they were formulated in co-crystals form, might be due to the higher co-crystallization lattice energy which leads to an increase in solubility. In addition, the decrease that occurs in melting points (thermal stability) of the co-crystals in comparison with both parent materials (paracetamol and naproxen) as confirmed by the DSC analysis may contribute to the enhancement of solubility in co-crystals. The increase in solubility was more obvious in the naproxen case due to it is very low water-saturated solubility. Naproxen solubility was increased by 2.2, 1.6, and 2.38 times in the case of N1, N2, and N3 co-crystals, respectively, when compared with pure naproxen solubility. This may be attributed to the co-crystal high energy that made co-crystal behave in a similar manner to amorphous form when dissolved in water by maintaining a supersaturated state which leads to giving a higher saturated solubility in comparison with their starting materials (56,57).

The improvement in naproxen solubility by co-crystal formation was reported in some previous researches, such as the naproxen-nicotinamide co-crystal (33). However, to our best knowledge, no work on naproxen multi-drug co-crystals was conducted before.

Conclusion
Multi-drug co-crystals formation is a simple technology to produce a new physical form of drugs with improved drug properties such as solubility without deteriorating the chemical properties or the pharmacological action. This work concluded that the production of paracetamol: naproxen by solvent evaporation method was feasible and demonstrated enhanced naproxen solubility with possible improved mechanical properties which enabled these co-crystals to be formulated as tablet dosage forms in the future.

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