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Research Article

Preparation and Characterization of Apixaban Cocrystals with Coformers for Improving Physical Properties

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Abstract

Background: Cocrystals are stoichiometric, multicomponent crystalline materials composed of an active pharmaceutical ingredient (API) and a coformer arranged in a crystalline structure. Apixaban (APX) is an oral blood thinner that has a low aqueous solubility of 0.028mg/mL at 24 °C and a weak oral bioavailability of about 50% for doses below 10 mg, decreasing as doses above 25 mg are taken. ***Objectives***: To develop and assess APX cocrystal to improve its solubility. ***Methods***: Cocrystals of APX with diverse coformers were synthesized using the solvent evaporation technique in varying molar ratios. The structure of the synthesized cocrystals was validated by DSC, PXRD, and FTIR analyses. Saturation solubility of APX and cocrystals in water was also investigated. ***Results***: APX cocrystals with diverse coformers exhibited distinct physicochemical features. The co-crystal of APX with oxalic acid at a 1:1 ratio exhibited a 2.54-fold enhancement in solubility relative to that of pure APX in water. Each coformer enhanced the solubility of the APX co-crystals. The FTIR spectra of the cocrystals indicated no interaction between the APX and the coformers. The DSC analysis revealed distinct endothermic peaks corresponding to its melting point, indicating the development of cocrystals. The PXRD diffractogram demonstrated fluctuation of 2 theta values of peaks and confirmed cocrystallization of APX. ***Conclusions***: Cocrystallization may serve as a potential method to improve the solubility of APX.

Keywords: Apixaban, Coformers, Cocrystals, Solubility.

تحضير وتوصيف بلورات Apixaban المشتركة مع المشكلات المشتركة لتحسين الخصائص الفيزيائية

الخلاصة

الخلفية: البلورات المشتركة هي مواد بلورية متكافئة متعددة المكونات تتكون من مكون صيدلاني نشط (API) وعامل مشكل مرتبة في بنية بلورية. Apixaban من مميعات الدم عن طريق الفم ذات قابلية ذوبان مائية منخفضة تبلغ 0.028 مجم/ مل عند 24 درجة مئوية والتوافر البيولوجي الفموي ضعيف بحوالي 50٪ للجرعات التي تقل عن 10 مجم، ويتناقص مع تناول الجرعات التي تزيد عن 25 ملغ. **الأهداف**: تطوير وتقييم بلورة APX لتحسين قابليتها للذوبان. **الطرق**: تم تصنيع بلورات APX مع مشكلات مترابطة متنوعة باستخدام تقنية تبخر المذيبات بنسب مولية متفاوتة. تم التحقق من صحة بنية البلورات المشتركة المركبة من خلال تحليلات DSC و PXRD و FTIR. كما تم فحص قابلية التشبع للذوبان في APX والبلورات المشتركة في الماء. **النتائج**: أظهرت بلورات APX المشتركة ذات المشكلات المشتركة المتنوعة سمات فيزيائية وكيميائية مميزة. أظهرت البلورة المشتركة ل APX مع حمض الأكساليك بنسبة 1: 1 تحسنا بمقدار 2.54 ضعفا في الذوبان مقارنة ب APX النقي في الماء. عزز كل مشكل قابلية ذوبان البلورات المشتركة apx. أشارت أطياف FTIR للبلورات المشتركة إلى عدم وجود تفاعل بين APX والمشكلات. كشف تحليل DSC عن قمم ماصة للحرارة مميزة تتوافق مع نقطة انصهارها، مما يشير إلى تطور البلورات المشتركة. أظهر مخطط حيود PXRD تذبذبا في قيمتين ثيتا للقمم وأكد التبلور المشترك ل APX. **الاستنتاجات**: قد يكون التبلور المشترك بمثابة طريقة محتملة لتحسين قابلية ذوبان APX.

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INTRODUCTION

The European Medicines Agency describes pharmaceutical cocrystals as stoichiometric, multicomponent crystalline structures. They are made up of an active pharmaceutical ingredient (API) and a cocrystal former (coformer) that are arranged in a crystal pattern [1]. Coformer can be an excipient or another drug [2]. Cocrystal is becoming more and more popular because it improves the physical, chemical, and biological properties of API, like how well it dissolves, how bioavailable it is, how permeable it is, how stable it is, how much water it can hold, and how quickly it dissolves [2-4]. Apx, a new anticoagulant [5], has a

chemical formula of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxo-1-piperidinyl) phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo3,4-cpyridine-3-carboxamide (Figure 1) [6].

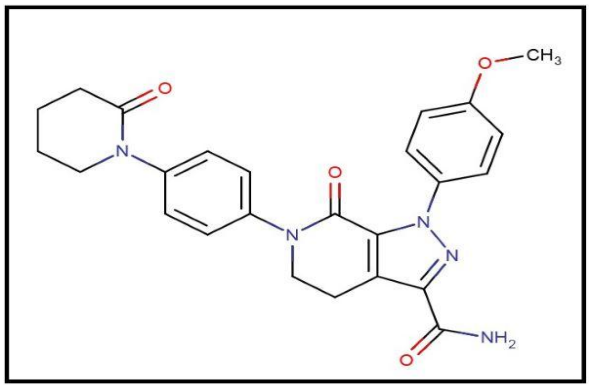

Figure 1: Chemical structure of Apixaban

It is a potent, direct, selective inhibitor for blood coagulation factor Xa [7,8]. Apixaban was associated with a better overall safety and effectiveness profile compared to vitamin K antagonists and other direct-acting oral anticoagulants [9]. APX is available as 2.5 and 5 mg film-coated tablets [10]. The United States, the European Union, and several other countries have approved APX for the prevention of systemic embolism following knee or hip replacement surgery, as well as for stroke prophylaxis in patients with nonvalvular atrial fibrillation [11-15]. Crystalline forms of APX are either polymorph, solvate, hydrate, or cocrystal. Crystalline polymorphs of APX were identified as Form H2-2 (hydrate) and Form N1 (neat). Furthermore, we designate the crystalline solvated forms of APX as formamide (FA-2) and dimethyl formamide (DMF-5) [16,17]. However, during manufacturing and storage, solvates and hydrates can become unstable due to solvent or water evaporating at low humidity and high temperature [18-20]. Moreover, the solvates FA-2 and DMF-5 are not suitable for medicinal use because of biologically unfavorable solvents [17]. The pharmaceutical industry rejects solvate and hydrate due to the alteration of these crystalline polymorphs in the formulation, as demonstrated by the HIV protease inhibitor ritonavir [21,22]. The only available form is APX N-1, which is the marketed product [9]. Although Form N-1 is an anhydrous and thermodynamically stable form, it has low aqueous solubility (0.028 mg/mL at 24°C) [23,24]. Also, APX displays poor oral bioavailability (around 50% for doses ≤ 10 mg) and decreases for doses ≥ 25 mg because of its poor aqueous solubility [23,25,26]. So, it is important for both science and medicine to come up with new dosage forms of APX that are better at dissolving and, as a result, more bioavailable. Furthermore, it is impossible to enhance the solubility of APX via salt formation because APX's molecular structure does not contain ionizable moieties. On the other hand, it is possible to form cocrystals because there are amide groups that bond to coformers via noncovalent hydrogen bonding. Researchers have not extensively studied the cocrystallization of APX. However, Zhang *et al*. [26] reported that cocrystals of a 1:1 molar ratio of APX and quercetin enhanced the solubility of both APX and quercetin; hence, their oral bioavailability. Asati *et al*. [27] prepared the drug as a mesoporous nanomatrix, which increased the solubility of APX by approximately seven times. Conversely, Lee *et al*. [28] enhanced the solubility of APX through solid dispersion, utilizing Soluplus as a polymer. Salman et al. [29] also controlled how well APX dissolved by making it a complex with hydroxyl propyl beta cyclodextrin in a 1:1 w/w rate. Therefore, the current study aimed to create pharmaceutical cocrystals of APX using various coformers such as citric acid, oxalic acid, succinic acid, urea, and ascorbic acid, while also evaluating these coformers to improve the drug's solubility.

METHODS

Materials

APX (form N-1) was purchased from HEC Pharmaceutical Co., Ltd. Citric acid was purchased from Lobachemi, India. Anhydrous oxalic acid was provided by Aladdin Industrial Corporation. Succinic acid, urea, and ascorbic acid were purchased from Sigma-Aldrich. All other reagents and chemicals were of analytical grade and were provided by SD Fine Chemicals Mumbai, India. Distilled water was used to prepare all aqueous solutions.

Preparation of apixaban cocrystals

Using the solvent evaporation method (Table 1), a group of cocrystals were made by mixing a known amount of Apixaban with one of five coformers (citric acid, oxalic acid, succinic acid, urea, or ascorbic acid) in 15 mL of water/methanol (1:1). The obtained solution was sonicated for 1 h at room temperature and allowed to stand for 7 days at ambient temperature (25°C). White precipitated crystals were dried overnight at room temperature [30,31]. Table 1 shows the composition of numerous APX cocrystal formulations in molar and weight ratios.

Saturation solubility study

The equilibrium solubility of pure APX and APX-cocrystals was measured using the rotary shaker method. Samples were made by dissolving an additional amount of APX or cocrystals in 10 mL of water in 15 mL glass vials. The vials were shaken using a rotary shaker for 72 hours at 37°C. After 72 hours, samples were filtered using a Millipore® filter (0.45 µm) and diluted in distilled water. The diluted samples were measured using a UV spectrophotometer at a maximum absorbance wavelength of 278 nm [32,33].

Table 1: Composition of prepared apixaban cocrystals

Formula No.	APX (mg)	Molar ratio	Weight ratio	Citric acid (mg)	Oxalic acid (mg)	Succinic acid (mg)	Urea (mg)	Ascorbic acid (mg)
F1	100	1:0.425	-	42.5	-	-	-	-
F2	100	1:0.200	-	-	20	-	-	-
F3	100	1:0.260	-	-	-	26	-	-
F4	100	1:0.132	-	-	-	-	13.2	-
F5	100	1:0.382	-	-	-	-	-	38.5
F6	100	-	1:1	100	-	-	-	-
F7	100	-	1:1	-	100	-	-	-
F8	100	-	1:1	-	-	100	-	-
F9	100	-	1:1	-	-	-	100	-
F10	100	-	1:1	-	-	-	-	100
F11	100	-	1:2	200	-	-	-	-
F12	100	-	1:2	-	200	-	-	-
F13	100	-	1:2	-	-	200	-	-
F14	100	-	1:2	-	-	-	200	-
F15	100	-	1:2	-	-	-	-	200

In vitro dissolution studies

Three sets of dissolution tests were performed on each of the three produced formulae with USP-II dissolution equipment (a paddle) in 900 mL of 6.8 phosphate buffer (0.05% SLS). The stirrer was set to spin at 75 rpm and the medium temperature was maintained at 37±0.5 ºC for the test [34]. We took a 5 mL aliquot of the media on a regular basis and replaced it with new medium. The samples were examined spectrophotometrically at 280 nm with a UV spectrophotometer and an apixaban calibration curve in buffer.

FTIR Study

This analysis is useful to inspect the stoichiometry of APX and coformers in the cocrystals. The Fourier Transform Infrared Spectrum of pure APX and APX cocrystals was recorded in the 4000-400 cm^{-1} region with a resolution of 4 cm^{-1} using KBr pellets and a Shimadzu IR Spectroscopy [35].

Differential scanning calorimetry thermogram

A DSC thermogram of pure APX and APX-cocrystals was conducted to find out the thermal behavior of APX alone and that of cocrystals. This study is carried out using Mettler Toledo DSC 822e Module. The thermogram was produced in the temperature range from 0 ºC to 300 ºC at a heating rate of 5 ºC/min under a nitrogen gas stream. Samples were put in an aluminum pan, and a similar empty pan was utilized as a reference [36].

Powder X-ray diffraction pattern study

X-ray diffraction analysis was employed to investigate the crystallinity of the drug in cocrystals. Pure APX and the white powder resulting from the APX-cocrystal synthesis of all formulas were examined by X-ray analysis using a Bruker D8 Advance Diffractometer (Bruker, Bremen, Germany), which was used to get the diffraction patterns. The apparatus was equipped with silicon sample holders and a fine-focus X-ray tube that operates at 40 kV and 30 mA. Each sample was put onto a goniometer head that was powered to allow rotation of the sample during the gaining of information. Diffraction pattern results of cocrystals were compared to the diffraction patterns of pure APX [36].

RESULT

When APX is mixed with oxalic acid in a 1:1 w/w ratio, it dissolves much more easily than when it is mixed with water alone. Figure 2 revealed the dissolution of the selected formula (F7) and the pure drug. It dissolves 2.54 times more easily. Pure APX showed an equilibrium solubility of 23.6 µg/mL in water at 37 °C after 72 hours. We found that the APX-oxalic acid cocrystal that was made by slowly evaporating in a 1:1 w/w ratio could dissolve in 60 µg/mL of water.

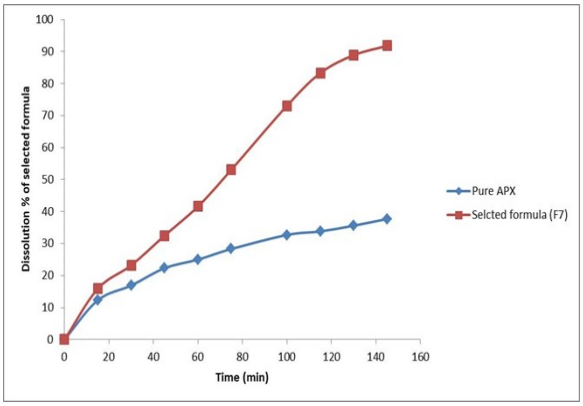

Figure 2: In-vitro release profile of formula 7 (APX-oxalic acid) compared with pure APX.

Also, the solubility of APX-cocrystals was improved with all prepared APX-cocrystals as shown in Table 2. It was clear that the FTIR spectrum of pure APX (Figure 3a) showed the primary amide at 3484.74 and 3312.14 cm^{-3} (N-H stretching absorption peak) and the lactam and the primary amide at 1661.62, 1629.55, and 1594.84 cm^{-3} (C=O stretching). Figure 3C displays the spectrum of oxalic cocrystals, revealing N-H stretches of

approximately 3439.42 and C=O stretches at 1742.37, 1665.23, and 1626.66, respectively.

Table 2: Solubility Results of Prepared Apixaban Cocrystals

Formula No.	Ratio type	Apixaban conformer ratio	Solubility (µg/mL)
F1	Stoichiometric	1:0.425	29.7
F2	Stoichiometric	1:0.200	36.0
F3	Stoichiometric	1:0.260	33.0
F4	Stoichiometric	1:0.132	37.0
F5	Stoichiometric	1:0.382	35.0
F6	Weight by weight	1:1	40.0
F7	Weight by weight	1:1	60.0
F8	Weight by weight	1:1	38.5
F9	Weight by weight	1:1	55.0
F10	Weight by weight	1:1	42.5
F11	Weight by weight	1:2	45.0
F12	Weight by weight	1:2	48.0
F13	Weight by weight	1:2	44.0
F14	Weight by weight	1:2	54.6
F15	Weight by weight	1:2	56.0
Pure drug	-	-	23.6

Also, the spectra of the ascorbic cocrystal and the urea cocrystal (Figures 3B and 3D) showed only small changes and wider peaks. This could be because the hydrogen bonds were stretching. It's clear that hydrogen bonding between molecules in APX cocrystals doesn't change the stretching frequencies of N-H and C=O in a meaningful way [37].

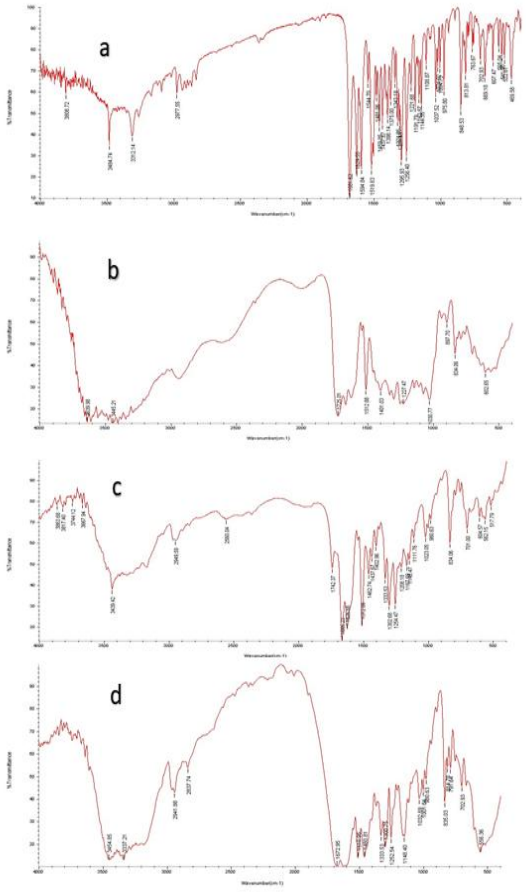

Figure 3: FTIR spectrum of (a) pure APX, (b) APX: ascorbic (c), APX: oxalic (d) APX: urea.

Figures 4a-d display the thermograms of pure APX, APX-oxalic acid, APX-urea, and APX-ascorbic acid cocrystals from the DSC analysis. The pure drug presented a characteristic endothermic sharp peak at 239.61 ºC, consistent with its melting point. However, the melting points corresponding to cocrystallization were as follows: apx-oxalic acid cocrystal (88.2 ºC), apx-urea (133.82 ºC), and apx-ascorbic acid (128.11 ºC).

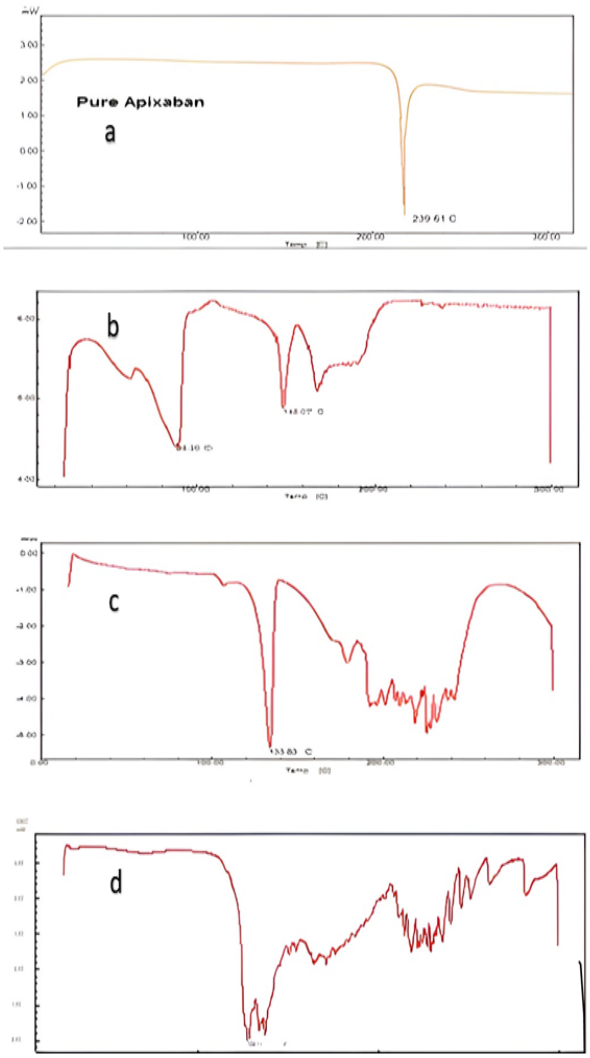

Figure 4: DSC thermograms of: (a) Pure apx (b) apx: oxalic acid (c) apx: urea (d) apx: ascorbic acid.

Figure 5 displays the PXRD diffractogram of pure APX, APX-oxalic acid cocrystals, and APX-urea cocrystals. The diffraction patterns for APX showed intense and sharp peaks at a 2θ value of 18, demonstrating the crystalline nature of APX as shown in Figure 5a. The peaks in the diffractogram of APX-urea cocrystals did not match those in the pattern for the pure drug. This is because new peaks showed up at different values (11.5, 15, 19, 26, and 29), and the peak that was there in pure APX went away. This may mean that APX and urea

interact. Also, the diffraction peak for APX-oxalic cocrystals was obtained at a 2θ value of 22.

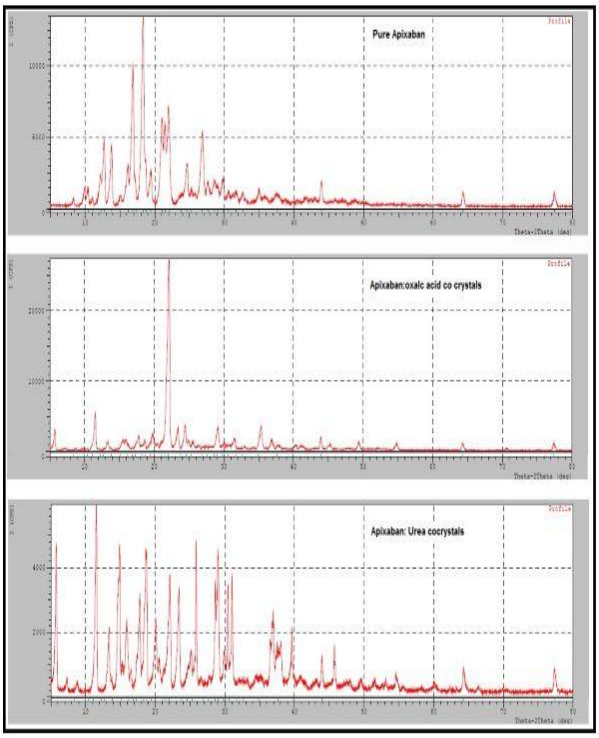

Figure 5: XRD patterns of pure Apixaban, Apixabn: Oxalic acid, Apixaban: urea

DISCUSSION

In the pharmaceutical industry, the apparent solubility and dissolution rate of APIs are crucial since greater apparent solubility may correspond to increased solubility-limited bioavailability. The primary benefit of cocrystal is that it improves a drug's solubility and dissolution without changing its chemical structure. In table 2, you can see that all the APX-cocrystal formulas made the drug more soluble. There were also significant differences ($p< 0.05$) between the pure drug and all the formulas. The rate of drug dissolution directly influences the aspects of bioavailability and drug delivery. In comparison to the pure drug, all the prepared formulations exhibited different release patterns with a similarity factor ($f2 < 50$). Dissolution of the selected formula (F7) can be related to the dissociation of hydrogen bonds between APX and coformers upon mixing with water that drew the coformer molecules out of the crystal lattice. Thus, the API molecules supersaturate in the surrounding aqueous solution, forming a metastable state with high energy that enhances its solubility [38]. Coformers elongate the metastable time, forming a parachute characterized by a high-energy, soluble, and stable form of the drug [38]. Succinic acid, oxalic acid, and citric acid are carboxylic acid-based coformers that possess a significant number of hydrogen-bond donors and acceptors, an essential component of cocrystal formation [39]. F7 made with oxalic acid coformer in a weight ratio of 1:100 had the best solubility. This might be because oxalic acid has a smaller molar mass than succinic acid and citric acid, which are other types of carboxylic acid–based coformers. Conversely, the structure of oxalic acid accounts for its superiority over urea and ascorbic acid. The two carboxylic acid groups in oxalic acid serve as excellent donors and acceptors of hydrogen bonds. This enhances the formation of robust hydrogen-bonding networks with active pharmaceutical ingredients. It's also important to note that the functional groups in oxalic acid often form strong supramolecular synthons (for example, O-H···O=C), which are needed for cocrystal stability and reproducibility [40]. Even though urea has two amine groups that can be bonded hydrogen, its flat shape and small number of bonding sites may make its interactions weaker or less frequent than oxalic acid's two carboxylic groups [40]. Despite its potential for hydrogen bonding through hydroxyl and carbonyl groups, the bulkier structure and steric hindrance of ascorbic acid can limit its effectiveness as a coformer in certain systems [41]. FTIR investigation was conducted to inspect potential chemical interaction between APX and coformers. Hence, the results of this study showed that there was no interaction between APX and coformer. Chen et al. reported similar results [35]. Other drugs, like piroxicam, exhibited similar changes in the FIIR spectra and were regarded as indicators of co-crystallization [36]. Changes in the C=O stretching frequency of the main amide and the lactam and N−H stretching frequencies show that the hydrogen bonding contacts around these functional groups in the APX-oxa cocrystal have moved. We conducted DSC analysis to investigate the crystalline and thermal properties of APX before and after cocrystallization. The melting point of cocrystals showed considerable transformation in comparison to pure APX (239.61ºC), as shown in Figure 4 (a-d). Ascorbic and oxalic acid cocrystals showed no thermal sharp peaks, likely due to the drug's dispersion within the mixture. Conversely, the DSC results suggest a molecular interaction between APX and coformers [41]. Moreover, the DSC analysis of cocrystals failed to identify the peak resulting from coformer fusion, indicating that cocrystal formation has been approved. The DSC analytical approach could immediately detect the APX-co-crystal, a result of the physical mixing of APX and coformers undergoing direct thermal modifications. These thermograms are in good agreement with data published earlier [35,36,42]. The PXRD was used to identify the crystalline phase purity of APX and the formation of the new crystalline phase APX-cocrystal (Figure 5). The outcome indicates the creation of a new crystalline phase, as the cocrystal pattern differs from that of pure APX. Thus, these results confirmed the formation of cocrystals. Previous investigations reported similar PXRD patterns [32]. Madan *et al.* also prepared APX as cocrystals, using caffeine as a coformer. The results revealed that the

synthesized APX-caffeine cocrystals had higher solubility and permeability than pure APX. The in vivo pharmacokinetic study demonstrated a more than threefold enhancement in the mean area under the curve of the synthesized APX cocrystal compared to the pure APX [43]. Chen *et al*. prepared Apixaban−Oxalic Acid Cocrystal Hydrate (APX-oxa-H2O, in a molar ratio of 4:3:0.5) [35]. The solubility of the cocrystal in 0.1 M HCl (pH 1.0) and phosphate buffer of pH 6.8 was evaluated, and the results show the solubility values of the cocrystal are approximately 2.2 and 2.1 times as large as those of apixaban form N-1 (the marketed product), respectively. The results of this study align with those of the two previously mentioned studies suggest the possibility of successfully preparing apixaban in this manner. In addition, the improvement of solubility in our study is higher than in previous studies, and the method of work is simpler with safer and cheaper excipients without need to filtration. Therefore, the method used in this study can be adopted to prepare APX on a wide scale with enhanced solubility and dissolution that can positively affect bioavailability.

Conclusion

Cocrystallization of apixaban (APX) with other coformers has been investigated as an approach for improving its physicochemical properties, particularly solubility. The chosen formula (1:1 cocrystal of APX with oxalic acid) can increase the solubility of APX in water by up to 2.54 times compared to pure APX.

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Conflict of interests

No conflict of interest was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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