

Molecular Docking-Guided Coformer Selection and Cocrystallization for Enhanced Biopharmaceutical Performance of Tolvaptan

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SUMMARY

Tolvaptan (TLV), a vasopressin V2 receptor antagonist, is limited by poor aqueous solubility and low oral bioavailability. Cocrystallization with suitable cofomers offers a promising strategy to enhance its solubility and dissolution. This study aimed to design, characterize, and evaluate TLV cocrystals with GRAS listed cofomers to improve solubility, dissolution, and immediate-release tablet performance. TLV cocrystals were prepared via solvent-drop grinding and characterized using melting point analysis, DSC, and PXRD. Molecular docking guided the selection of nicotinic acid as a suitable cofomer. The synthesized cocrystals were subjected to solubility and dissolution studies, and the nicotinic acid cocrystal was formulated into tablets with various disintegrants. The formulations were evaluated through pre- and post-compression studies, while the dissolution profile of the optimized formulation was analyzed in terms of similarity factor (f₂) in comparison with the marketed tablet. DSC and PXRD analyses confirmed the formation of new crystalline phases. The optimized tablet formulation (F₄, 2:3 TLV-to-nicotinic acid ratio with crospovidone as the disintegrant) exhibited rapid disintegration (<20 s), excellent flow properties, and enhanced dissolution (~69% in 60 min). When compared with marketed tablets, F₄ displayed a distinct f₂ value (13.9), demonstrating its superior performance. Cocrystallization with nicotinic acid markedly enhanced TLV solubility, dissolution, and tablet performance, representing an effective strategy to overcome solubility-limited bioavailability.

Keywords: Tolvaptan, cocrystallization, nicotinic acid, solubility enhancement, immediate-release tablets.

Moleküler Yerleştirme Rehberliğinde Koformör Seçimi ve Kökristalizasyon: Tolvaptan'ın Biyofarmasötik Performansının Artırılması

ÖZ

Vazopressin V2 reseptör antagonisti olan tolvaptan (TLV), zayıf suda çözünürlüğü ve düşük oral biyoyararlanımı nedeniyle sınırlıdır. Uygun koformatörlerle eş-kristalizasyon, çözünürlüğünü ve çözünmesini artırmak için umut verici bir strateji sunar. Bu çalışma, çözünürlüğü, çözünmeyi ve hızlı salımlı tablet performansını iyileştirmek için GRAS onaylı eş-formatörlere sahip TLV eş-kristallerini tasarlamayı, karakterize etmeyi ve değerlendirmeyi amaçlamaktadır. TLV eş-kristalleri, çözücü damla öğütme yöntemiyle hazırlanmış ve erime noktası analizi, DSC ve PXRD kullanılarak karakterize edilmiştir. Moleküler yerleştirme, uygun bir eş-formatör olarak nikotinik asidin seçilmesine rehberlik etmiştir. Sentezlenen eş-kristaller çözünürlük ve çözünme çalışmalarına tabi tutulmuş ve nikotinik asit eş-kristalleri çeşitli dağıtıcılarla tabletler halinde formüle edilmiştir. Formülasyonlar, sıkıştırma öncesi ve sonrası çalışmalarla değerlendirilirken, optimize edilmiş formülasyonun çözünme profili, piyasadaki tabletle karşılaştırıldığında benzerlik faktörü (f₂) açısından analiz edildi. DSC ve PXRD analizleri, yeni kristal fazların oluşumunu doğruladı. Optimize edilmiş tablet formülasyonu (F₄, krosprovidon dağıtıcı olarak 2:3 TLV/nikotinik asit oranı), hızlı parçalanma (<20 saniye), mükemmel akış özellikleri ve gelişmiş çözünme (~60 dakikada %69) sergiledi. Piyasadaki tabletlerle karşılaştırıldığında, F₄ belirgin bir f₂ değeri (13,9) sergileyerek üstün performansını kanıtladı. Nikotinik asitle eş kristalleştirme, TLV çözünürlüğünü, çözünmesini ve tablet performansını önemli ölçüde artırarak, çözünürlükle sınırlı biyoyararlanımın üstesinden gelmek için etkili bir strateji sundu.

Anahtar Kelimeler: Tolvaptan, eş kristalleştirme, nikotinik asit, çözünürlük artışı, hızlı salımlı tabletler.

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INTRODUCTION

Many newly discovered and marketed drugs suffer from poor aqueous solubility, limiting oral absorption and reducing bioavailability. As dissolution often controls drug uptake, low solubility can compromise therapeutic efficacy. Despite these challenges, the oral route remains the most widely accepted and preferred mode of drug administration due to its convenience, safety profile, and cost-effectiveness.

Solid-state modification is a key approach to address solubility challenges of poorly water-soluble APIs (Göke et al., 2018). Among various solid forms, cocrystals—comprising an API and a pharmaceutically acceptable coformer stabilized by noncovalent interactions—offer enhanced solubility, dissolution, bioavailability, stability, and mechanical properties while preserving the drug's pharmacological activity (Sah et al., 2025). The use of GRAS-listed cofomers further expands their applicability in pharmaceutical formulations (Nugrahani & Jessica, 2021; Wouters et al., 2011). TLV is a selective vasopressin V₂ receptor antagonist indicated for hyponatremia and autosomal dominant polycystic kidney disease (ADPKD) (Blair & Keating, 2015). TLV, a BCS Class IV drug (Kato et al., 2023), exhibits low aqueous solubility and poor intestinal permeability, leading to suboptimal oral bioavailability (40–50%) (Therapeutic Goods Administration, 2018). Its limited solubility hinders gastrointestinal absorption and therapeutic efficacy, and no cocrystal forms have been reported (McNeely et al., 2013). This study aims to develop novel TLV cocrystals to enhance solubility and dissolution while maintaining pharmacological activity, potentially improving bioavailability and clinical performance.

MATERIALS AND METHODS

Materials

TLV was supplied by Aurore Pharmaceuticals Pvt. Ltd. (India). Cofomers utilized in this study included caffeine, glycine (S.D. Fine Chemicals Ltd., Mumbai); nicotinic acid (Elegant Fine Chemicals Ltd., Hyder-

abad); and nicotinamide (Sai Nakshatra Bio Solutions, India).

In silico screening

Molecular docking was performed using AutoDock 4.2 (Morris et al., 2009). TLV (PubChem CID: 216237) and cofomers retrieved from PubChem were geometry-optimized using Gaussian 09 with the 3-21G base set Density Functional Theory (DFT) B3LYP method. A rigid–flexible docking protocol was applied, keeping the receptor rigid and the optimized ligands flexible during docking. Docking employed a 40 × 40 × 40 Å grid (0.375 Å spacing) with 10 conformations generated via the Lamarckian Genetic Algorithm. Binding energies and hydrogen-bond interactions were analyzed using VMD 1.9.2 and BIOVIA Discovery Studio 2020.

Preparation of cocrystals

The solvent-drop grinding technique was employed for the preparation of TLV cocrystals, with the drug and coformer mixed in a 1:1 molar ratio. Equimolar amounts of TLV and coformer were triturated with 0.5 mL of methanol for 30–45 min, followed by drying. Cocrystal formation was confirmed by DSC and PXRD (Lee & Lee, 2022; Nijhawan et al., 2014).

Melting points

The melting points of TLV and formulated cocrystals selected for this study including nicotinic acid, caffeine, nicotinamide, and glycine, were measured using the capillary tube method, and their stability was monitored for four weeks to assess any changes in thermal behavior (Liu et al., 2020).

Differential scanning calorimetry (DSC)

DSC analysis of TLV and formulated cocrystals was performed using a Mettler Toledo DSC 821e, and the thermograms were compared with those of TLV to evaluate thermal behavior and potential interactions (Panzade et al., 2017).

Powder X-Ray diffraction (PXRD)

The crystalline characteristics of TLV, coformers, and formulated cocrystals were examined by X-ray diffraction (XRD) using a Shimadzu XRD 7000 diffractometer, with a 2θ scanning range of $5-40^\circ$ at 40 kV and 40 mA (Desai et al., 2022).

Analytical method

Quantification of the TLV was performed using a first-order derivative UV spectrophotometric method. The derivative amplitudes were measured at the zero-crossing wavelengths of the coformers, namely 262.31 nm for caffeine and 238.67 nm for nicotinic acid, at which the coformers show zero contribution to the signal. This zero-crossing derivative approach enabled selective, accurate, and interference-free determination of the drug in the presence of the coformers.

Saturation solubility studies

TLV and its cocrystals with nicotinic acid and caffeine were subjected to saturation solubility studies at pH 1.2 and analyzed by the UV spectrophotometer (Aithal et al., 2017).

Phase solubility studies (TLN–Nic acid, 2:3)

Phase solubility studies based on the Higuchi–Connors method were carried out in distilled water at $25 \pm 2^\circ\text{C}$ using excess TLV and varying concentrations of nicotinic acid. The equilibrium solutions were analyzed by UV spectroscopy, and the stoichiometry of cocrystal formation was deduced from solubility diagrams (Mulye et al., 2012).

Dissolution studies

Dissolution of TLV and its cocrystals (75 mg TLV equivalent) was performed using a USP Type II apparatus in 900 mL pH 1.2 buffer at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. Samples were collected at specific intervals between 10 min and 120 min, filtered ($0.45\ \mu\text{m}$), and analyzed. Dissolution profiles of TLV, TLV–nicotinic acid, and TLV–caffeine cocrystals were compared (Mehta et al., 2023).

Tablet formulation

Optimized TLV–nicotinic acid cocrystals were compressed into immediate-release tablets (F1–F4) using varying disintegrants (croscarmellose sodium, sodium starch glycolate, crospovidone) and binders (MCC, PVP K-30) (Tamang et al., 2025), outlined in Table 1.

Table 1. Formulation table of TLV–Nicotinic acid cocrystal tablets

Sr. No.	Ingredients (mg)	TLV–Nic acid F1 (2:3)	TLV–Nic acid F2 (2:3)	TLV–Nic acid F3 (2:3)	TLV–Nic acid F4 (2:3)
1	TLV–Nicotinic acid cocrystal	85	85	85	85
2	Croscarmellose sodium (CCS)	12.5	12.5	37.5	–
3	Sodium starch glycolate (SSG)	–	87	87	–
4	Crospovidone	–	–	–	15
5	Microcrystalline cellulose (MCC) (Binder)	37.5	37.5	12.5	141.25
6	PVP K-30 (Binder)	–	–	–	7.5
7	Magnesium stearate (Lubricant)	2.5	2.5	2.5	1.25
8	Mannitol (Diluent)	112.5	25.5	25.5	–

Evaluation of micromeritic properties (flowability)

To ensure uniform tablet weight and compressibility, flow properties of pure TLV and formulated cocrystals were assessed. Angle of repose (fixed funnel method), Carr's index, and Hausner's ratio were determined (Jadhav et al., 2025).

Post-compression studies

The TLV–nicotinic acid cocrystal tablets were assessed for disintegration and mechanical strength. Tablet hardness was measured with a Monsanto hardness tester, and disintegration was determined using a USP disintegration apparatus in 0.1 N HCl, and results are tabulated in Table 4.

Dissolution studies of cocrystal tablets

In vitro dissolution of TLV–nicotinic acid cocrystal tablets was conducted using a USP Type II (paddle) apparatus in 0.1 N HCl over 2 hours. Samples were withdrawn at predetermined intervals, filtered, and analyzed using the first-order derivative spectrophotometric method to eliminate spectral overlap. Caffeine and nicotinic acid showed zero absorbance at 262.31 nm and 238.67 nm, respectively, enabling selective and accurate quantification of TLV in the presence of cofomers (Tamang et al., 2025). The dissolution profile of formulation F4 (2:3 ratio) was compared with the marketed tablet using the similarity factor.

The dissolution profile of formulation F4, prepared in a 2:3 molar ratio of TLV to nicotinic acid, was compared with that of the marketed tablet using the similarity factor (f_2). The similarity factor is calculated using the equation:

$$f_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}$$

where n is the number of sampling time points, is

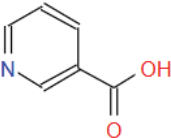
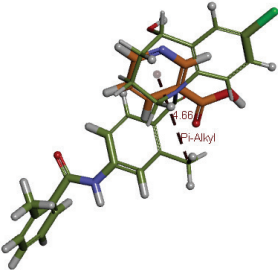
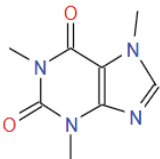
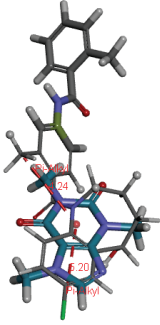
the percentage of drug dissolved from the reference (marketed) formulation at time t , and is the percentage dissolved from the test (F4) formulation at the same time. An f_2 value between 50 and 100 indicates that the test and reference dissolution profiles are similar, with higher values reflecting closer similarity. This approach provides a quantitative measure of how closely the cocrystal formulation replicates the dissolution behavior of the marketed product.

RESULTS

Computational screening of cofomers for TLV cocrystal design

Molecular docking was carried out to evaluate the interaction profiles between TLV and selected cofomers. The study revealed binding affinities, orientations, and complex stability, with interactions such as hydrogen bonding, π – π stacking, hydrophobic forces, and Van der Waals interactions contributing to potential cocrystal formation in Table 2. Comparative binding energy values identified the most promising TLV–coformer pairs for improving physicochemical properties in Table 3.

Table 2. Computational assessment of interaction patterns between TLV and cofomers

Coformer	2D Structure	Interaction
TLV-nicotinic acid		 Pi-alkyl interactions
TLV-caffeine		 Pi-alkyl interaction

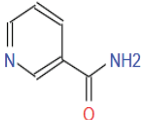
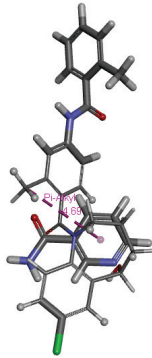
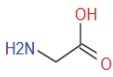
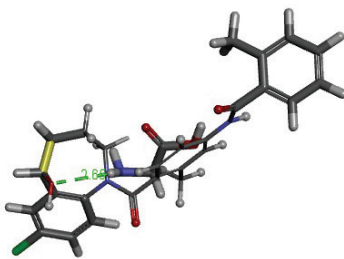
TLV-nicotinamide		 pi-alkyl interaction
TLV-glycine		 Hydrogen bonding interaction

Table 3. *In silico* interaction energy profile of selected cofomers with TLV

Cofomer	ΔG (k _{cal} /mol)	$E_{\text{inter-mol}}$ (k _{cal} /mol)	E_{VHD} (k _{cal} /mol)	E_{elec} (k _{cal} /mol)	E_{total} (k _{cal} /mol)	$E_{\text{torsional}}$ (k _{cal} /mol)
Nicotinic acid	-2.93	-4.12	-3.27	-0.85	+3.36	+1.19
Caffeine	-4.06	-4.66	-4.59	-0.07	+15.56	+0.6
Nicotinamide	-2.98	-3.87	-3.97	+0.1	+5.44	+0.89
Glycine	-0.99	-1.89	-1.89	+0.0	-0.25	+0.89

The binding free energy (ΔG) reflects the overall thermodynamic favorability of drug-coformer interactions, where more negative values indicate stronger binding affinity; the intermolecular interaction energy ($E_{\text{inter-mol}}$) represents the sum of non-bonded interactions, with lower values corresponding to stronger molecular association; the EVHD term accounts for van der Waals forces, hydrogen bonding, and desolvation contributions, providing insight into packing efficiency and potential cocrystal stability; the electrostatic energy (E_{elec}) describes charge-based interactions, with negative values indicating favorable electrostatic attraction; the total binding en-

ergy (E_{total}) integrates all interaction components, with more negative values signifying enhanced complex stability; and the torsional energy ($E_{\text{torsional}}$) reflects conformational strain upon binding, where lower values indicate minimal structural distortion. The TLV-caffeine complex is primarily stabilized by π -alkyl interactions between the aromatic purine ring of caffeine and the alkyl groups of TLV (4.24 and 5.20 Å), resulting in the most favorable binding free energy ($\Delta G = -4.06$ kcal/mol) due to efficient planar stacking, edge-to-face interactions, and minimal torsional strain; TLV-nicotinic acid and TLV-nicotinamide complexes also exhibit π -alkyl interactions involving

their aromatic rings with TLV alkyl moieties at 4.66 Å and 4.69 Å, respectively, indicating moderate stabilization, whereas the TLV–glycine complex is mainly governed by hydrogen bonding between the $-NH_2$ group of glycine and hydroxyl group of TLV, but its weak binding energy ($\Delta G = -0.99$ kcal/mol) suggests poor compatibility.

Overall, based on conformationally optimized docking results, caffeine was identified as the most promising coformer due to its superior interaction

energy profile and minimal conformational penalty.

Determination of physical constant (melting point)

Melting point analysis showed that TLV cocrystals with nicotinic acid, caffeine and glycine differed from pure TLV (235 °C), indicating successful cocrystal formation, while TLV–nicotinamide showed minimal changes, suggesting no cocrystal formation. The melting points of TLV and its cocrystals are tabulated in Table 4.

Table 4. The melting point values of TLV, the selected coformers, and the synthesized cocrystals are presented

Sr. No.	Name of TLV/Formulation	Melting points (Literature Value)	Melting range of prepared cocrystals (Observed Value)	Inference
1	TLV (Drug)	235°C	230-235°C	-
2	TLV-nicotinic acid formulation	237°C	172-178°C	Cocrystal might have formed
3	TLV-caffeine formulation	234-238°C	164-167°C	Cocrystal might have formed
4	TLV-nicotinamide formulation	128°C	127-136°C	Cocrystal might not have formed
5	TLV-glycine formulation	233°C	220-230°C	Cocrystal might not have formed

The observed depression in melting points for the TLV–nicotinic acid and TLV–caffeine formulations is characteristic of cocrystal formation, where the interaction between drug and coformer results in a new crystalline lattice with altered thermal properties. Such changes confirm strong molecular interactions and the generation of a distinct solid phase. The TLV–nicotinic acid, TLV–caffeine, and suggesting possible cocrystal formation, while TLV–nicotinamide and TLV–glycine formulations did not exhibit any significant change. Based on these results, caffeine and nicotinic acid were selected as promising coformers for further evaluation. Melting point analysis revealed distinct thermal behavior for the prepared formulations, indicating the formation of new solid phases. The observed depression in melting points for the TLV–nicotinic acid and TLV–caffeine formulations is characteristic of cocrystal formation, where the interaction between

drug and coformer results in a new crystalline lattice with altered thermal properties. Such changes confirm strong molecular interactions and the generation of a distinct solid phase. The TLV–nicotinic acid and TLV–caffeine showed changes, suggesting possible cocrystal formation, while TLV–nicotinamide and TLV–glycine did not exhibit any significant change. Based on these results, caffeine and nicotinic acid were selected as promising coformers for further evaluation.

Differential scanning calorimetry

The DSC analysis compared literature values of TLV and coformers with the observed melting points of the prepared cocrystals. Single distinct melting points suggested possible cocrystal formation, while multiple peaks or values close to the individual components indicated no cocrystal formation. The DSC thermograms of the studied systems are presented in Figures 1–3.

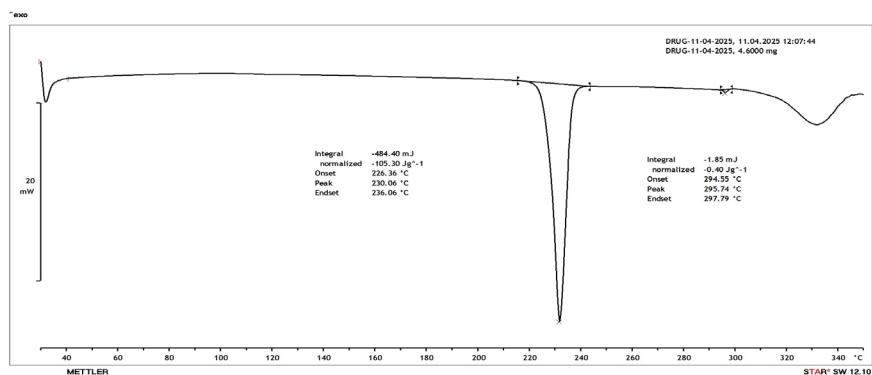


Figure 1. DSC thermogram of TLV

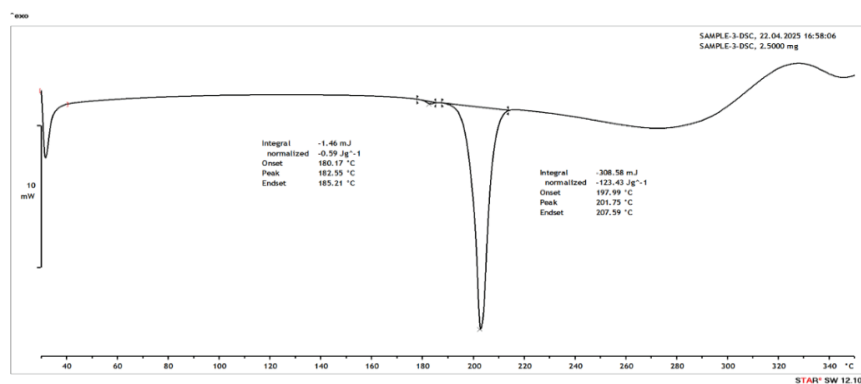


Figure 2. DSC thermogram of TLV- nicotinic acid formulation

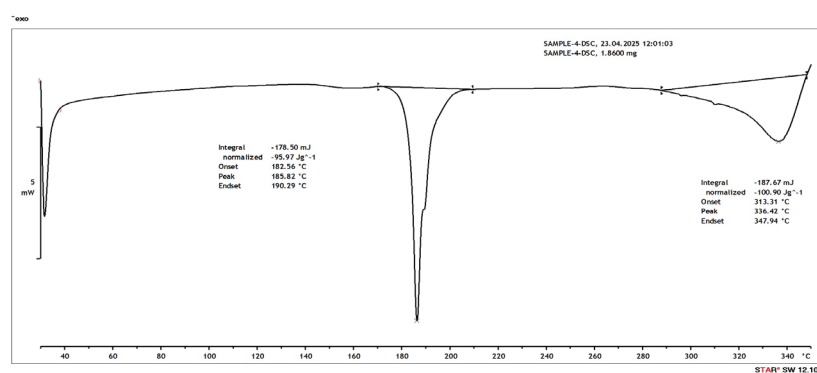


Figure 3. DSC thermogram of TLV-caffeine formulation

Differential scanning calorimetry (DSC) analysis provided clear evidence of cocrystal formation for TLV-nicotinic acid and TLV-caffeine, as indicated by distinct and sharp melting endotherms at 168–172 °C and 185.82 °C, respectively. The appearance of new thermal peaks, distinct from the melting points of the individual components, suggests the formation of

a stable, homogeneous crystalline phase. In contrast, other TLV-coformer combinations exhibited additional or unchanged thermal events, indicating incomplete or negligible cocrystallization. These results suggest that nicotinic acid and caffeine are the most compatible cofomers for TLV, likely due to favorable molecular interactions stabilizing the cocrystal lattice.

Caffeine and nicotinic acid showed the most favorable interactions with TLV, characterized by strong π -alkyl contacts, efficient stacking, and low torsional strain, as supported by distinct DSC melting endotherms indicating stable cocrystal formation, whereas weaker interactors such as glycine exhibited poor compatibility, highlighting that the combined use of molecular docking and experimental analyses is effective for rational coformer selection to enhance cocrystal stability and pharmaceutical performance.

Powder XRD

The PXRD pattern of pure caffeine exhibited characteristic reflections at 2θ values of 12.25° , 14.83° , 16.14° corresponding to its crystalline fingerprint. PXRD analysis of nicotinic acid exhibited sharp crystalline peaks at $2\theta \approx 15.80^\circ$, 20.69° , 21.58° , and 24.17° , with the most intense peak at 15.80° . In the TLV–caffeine cocrystal, the characteristic reflections of pure TLV at 22.2406° , 23.9719° , and 28.8278° were absent, while new peaks emerged at 22.1524° , 27.5241° , 26.8940° , and 12.2434° with notable intensities. A

similar pattern was observed in the TLV–nicotinic acid cocrystal, where TLV peaks disappeared, and distinct new reflections appeared at 22.0742° , 27.5241° , 26.8940° , and 12.2434° . Additionally, the slight shift in the principal reflection near 22° (from 22.2406° in TLV to 22.1524° in the caffeine cocrystal and 22.0742° in the nicotinic acid cocrystal) indicates changes in the lattice arrangement. The disappearance of TLV's characteristic peaks, along with the emergence of new reflections and slight peak shifts (Figures 4–5), are well-recognized indicators of cocrystal formation rather than simple physical mixing. These changes reflect alterations in the crystal lattice resulting from specific molecular interactions between TLV and the coformers. The formation of these distinct crystalline phases confirms that the drug and coformers interact at the molecular level to produce stable cocrystals. Such structural transformations are important, as they can significantly influence the physicochemical and biopharmaceutical properties of TLV, including solubility and dissolution behavior.

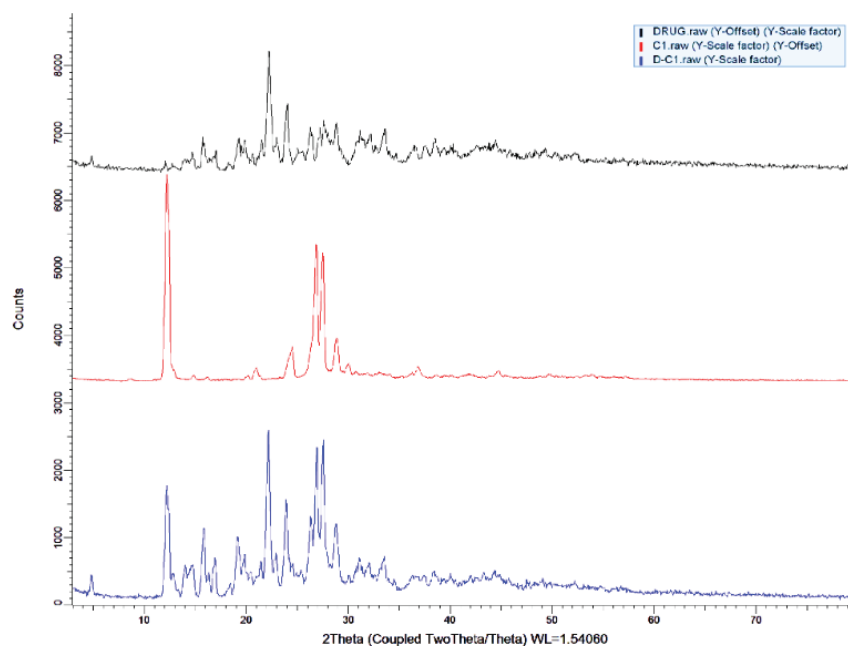


Figure 4. PXRD comparison of TLV–caffeine cocrystal, TLV and, caffeine

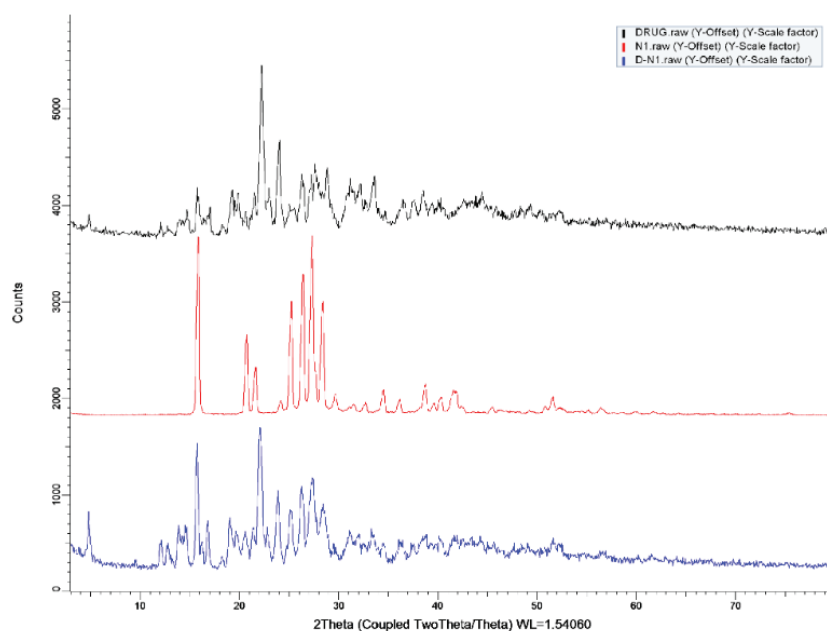


Figure 5. PXRD comparison of TLV–nicotinic acid cocrystal, TLV and, nicotinic acid

Saturation solubility studies

TLV displayed poor solubility (0.036 ± 0.0012 mg/mL). The TLV–caffeine cocrystal showed a modest enhancement (0.043 ± 0.0021 mg/mL), while the TLV–nicotinic acid cocrystal exhibited a marked increase in solubility (0.124 ± 0.0447 mg/mL), demonstrating a significant improvement over the parent drug. These results validate the effectiveness of the cocrystallization strategy in enhancing drug solubility. In pH 1.2 medium, pure TLV exhibited poor solubility

(0.036 ± 0.0012 mg/mL). The TLV–caffeine cocrystal showed a modest enhancement (0.043 ± 0.0021 mg/mL), while the TLV–nicotinic acid cocrystal exhibited a marked increase in solubility (0.124 ± 0.0447 mg/mL), demonstrating a significant improvement over the parent drug. These results validate the effectiveness of the cocrystallization strategy in enhancing drug solubility.

The comparative solubility data are graphically illustrated in Figure 6.

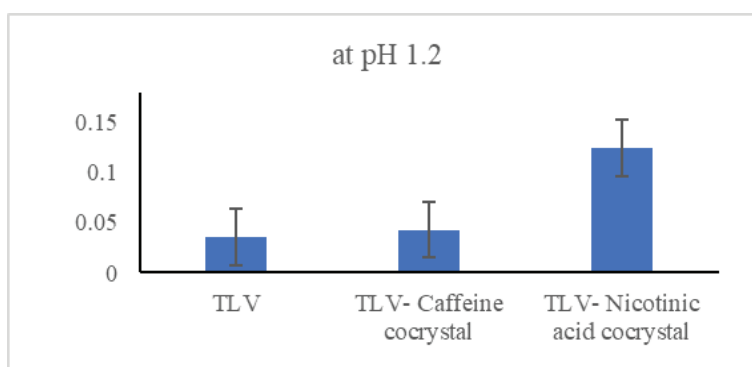


Figure 6. Solubility behavior of TLV and its cocrystals at pH 1.2

Phase solubility studies

Phase solubility studies demonstrated that TLV solubility increased with increasing amounts of nicotinic acid, indicating the formation of soluble drug-coformer complexes, and strong molecular interactions were graphically illustrated in Figure 7. The linear profile further suggests stoichiometric complexation (2:3), supporting TLV–nicotinic acid cocrystal formation, while minor deviations at higher

concentrations likely reflect site saturation, consistent with previous reports (Aitipamula et al., 2012; Vishweshwar et al., 2006). The positive slope indicates effective incorporation of TLV into the cocrystal lattice, resulting in increased apparent solubility with rising nicotinic acid concentration. The strong linear correlation ($R^2 \approx 0.95$) confirms that this enhancement is predictable and concentration-dependent, supporting the formation of a stable TLV–nicotinic acid cocrystal.

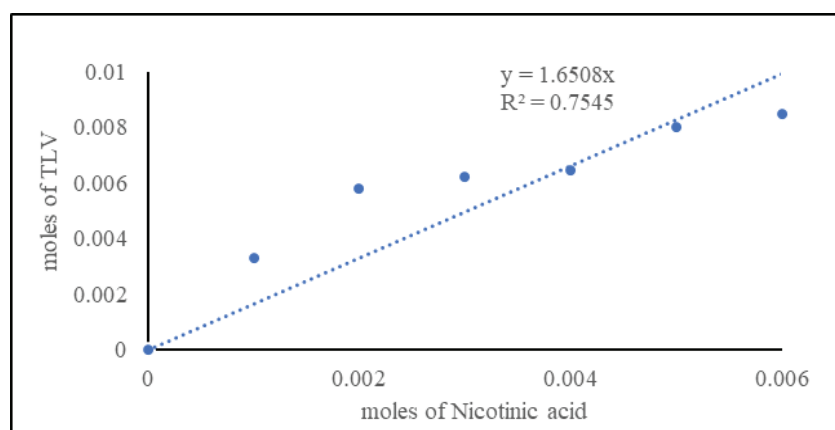


Figure 7. Phase solubility curve of TLV in nicotinic acid solution

In vitro dissolution of cocrystals

Pure TLV displayed very limited dissolution, with only 16.43% release after 120 minutes. The TLV–caffeine cocrystal showed a moderate improvement, reaching 36.65%, though the release plateaued early. In comparison, the TLV–nicotinic acid (1:1) cocrystal demonstrated superior performance, achieving 51.36% release, while the 2:3 cocrystal provided the greatest enhancement, with 43.8% release within 10 minutes and 52.89% at 120 minutes, as shown in Figure 8. These findings confirm that cocrystallization markedly improves TLV solubility, with nicotinic acid (2:3) emerging as the most effective coformer ratio.

Molecular docking was employed as a preliminary screening approach to identify coformers capable of forming favorable intermolecular interactions with TLV. The progressive improvement in dissolution performance observed for the nicotinic acid cocrystals is consistent with the strong intermolecular interactions predicted by molecular docking, which likely contribute to altered crystal packing. Collectively, these findings demonstrate that docking-guided coformer selection provides a reliable qualitative framework, with experimental dissolution studies thereby experimentally substantiating the *in silico*–guided screening process.

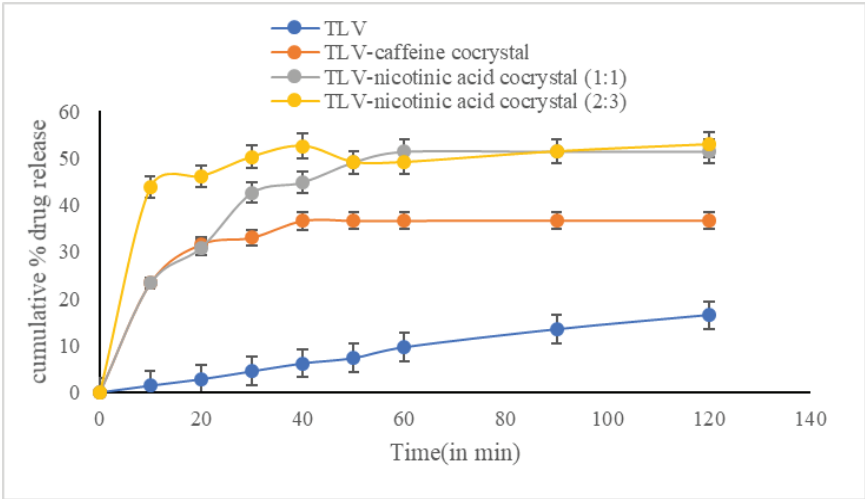


Figure 8. Cumulative % release profiles of TLV and TLV cocrystals at pH 1.2

Evaluation of micromeritic properties

The pre-compression studies of TLV–nicotinic acid cocrystal tablets (F4), as presented in Table 5, ex-

hibited higher bulk and tapped densities along with excellent Carr’s index and angle of repose values, indicating superior packing characteristics and good flow properties.

Table 5. Pre-compression properties of TLV–nicotinic acid cocrystal tablet formulations (F4)

Sr. No.	Evaluated factors	Observations (F4)	Inference
1.	Tapped density (g/mL)	0.961	-
2.	Bulk density (g/mL)	0.694	-
3.	Carr’s Index (%)	2.1	Excellent
4.	Hausner’s ratio	1.384	Passable
5.	Angle of repose (°)	15.94	Excellent

Post compression evaluation

TLV–nicotinic acid cocrystal tablet formulations for immediate-release application, ensuring faster drug release and potentially improved bioavailability of TLV, as presented in Table 6. Disintegration studies revealed that formulations F1 and F2 showed prolonged disintegration times (80 and 60 seconds, respectively), which may hinder compliance with pharmacopeial standards for immediate release tablets. Formulation F3 demonstrated better performance with a disintegration time of 40 seconds, whereas F4 exhibited rapid disintegration within 20 seconds, meeting the requirements for immediate-release. All formulations maintained a consistent hardness of 4 kg/cm², confirming adequate mechanical strength to

endure handling and packaging without affecting disintegration. Overall, F4 emerged as the most suitable TLV–nicotinic acid cocrystal tablet formulation for immediate-release application, ensuring faster drug release and potentially improved bioavailability of TLV presented in Table 6.

Table 6. Disintegration time and hardness of TLV-nicotinic acid cocrystal tablets

Formulation Code	Disintegration Time (in seconds)	Hardness (kg/cm ²)
(F1)	80	4
(F2)	60	4
(F3)	40	4
(F4)	20	4

***In vitro* dissolution studies of TLV-nicotinic acid cocrystal tablets using 0.1 N HCl**

The dissolution profiles of TLV tablets, TLV-nicotinic acid cocrystal tablets (F4), and the marketed formulation are shown in Figure 9. Pure TLV exhibited poor dissolution, with <2% release after 120 minutes, confirming its dissolution-limited bioavailability. In

contrast, the TLV-nicotinic acid cocrystal (2:3 ratio, F4) showed markedly enhanced dissolution (~69% in 60 minutes), attributed to strong hydrogen bonding, reduced lattice energy, and improved wettability from the hydrophilic coformer. The marketed tablet achieved only ~19% release at 120 minutes, emphasizing that cocrystallization significantly enhances TLV dissolution compared to conventional formulations.

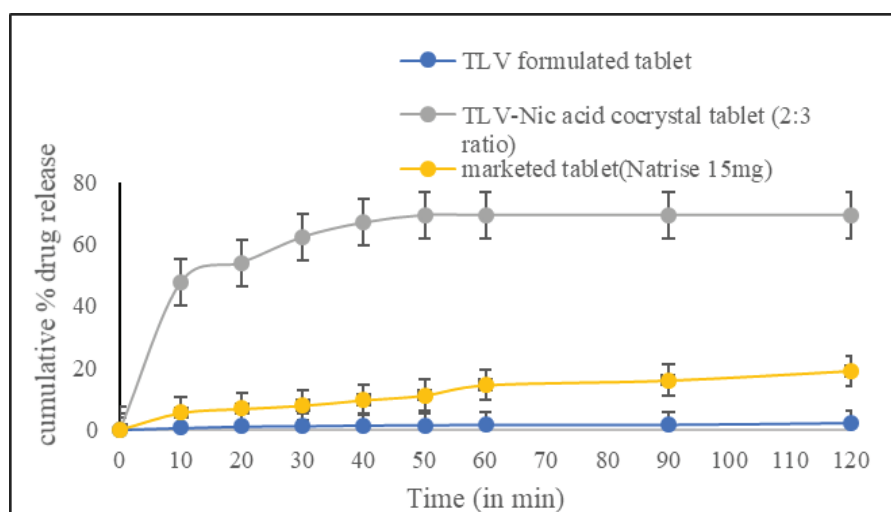


Figure 9. Comparative dissolution profiles of TLV, TLV-nicotinic acid cocrystal tablet, and marketed tablet

Overall, the results clearly establish that cocrystallization with nicotinic acid is an effective strategy for enhancing the solubility and dissolution behavior of TLV. Among the formulations studied, the 2:3 TLV-nicotinic acid cocrystal (F4) demonstrated the most favorable profile, and thus can be considered the optimized formulation for further development.

The dissolution profiles of the TLV-nicotinic acid cocrystal tablet (F4, 2:3) and the marketed tablet were compared using the similarity factor (f_2), a model-independent method recommended for dissolution profile evaluation. The f_2 value, calculated from the percentage drug released at corresponding time points, was 13.92, which is well below the acceptance range of 50–100, indicating a pronounced dissimilarity between the two dissolution profiles and confirming the superior release performance of the cocrystal formulation.

To further substantiate this difference, an unpaired t-test was performed to statistically compare the dissolution performance of the TLV-nicotinic acid cocrystal (F4) and the marketed tablet. The cocrystal exhibited a significantly higher drug release ($t = 15.39$, $p < 0.0001$), further confirming that the cocrystal formulation exhibits substantially superior dissolution performance compared with the marketed product.

CONCLUSION

Molecular docking served as a qualitative pre-screening tool for coformer selection, with the strong interactions predicted for nicotinic acid being experimentally validated through successful cocrystal formation and enhanced dissolution, particularly for the TLV-nicotinic acid (2:3) system. Cocrystallization markedly improved the solubility, dissolution, and tablet performance of TLV, with the 2:3 cocrystal exhibiting over threefold higher solubility and achieving

69.46% drug release, outperforming other formulations and the marketed product. Overall, this study demonstrates that cocrystallization is an effective and practical strategy to overcome solubility-limited bioavailability and improve the oral delivery of poorly water-soluble drugs.

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AUTHOR CONTRIBUTION STATEMENT

Concept, Design - MN; Data Collection and /or Processing - MN, DGSV; Literature Search - MN, DGSV, RA, SG, GKRS; Analysis and/or Interpretation - MN, DGSV; Writing - MN, DGSV, RA, SG, GKRS.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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