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DICLOFENAC POTASSIUM AND ISONICOTINAMIDE COCRYSTALS FOR ENHANCED SOLUBILITY: IN VITRO EVALUATION OF HARD GELATIN CAPSULES

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Abstract: Diclofenac potassium (DIC-K), classified as a Biopharmaceutics Classification System (BCS) Class II drug, exhibits low solubility and high permeability. It is a widely used non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic, and analgesic effects. This study aimed to enhance the solubility of DIC-K by preparing cocrystals with isonicotinamide (INA) as a coformer and to evaluate their in vitro performance. The prepared DIC-K+INA cocrystals were characterized using powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). Solubility studies were conducted for pure DIC-K and DIC-K+INA cocrystals in different media (0.1 N HCl, pH 1.2; phosphate buffer (PB), pH 4.5; and PB, pH 6.8). Hard gelatin capsules containing either pure DIC-K or DIC-K+INA cocrystals were formulated using the dry granulation method, and their dissolution profiles were evaluated in PB (pH 6.8). At 15 min, the amount of DIC-K dissolved from the pure DIC-K capsules was 72%, whereas that from the DIC-K+INA cocrystal capsules reached 92%. PXRD, FTIR, and DSC analyses supported the formation of a new crystalline phase, indicating successful cocrystal formation between DIC-K and INA. Overall, DIC-K+INA cocrystals enhanced the solubility and dissolution performance of DIC-K, demonstrating the potential of cocrystallization as a formulation strategy for poorly soluble drugs.

Keywords: Diclofenac potassium, Isonicotinamide, Cocrystal, Solubility enhancement, Capsule

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1. Introduction

In the development of solid dosage forms, factors such as particle size, solubility, and stability play crucial roles in determining the therapeutic effectiveness of active pharmaceutical ingredients (APIs). Poor aqueous solubility and low bioavailability remain major challenges, particularly for Biopharmaceutics Classification System (BCS) Class II drugs, which are characterized by high permeability but low solubility (Rodrigues et al., 2018; Yadav et al., 2009; Guo et al., 2021). To address these limitations, various solid-state modification strategies such as salt formation, polymorphism, and pharmaceutical cocrystallization have been employed (Yadav et al., 2009; Rodrigues et al., 2018).

Pharmaceutical cocrystals are multicomponent crystalline systems composed of an API and a neutral coformer in a defined stoichiometric ratio, held together through non-covalent intermolecular interactions such as hydrogen bonding, π–π stacking, halogen bonding, or van der Waals forces (European Medicines Agency, 2015; U.S. Food and Drug Administration, 2018). Unlike conventional salts, cocrystals are generally formed without proton transfer between the API and the coformer. This approach enables modification of physicochemical properties without altering the chemical structure or pharmacological activity of the API (U.S. Food and Drug Administration, 2018). Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) recognize pharmaceutical

cocrystals as valuable solid-state forms with the potential to improve properties such as solubility, stability, manufacturability, and bioavailability (European Medicines Agency, 2015; U.S. Food and Drug Administration, 2018; Yuliandra et al., 2018). Diclofenac (DIC) is a non-steroidal anti-inflammatory drug (NSAID) widely used for its analgesic, antipyretic, and anti-inflammatory properties. It is a phenylacetic acid derivative formulated in various salt forms, most commonly as sodium and potassium salts. Among these, diclofenac potassium (DIC-K) is classified as a Biopharmaceutics Classification System (BCS) Class II drug, characterized by high permeability and poor aqueous solubility (Báthori et al., 2011; Rolfe, 2014). Therefore, improving the solubility and dissolution behavior of DIC-K represents an important formulation strategy for optimizing its biopharmaceutical performance.

Isonicotinamide (INA), a constitutional isomer of nicotinamide, is a commonly used coformer in pharmaceutical cocrystal studies. Its pyridyl nitrogen and amide groups provide complementary hydrogen-bonding sites that can participate in intermolecular interactions with suitable functional groups of APIs (Báthori et al., 2011). Although diclofenac potassium exists in a salt form, its carboxylate group can participate in intermolecular interactions with INA, favoring the formation of a stable multicomponent crystalline system. In addition to this molecular complementarity, INA has been employed in pharmaceutical cocrystal engineering to modify the physicochemical properties of drug substances (Báthori et al., 2011; Karakthala et al., 2023). Therefore, its favorable intermolecular interaction potential and established use as a pharmaceutical coformer provided the rationale for selecting INA for the development of DIC-K cocrystals.

Importantly, the distinction between salts, cocrystals, and ionic cocrystals should be considered. In salts, proton transfer occurs between an ionizable API and a counterion, whereas in cocrystals, the components interact through non-ionic supramolecular interactions without proton transfer. Ionic cocrystals (also referred to as salt cocrystals) represent a distinct category in which at least one component is present in an ionic form, such as a salt, and participates in additional supramolecular interactions with a neutral coformer (Nugrahani et al., 2020). Accordingly, the DIC-K+INA system can be described as an ionic cocrystal, in which ionic and non-ionic interactions coexist within the same crystalline lattice, potentially contributing to improved solubility and dissolution characteristics (Nugrahani et al., 2020). In this study, DIC-K+INA ionic cocrystals were prepared with the aim of improving the solubility and dissolution behavior of DIC-K. The resulting solid phase was characterized by PXRD, FTIR, and DSC, and its solubility was evaluated at different pH conditions. Furthermore, the DIC-K+INA ionic cocrystals were incorporated into hard gelatin capsules, and their in vitro dissolution performance was compared with that of capsules containing pure DIC-K.

2. Materials and Methods

2.1. Materials

DIC-K and INA were purchased from Sigma (USA). Methanol was obtained from Merck (Germany). All materials used in this study were analytical grade.

2.2. Methods

2.2.1. Development of HPLC method

High-performance liquid chromatography (HPLC) analysis was performed using a Shimadzu Nexera 2 system (Japan) equipped with a solvent delivery unit, injection valve, and diode-array detector (DAD/PDA). Chromatographic separation was achieved using a C18 analytical column (4.6 × 250 mm, 5 µm; GL Sciences). The mobile phase consisted of 50 mM phosphate buffer (pH 2.5) and methanol at a ratio of 30:70 (v/v), delivered at a flow rate of 1.0 mL/min. The injection volume was 10 µL. Detection was performed at 280 nm for DIC-K and 210 nm for INA (Rubim et al., 2013; Panda et al., 2012; Alquadeib, 2019). A stock solution of DIC-K (100 µg/mL) was prepared in methanol and subsequently diluted with the mobile phase to obtain calibration standards over the concentration range of 2.5–40 µg/mL. An INA stock solution (100 µg/mL) was prepared in the same manner, and calibration standards were prepared over the same concentration range.

2.2.2. Validation of the HPLC method

The HPLC method was validated in terms of linearity, selectivity, limit of detection (LOD), limit of quantification (LOQ), accuracy, precision, and stability (International Council for Harmonisation, 2005; Shabir, 2003). Selectivity was evaluated by analyzing the mobile phase and blank formulation (capsule formulation without the active ingredient) under the same chromatographic conditions to assess the presence of potential interfering peaks. Precision was evaluated in terms of repeatability and reproducibility at three concentration levels (5, 15, and 30 µg/mL) for both DIC-K and INA, and the results were expressed as relative standard deviation (%RSD). Accuracy was assessed at three concentration levels (5, 15, and 30 µg/mL) within the calibration range for both DIC-K and INA. Intra-day accuracy was evaluated by analyzing each concentration six times within a single day, whereas inter-day accuracy was evaluated over six consecutive days, and the results were expressed as %RSD. Stability was evaluated only for DIC-K. Samples at concentrations of 15 and 30 µg/mL were either exposed to or protected from daylight for 8 h at room temperature and subsequently analyzed by HPLC. The results were compared with the initial concentrations to evaluate the photostability of DIC-K.

2.2.3. Preparation of DIC-K+INA cocrystals

DIC-K+INA cocrystals were prepared using the solvent evaporation method at a DIC-K:INA stoichiometric molar ratio of 1:1. DIC-K and INA were initially mixed and ground using a mortar and pestle. Methanol was added

dropwise, and the mixture was continuously ground for approximately 15 min until dry (Shabir, 2003; International Council for Harmonisation, 2005; Panda et al., 2012; Rubim et al., 2013; Nugrahani et al., 2018; Alquadeib, 2019; Nugrahani et al., 2020). The resulting mixture was then dissolved in a sufficient amount of methanol, and the solvent was evaporated to approximately half of its initial volume using a rotary evaporator. The remaining solvent was allowed to evaporate at room temperature for 24 h to obtain the DIC-K+INA cocrystals.

2.2.4. Determination of DIC-K and INA contents of the prepared cocrystals by HPLC

To prepare the stock solution (200 µg/mL), 5 mg of cocrystals were dissolved in methanol and the volume was completed to 25 mL with methanol (in volumetric flask). 125 µL of the prepared stock solution was taken and diluted to 1000 µL with mobile phase and analyzed by HPLC to determine the amounts of DIC-K and INA in the cocrystal.

2.2.5. Solubility study

Solubility studies were conducted to select an appropriate medium for the subsequent dissolution experiments. The solubility of pure DIC-K and DIC-K+INA cocrystals was evaluated in three different media: 0.1 N HCl (pH 1.2), phosphate buffer (PB, pH 4.5), and phosphate buffer (PB, pH 6.8). The samples were maintained in a horizontal shaker at 37 °C for 24 h to allow equilibration. Following the incubation period, the samples were filtered through a 0.45 µm membrane filter and analyzed using the validated HPLC method to determine the DIC-K concentration. The obtained solubility data were used to select the dissolution medium for the comparative in vitro dissolution studies.

2.2.6. FT-IR analysis

FT-IR spectra of pure DIC-K, INA and the prepared cocrystal were recorded (in the range of 4000-400 cm^{-1}) on a Jasco, FT/IR-6700 spectrophotometer using KBr disks containing 1% of the substance.

2.2.7. DSC analysis

DSC analyzes of pure DIC-K, INA and the prepared cocrystal was performed using a Mettler Toledo DSC3 differential scanning calorimeter. Samples placed in *aluminum* pans were heated at 20°C/min from 25 to 600 °C under nitrogen atmosphere and DSC thermograms were taken (Karakthala et al., 2023).

2.2.8. PXRD analysis

PXRD data were recorded at room temperature on an Empyrean Multi-Purposed diffractometer using Cu Kα1 (λ = 1.5406 Å) and Cu Kα2 radiation (λ = 1.544426 Å), 45 kV voltage and a current of 40 mA. The samples were scanned from 10˚ to 60˚ (2θ) at a step size of 0.013˚ counting time of 74 s per step.

2.2.9. Hard capsule formulation

Microcrystalline cellulose and lactose were preferred as diluents in the formulation. Sodium starch glycolate was used as a disintegrant and colloidal silicon dioxide and magnesium stearate were used as lubricants. The selected excipients are the most preferred excipients in solid dosage forms (Table 1). Granules were prepared using the dry granulation method (mechanical compression/slugging method) to improve powder flow properties. First of all, the excipients (lactose, mycrystalline cellulose, sodium starch glycolate) and pure DIC-K or DIC-K+INA cocrystals were mixed and pressed into tablets on a conventional tablet press. Then, the tablets were milled into granules and sieved using a #10 sieve. The final granules were blended with colloidal silicon dioxide and magnesium stearate and evaluated its flow properties before filling into hard gelatine capsules (Capsule number 1). 80 mg cocrystal was added to the DIC-K+INA formulation, equivalent to 50 mg diclofenac potassium.

Table 1. Capsules' formulation

Ingredients	mg/DIC-K capsule	mg/DIC-K+INA capsule
DIC-K	50	-
DIC-K+INA cocrystals	-	80*
Microcrystalline cellulose	150	120
Lactose	82	82
Sodium starch glycolate	6	6
Colloidal silicon dioxide	9	9
Magnesium stearate	3	3

DIC-K-capsule= pure DIC-K-containing capsule, DIC-K+INA–capsule= DIC-K+INA cocrystals-containing capsule, *Equivalent to 50 mg DICK.

2.2.10. Flow properties

For granular filling mixture, angle of repose, flow time, bulk density, tapped density, compressibility index (equation 1) and Hausner ratio (equation 2) was determined.

Compressibility index=100 (tapped density-bulk density)/tapped density) (1)

Hausner ratio= Tapped density/bulk density (2)

2.2.11. The characterization of hard capsules containing DIC-K or DIC-K+INA cocrystals

After granular mixture filling into capsules, average capsule weight and disintegration time were determined and dissolution studies were carried out. The capsules were tested for disintegration time based on recommendations by USP 43 general chapter <701Disintegration> (United States Pharmacopeia, 2019a).

Moreover, the capsules were tested for dissolution based on recommendations by USP 43 general chapter <711> (United States Pharmacopeia, 2019b) and according to FDA dissolution study data (U.S. Food and Drug

Administration, 2016). This study was performed in a 6vessel USP dissolution apparatus Type I (Basket; Pharma Test Dissolution Testing Instrument, Germany). The dissolution medium was chosen based on the solubility study. The prepared capsules were immersed in 900 mL of PB pH 6.8 at 50 rpm stirring speed, and the temperature was 37±0.5°C. During the study, 1 mL of sample was withdrawn from the medium at 5, 10, 15, 20, 30, 45, and 60 min and and was replaced with the same volume of fresh dissolution medium. The samples were filtered (0.45 µm hydrophilic politetrafluoroethylene membrane filter) and analyzed by HPLC.

3. Results

We developed an isocratic HPLC method for analyzing DIC-K in solubility and dissolution studies and the DIC-K and INA contents of the prepared cocrystals. In addition, we validated this method at some parameters (linearity, accuracy, precision, selectivity, LOD, and LOQ). The capacity of an analytical technique to identify and measure the analyte in the presence of other sample constituents is known as selectivity. The chromatograms of mobile phase and blank formulation (the capsule formulation without active ingredient) were obtained (Figure 1). Figure 1 verified the given method's selectivity. We performed DIC-K and INA analyses at 280 nm and 210 nm, respectively, given in the method section. The and INA (at concentrations of 2.5, 15, 25, 40 µg/mL) are retention time values of DIC-K and INA were about 13.5 presented in Figure 2 and 3. The calibration equation, R2, and 3.2 min, respectively. The chromatograms of DIC-K (at LOD and LOQ values are presented in Table 2. The semantic model was formally developed with the architecture to be a deeply semantically rich knowledge graph for the entire physical and chemical lifecycle of coffee. The development lifecycle followed very closely the accepted ontological engineering methodologies which specify a very iterative lifecycle of initial domain analysis, integration of existing ontologies, extraction of expert terminology, rigorous definition of the class hierarchy, mapping of object properties and formulation of logical constraints. The ontology was built using the Web Ontology Language (OWL) within the Protégé computational environment and strictly adhering to the standards of the World Wide Web Consortium.

The primary existential entities in the coffee domain constitute the taxonomic backbone of the ontology. This gave rise to a deep and strongly structured hierarchical tree, which explicitly separated botanical living entities, physical states of the agricultural product, highly mechanized industrial processes, and subjective human sensory evaluations. The main ontological super-classes are defined with their respective hierarchical descendants as shown in Table 1.

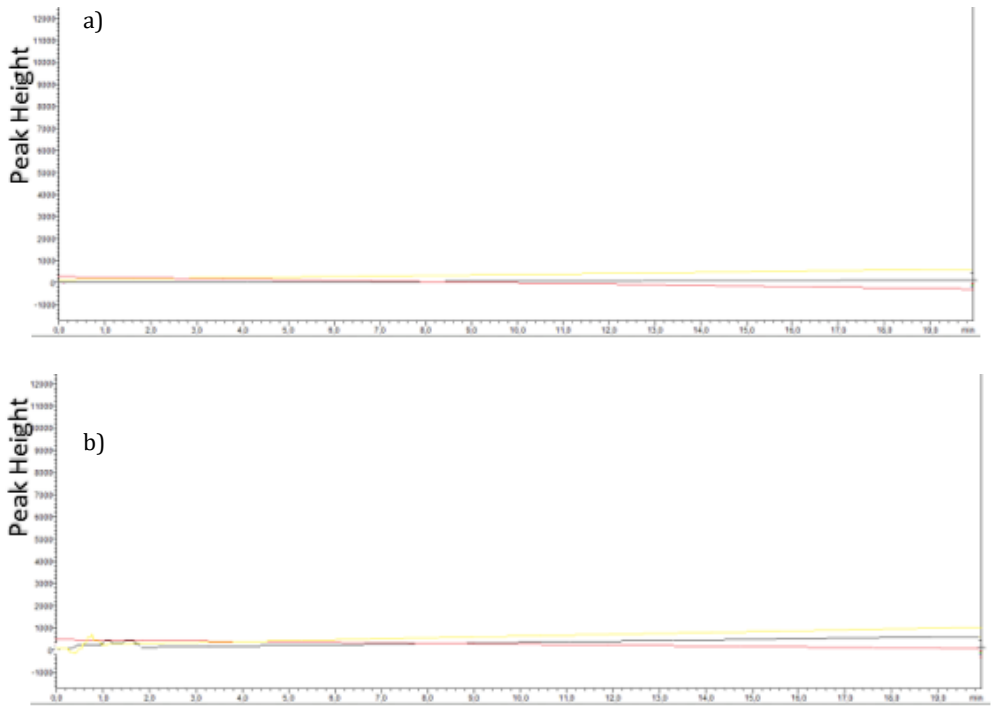

Figure 1. The chromatograms of mobile phase (a) and blank formulation (b).

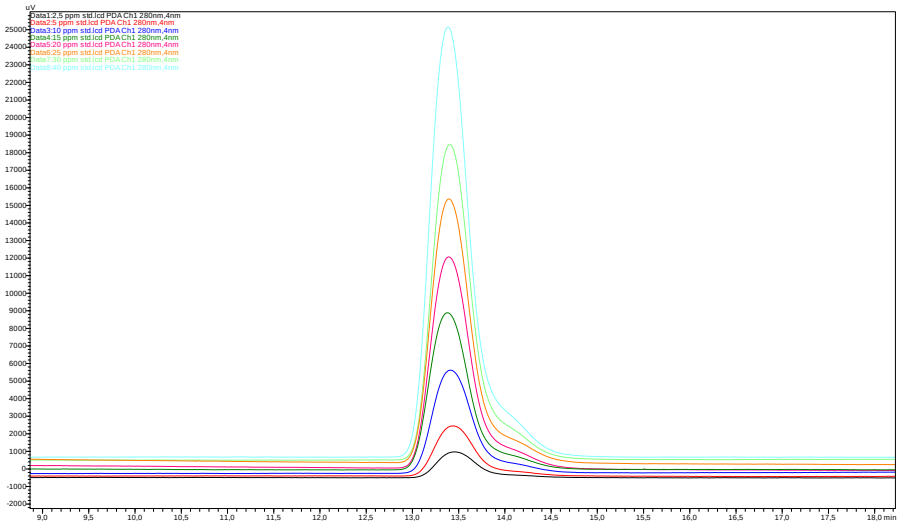

Figure 2. HPLC chromatograms of DIC-K (2.5-40 µg/mL).

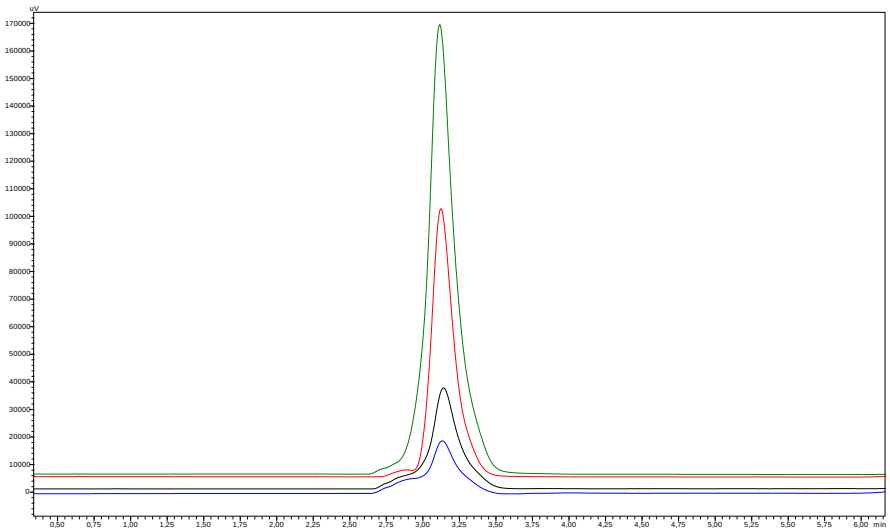

Figure 3. HPLC chromatograms of INA (2.5, 15, 25, 40 µg/mL).

Table 2. The calibration equation, R^2, LOD and LOQ values

	DIC-K	INA
Calibration equation	y=19370x-3701.4	y=12744x-2433
R^2	0.9999	0.9999
Linearity Range (µg/mL)	2.5-40	2.5-40
LOQ (µg/mL)	2.44	2.48
LOD (µg/mL)	0.85	0.89

R2 (determination coefficient) values determined for DIC and INA being close to 1 indicates adequate method linearity (Table 2). The accuracy of the method was determined at three different concentrations (5, 15, and 30 µg/mL), and the results were expressed as the percentage of difference between the added and measured concentrations (Table 3). %RSD values which is less than 2% was taken as an indication of sufficient intra- and inter-day accuracy of the developed method (Table 3). Furthermore, %RSD values calculated for repeatability and reproducibility studies were less than 2%, indicating that the method works with the required precision (Table 4). For photostability of the samples (at concentrations of 15 and 30 µg/mL for DIC-K) exposed or not exposed to daylight (8 h) at room temperature were evaluated. The calculated % recovery values showed that DIC-K was photostable during the whole analytical procedure (Table 5). Furthermore, all standard solutions were prepared fresh daily for HPLC analysis.

3.1. Determination of DIC-K and INA Contents of the Prepared Cocrystals by HPLC

Since 5 mg DIC-K+INA cocrystal was found to contain 3.125±0.02 mg (n=3) DIC-K, 1.256±0.12 mg (n=3) INA and the DIC-K+INA capsule formulation contains 80 mg DICK+INA cocrystal equivalent to 50 mg DIC-K.

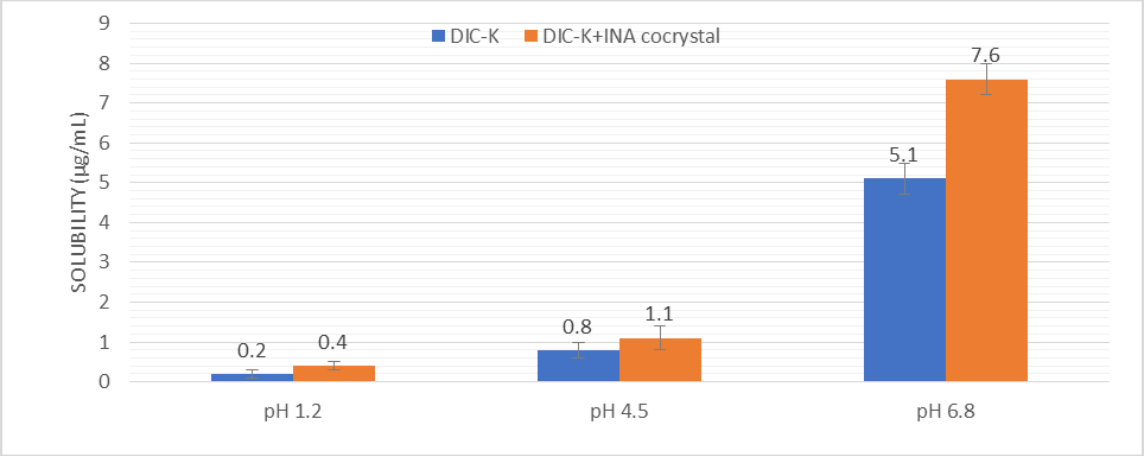

Figure 4. DIC-K and DIC-K+INA cocrystal's solubilities at media with different pH.

Table 3. The obtained results for intra- and inter-day accuracy

Added Concentration (5, 15, 30 µg/mL)		Measured Concentration (µg/mL) (DIC-K/INA)			Percentage (%)		
	Intra-day	5.00/5.05	15.04/15.00	30.03/30.01	100.00/ 101.00	100.27/ 100.00	100.10/ 100.03
		5.04/5.04	15.03/15.00	30.00/30.00	100,80/ 100.80	100.20/ 100.00	100.00/ 100.00
		4.98/5.02	15.05/15.02	3.05/30.02	99.60/ 100.40	100.33/ 100.13	100.17/ 100.07
		5.03/5.03	14.96/15.01	30.00/30.01	100.60/ 100.60	99.73/ 100.07	100.00/ 100.03
		5.05/4.98	15.04/15.05	30.01/30.00	101.00/ 99.60	100.27/ 100.33	100.03/ 100.00
		5.08/5.05	15.05/14.98	30.02/30.01	101.60/ 101.00	100.33/ 99.87	100.07/ 100.03
Mean		5.03/5.03	15.03/15.01	30.02/30.01	100.60/ 100.57	100.19/ 100.07	100.06/ 100.03
SD		0.04/0.02	0.03/0.02	0.02/0.01	0.72/0.53	0.23/0.16	0.07/0.03
RSD(%)		0.71/0.52	0.23/0.16	0.06/0.03	0.71/0.52	0.23/0.16	0.07/0.03
	Inter-day	5.10/5.05	14.91/15.18	30.11/30.12	102.00/ 100.40	99.40/ 101.20	100.37/ 100.40
		5.05/4.92	14.85/15.05	30.16/30.21	101.00/ 100.70	99.00/ 100.33	100.53/ 100.70
		4.95/4.94	15.12/15.11	29.89/30.13	99.00/ 100.43	100.80/ 100.73	99.63/ 100.43
		5.11/5.10	15.02/15.10	29.87/30.12	102.20/ 100.40	100.13/ 100.67	99.57/ 100.40
		5.12/4.90	15.09/14.80	29.88/30.20	102.40/ 100.67	100.60/ 98.67	99.60/ 100.67
		4.90/5.11	15.18/15.15	29.86/30.21	98.00/ 100.70	101.20/ 101.00	99.53/ 100.70
Mean		5.04/5.00	15.03/15.07	29.96/30.18	100.77/ 100.55	100.19/ 100.43	99.87/ 100.55
SD		0.09/0.09	0.13/0.13	0.14/0.04	1.85/0.15	0.85/0.91	0.45/0.15
RSD(%)		1.83/1.89	0.85/0.91	0.45/0.14	1.83/0.15	0.85/0.91	0.45/0.15

Table 4. Repeatability and reproducibility results

Sample Number	Repeatability			Reproducibility		
	Concentrations for DIC-K/INA (µg/mL)			Concentrations for DIC-K/INA (µg/mL)		
	5	15	30	5	15	30
1	5.50/5.12	15.48/15.11	30.01/30.02	5.50/5.13	15.51/15.23	30.09/30.09
2	5.50/5.23	15.48/15.21	29.98/30.11	5.50/5.12	14.93/15.12	30.91/30.09
3	5.48/5.22	15.51/14.98	29.78/30.05	5.23/5.23	15.38/15.14	29.86/30.11
4	5.46/5.13	15.49/15.05	29.98/30.08	5.46/5.22	15.58/15.16	29.82/30.12
5	5.51/5.14	15.50/15.07	30.05/29.98	5.52/5.20	15.53/15.07	29.94/30.05
6	5.52/5.12	15.52/15.07	30.00/30.04	5.46/5.10	15.01/15.01	30.76/30.06
Mean	5.50/5.16	15.50/15.08	29.97/30.05	5.45/5.17	15.32/15.12	30.23/30.09
SD	0.02/0.05	0.02/0.08	0.10/0.05	0.11/0.06	0.28/0.08	0.48/0.03
RSD (%)	0.39/0.98	0.11/0.50	0.32/0.15	1.98/1.09	1.84/0.50	1.59/0.09

SD= standard deviation, RSD= relative standard deviation.

Table 5. Photostability results for DIC-K

Time (h)	Added Concentration (µg/mL)	Protected from daylight		Not protected from daylight	
		Measured Concentration (µg/mL; n=6)	Recovery (%)	Measured Concentration (µg/mL; n=6)	Recovery (%)
0	15	15.00±0.01	103.2	15.50±0.01	99.74
8	15	15.48±0.02		15.46±0.01	
0	30	29.98±0.11	100	29.95±0.15	99.73
8	30	29.98±0.12		29.87±0.13	

3.2. Solubility Studies

The solubility studies for DIC-K and DIC-K+INA cocrystals were carried out at the media with different pH values (0.1 N HCl pH 1.2, PB pH 4.5, and PB pH 6.8). Figure 1 shows the results of the solubility studies. DIC-K is a Class II drug according to the biopharmaceutical classification system. This classification suggests that DIC-K may have challenges in dissolution and absorption in the body that may affect its therapeutic efficacy. Appropriate formulation strategies (such as increasing the solubility of DIC-K) are required to optimize the distribution and bioavailability of DIC-K. In our study, the solubility of DICK in pH 6.8 buffer was 5.1 µg/mL, while the solubility of DIC-K in pH 6.8 was 7.6 µg/mL after the cocrystallization process (Figure 4). According to the solubility data, there is an increase in DIC-K solubility after cocrystallization. The solubility studies have been a guide for dissolution studies. Since the solubility of DIC-K was pretty low in the media with pH 1.2 and pH 4.5, dissolution rate studies were carried out in the medium with pH 6.8 (Figure 4).

3.3. FT-IR Spectrum of Cocrystals

FT-IR spectra of DIC-K, INA and DIC-K+INA cocrytals are given in Figure 5a, 5b and 5c. In these spectra, characteristic peaks were analyzed. The INA molecule is a type of amide which is comprises of carbonyl and amino groups. According to FT-IR spectrum of INA, two N-H stretching bands are observed at 3361.11 cm^{-1} and 3177.28 cm^{-1} (medium band). The N-H stretching vibration usually observed in the region 3000-3500 cm^{-1}. Generally, carbonyl group vibrations occur in the region 1780-1680 cm^{-1}. The pyridine and its related compounds show a strong absorption band in the region 1600-1500 cm^{-1} due to C=N ring stretching vibration. In this study, the C=O stretching band (medium band) and C=N stretching band (medium band) are shown at the expected area between 1652.71-1549.44 cm^{-1} (Figure 5b). These findings are consistent with the reported values (Akalin et al., 2005).

Considering the FT-IR spectrum of DIC-K, secondary aromatic -NH- stretching band and -COOH stretching band are observed around 3245.17 cm^{-1} (weak band) and 3066 cm^{-1} (weak band). The C=O stretching band of carboxylic acid group is observed at 1577.79 cm^{-1} (very strong band) (Figure 5-a) (Palomo et al., 1999; Siozou et al., 2021). The C-Cl, -C-N-, -N-H bands at the fingerprint area was also seen.

FT-IR spectrum of DIC-K+INA cocrytals showed that differences of peak intensities were observed. Characteristic peaks belonging the compounds are seen

at 1682.5, 1576.18, 846.02 744.84 cm^{-1} that confirming the presence of both DIC-K and INA in the cocrystals (Figure 5-c).

3.4. DSC Analysis of Cocrystals

The DSC thermograms for DIC-K, INA, and the DIC-K-INA cocrystal are presented in Figures 6a–c. The DSC profile of DIC-K (Figure 6a) exhibits an exothermic peak at 323.56 °C and an endothermic peak at 318.78 °C. Literature data (Nugrahani et al., 2020) indicate that DIC-K melts near 300 °C (observed as a small endothermic peak), followed by decomposition at approximately 317 °C, as indicated by an exothermic peak. These results are consistent with the literature. For INA, the DSC thermogram (Figure 6b) shows three endothermic peaks at 133.21 °C, 157.85 °C, and 321.22 °C. The sharp endothermic peak at 157.85 °C corresponds to the melting point of INA, aligning well with previous findings in the literature (Jiaxuan et al., 2020).

The DSC thermogram of the DIC-K+INA cocrystal (Figure 6c) displays distinct exothermic and endothermic peaks, different from those observed for the individual components. These newly observed peaks may result from the melting or crystallization of the cocrystal, as well as the disappearance of peaks associated with the active substance and coformer melting. This behavior suggests an interaction between DIC-K and INA and supports the potential formation of a cocrystal during heating (Saganowska and Wesolowski, 2018).

Notably, the melting point of the cocrystal differs from that of the starting materials. It is well-documented that more than 50% of cocrystals have melting points lower than both their active substances and coformers. Additionally, variations in the melting point of cocrystals can be attributed to differences in the solvents used and the crystallization procedures employed (Garbacz et al., 2020).

3.5. PXRD Study

The PXRD pattern of pure DIC-K showed sharp and welldefined diffraction peaks corresponding to its crystalline structure, while INA exhibited a different set of reflections. In contrast, the DIC-K+INA cocrystal displayed a unique diffraction profile, characterized by the disappearance of certain peaks belonging to the parent compounds and the emergence of new ones. This clear difference from both pure DIC-K and INA demonstrates the formation of a novel crystal lattice rather than a simple physical mixture. When directly compared to DIC-K, the cocrystal pattern no longer resembles the original drug, further confirming the successful cocrystallization process with isonicotinamide. The PXRD pattern of the DIC-K, INA and DIC-K+INA cocrystal were shown in Figure 7-1a. Characteristic peaks at 14.34, 15.28, 16.45, 21.70, 25.22, 26.04, 26.88, and 27.80°, etc. 2θ values in the PXRD pattern of pure DIC-K were observed, which are consistent with the reported data for DIC-K (Han et al., 2017). The cocrystal product (Figure 7-1a and 1b) also presents the characteristic peak position of pure DIC-K which were slightly shifted towards 14.38, 15.32, 16.47, 21.72, 25.25,

26.08 26.90 and 27.83° 2θ values. It clearly shows that the 11.44, 18.46, 23.00, 24.27, 28.55 and 36.62 and 29.91° 2θ additional peaks of the cocrystal PXRD pattern are distinguishable from the pure DIC-K PXRD pattern, which indicates the formation of a new solid phase. Significant differences were observed between the PXRD patterns of the INA and cocrystal (Figure 7-1a). The PXRD pattern of cocrystal indicated severe preferred orientation of the crystallites with a with high intensity sharp peak at 23.0°, similarly which that observed for INA PXRD pattern at peak position 23.30° 2θ, consistent with the reported data for INA (Caira and Vicatos, 2019) and which also confirms the formation of the cocrystal. The PXRD pattern of the DIC-K+INA cocrystal revealed new diffraction peaks at different 2θ values, accompanied by the disappearance of characteristic reflections of the parent compounds. These changes confirm the generation of a distinct crystalline phase, providing strong evidence for successful cocrystallization.

Characterization of Capsule Formulations

The flow properties of the granular filling mixture were evaluated (after the addition of the lubricants). The obtained parameters are given in Table 6. The angle of repose values were found to be 29.30±0.78° (for the granular filling mixture-DIC-K capsule) and 27.10±0.64° (for the granular filling mixture-DIC-K+INA capsule) (Table 6). The angle of repose in the range of 25–30° indicates that the powder exhibits excellent flow properties (United States Pharmacopeia, 2019c).

Compressibility index and Hausner ratio are simple and fast methods to predict the flow properties of powder. These may predict powder flow properties as being affected by shape, size, surface area, cohesiveness and moisture content of powder, etc. Powders with compressibility index in the range of 11-15% and 16-20% show good and fair flow properties, respectively. In addition, the powders with Hausner ratio values in the range of 1.12-1.18 and 1.19-1.25 exhibit good and fair flow properties, respectively (United States Pharmacopeia, 2019d). According to the results, the content prepared for DIC-K+INA–capsule in our study has good flow properties (Table 6). The flow properties of granules prepared using cocrystals improved (from fair to good).

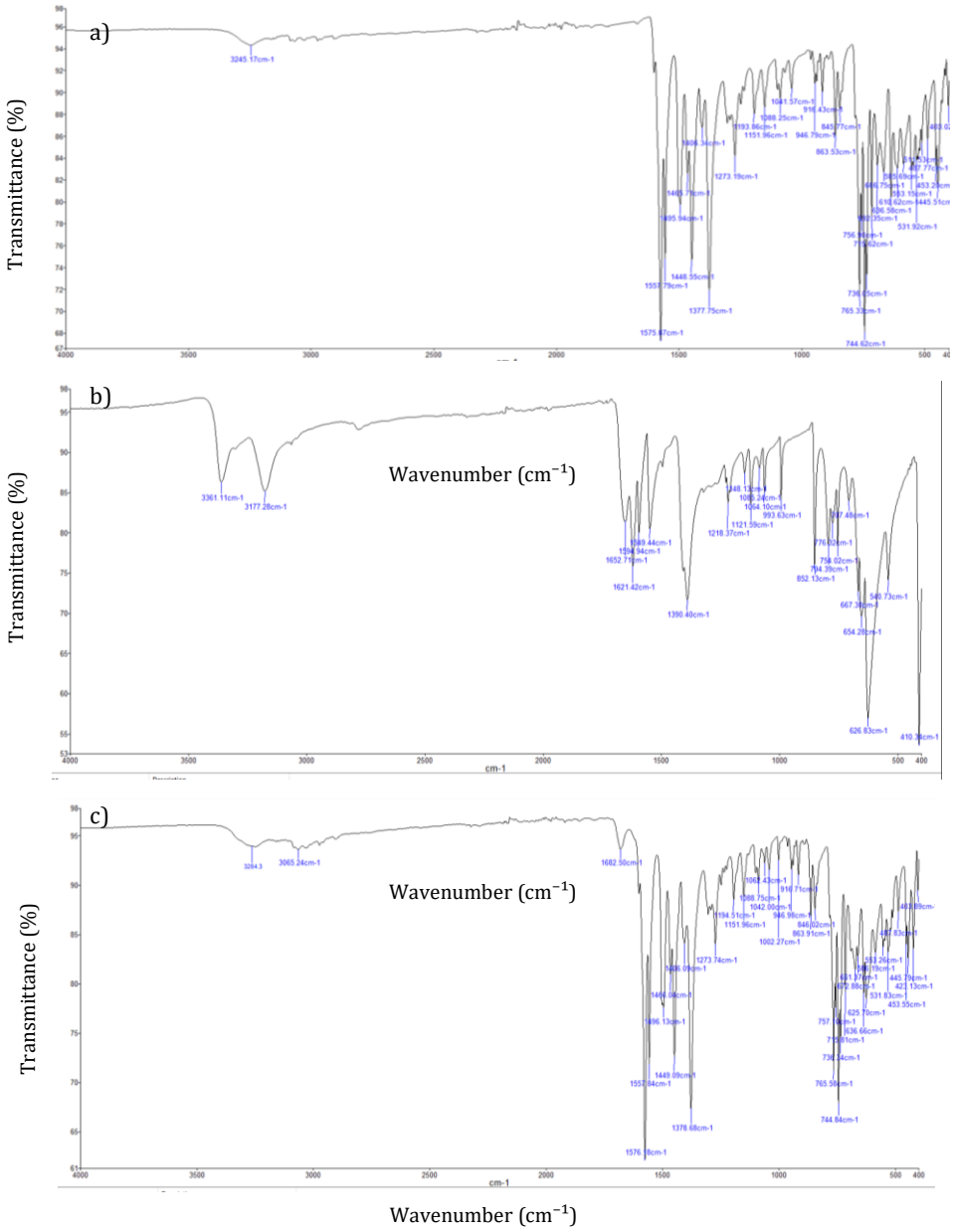

Figure 5. DIC-K (a), INA (b) and DIC-K+INA cocrystal (c)´s FT-IR spectra.

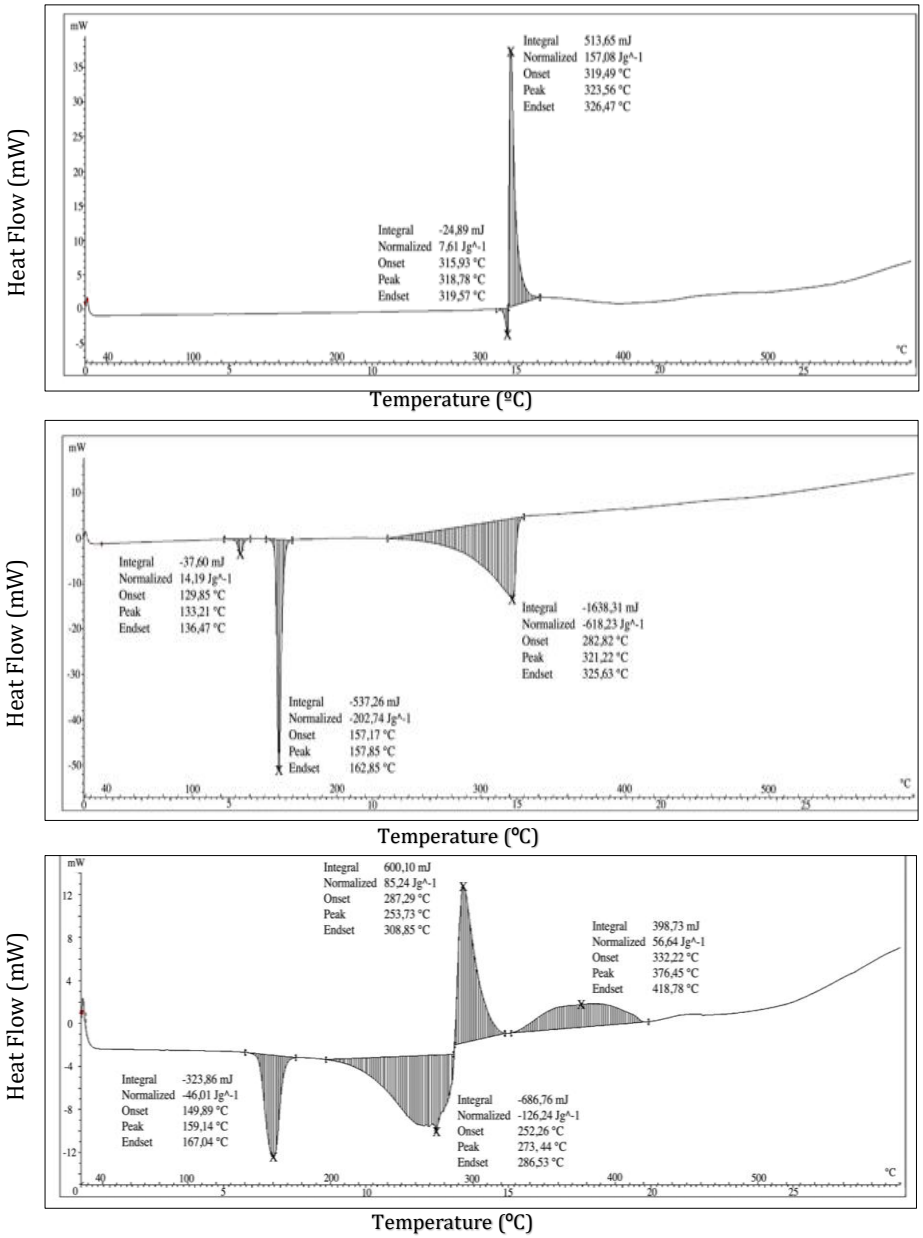

Figure 6. DIC-K (a), INA (b) and DIC-K+INA cocrystal (c)´s DSC thermograms.

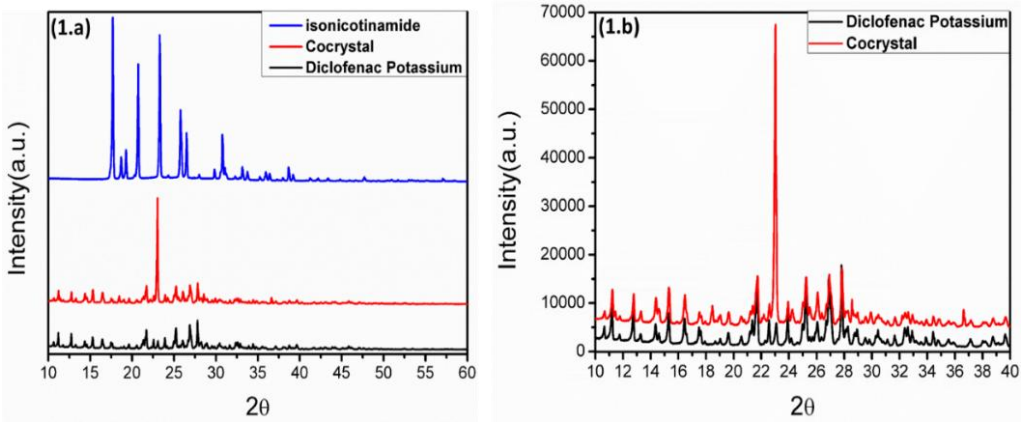

Figure 7. 1a. PXRD patterns of pure DIC-K, INA and DIC-K+INA cocrystal. 1.b. PXRD patterns of pure DIC-K and DIC-K+INA cocrystal.

Table 6. Flow characteristics of the prepared powder mixture. (Mean±SD, n=3)

Parameter	The granular filling mixture for DIC-K capsule	The granular filling mixture for DIC-K+INA capsule
Angle of repose	29.30±0.78°	27.10±0.64°
Flow time (sec)	6.00±1.01	4.00±1.02
Bulk density (g/mL)	0.62±0.08	0.63±0.06
Tapped density (g/mL)	0.74±0.05	0.73±0.05
Compressibility index (%)	16.22±0.06	13.70±0.05
Hausner ratio	1.19±0.06	1.16±0.05

DIC-K-capsule: Pure DIC-K-containing capsule; DIC-K+INA–capsule: DIC-K+INA cocrystals-containing capsule; SD: Standard deviation

Using an electronic analytical balance, the weight of each granule-filled capsule was measured (for 20 capsules) and the average capsule weights were determined as 302±11 mg (DIC-K capsule) and 303±9 mg (DIC-K+INA capsule). The disintegration time values for DIC-K capsule and DIC-K+INA capsule were found to be 3 min 20 sec and 2 min 50 sec, respectively. A decrease in the disintegration time of the capsules prepared with the cocrystal form was observed.

Moreover, DIC-K content of capsules (DIC-K capsule and DIC-K+INA capsule) were evaluated according to USP 43 (905-Uniformity of dosage units) (United States Pharmacopeia, 2019e). According to USP 43, the capsules (DIC-K capsule and DIC-K+INA capsule) met the content uniformity requirements with a DIC-K content of 98-102% of the theoretical amount of 50 mg DIC-K.

In addition, a dissolution study was performed in our study. The dissolution profiles obtained for the capsules (DIC-K capsule and DIC-K+INA capsule) are presented Figure 8. For the DIC-K capsule, the percentage of dissolved DIC-K in PB pH 6.8 was 72% at 15 min, while for the DIC-K+INA capsule, the percentage of dissolved DIC-K at 15 min was 92% (Figure 8).

The USP 43-DIC-K tablet monograph includes the following information: When a dissolution test for the DIC-K tablet is performed in 900 mL of simulated intestinal fluid (no enzyme) using apparatus 2 (50 rpm, 60 min), ≥75% of the labeled amount of DIC-K should be dissolved (United States Pharmacopeia, 2019e).

Solubility and dissolution are significant factors in determining the oral absorption of active substances. One of the powerful strategies used in the pharmaceutical field to improve the solubility of poorly water-soluble active substances is cocrystallization. However, the solubility of cocrystals varies with solution conditions such as solubilizing agents and pH. Cocrystals may exhibit equal, higher or lower solubility compared to pure active substances, depending on solution conditions (Cao et al., 2018; Thakuria et al., 2013; Moulton and Zaworotko, 2001; Childs et al., 2007). In our study, it was observed that the solubility and dissolution of DIC-K in PB pH 6.8 medium was improved by cocrystal preparation.

Conclusion

Pharmaceutical cocrystallization has emerged as an efficient crystal engineering strategy for improving the physicochemical performance of poorly soluble drugs. In the present study, DIC-K+INA cocrystals were successfully designed, synthesized, and confirmed by complementary solid-state characterization techniques, including DSC, PXRD, and FT-IR analyses. The results clearly indicated the formation of a novel crystalline phase distinct from the parent components. Importantly, in vitro dissolution studies demonstrated that the cocrystal-based capsule formulation significantly enhanced the dissolution profile of diclofenac potassium compared to its conventional formulation, with a marked increase in the percentage of drug released within the first 15 minutes. Such a rapid and improved dissolution is expected to translate into better oral absorption and bioavailability, thereby improving the therapeutic performance of diclofenac potassium. Overall, these findings emphasize the potential of isonicotinamide as a pharmaceutically acceptable coformer and highlight the relevance of cocrystal technology as a practical and scalable approach for overcoming solubility limitations. Future studies focusing on pharmacokinetics, stability, and large-scale manufacturing will further establish the clinical applicability of DIC-K+INA cocrystals and support their development into patient-friendly dosage forms.

Author Contributions

The percentages of the authors' contributions are presented below. All authors reviewed and approved the final version of the manuscript.

	E.D.	G.G.	M.N.	C.Y.	M.C.	Y.C.
C	20	20	20	15	15	10
D	20	20	20	15	15	10
S	20	20	20	15	15	10
DCP	20	20	20	15	15	10
DAI	20	20	20	15	15	10
L	20	20	20	15	15	10
W	20	20	20	15	15	10
CR	20	20	20	15	15	10
SR	20	20	20	15	15	10
PM	20	20	20	15	15	10
FA	20	20	20	15	15	10

C= concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Consideration

Ethics committee approval was not required for this study because of there was no study on animals or humans.

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