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SOLUBILITY ENHANCEMENT OF VORICONAZOLE BY PHARMACEUTICAL CO-CRYSTALLIZATION WITH NICOTINIC ACID AND SUCCINIC ACID

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ABSTRACT

Voriconazole (VCZ) is a poorly water-soluble antifungal drug whose limited aqueous solubility may restrict its dissolution and oral biopharmaceutical performance. The present study investigated pharmaceutical co-crystallization as a strategy to enhance the aqueous solubility and dissolution characteristics of VCZ. Co-crystals were prepared using nicotinic acid (NA) and succinic acid (SA) as pharmaceutically acceptable cofomers at 1:1 and 1:2 drug-to-coformer ratios (w/w) by Liquid-Assisted Grinding (LAG) and Solvent Evaporation (SE) methods. Eight co-crystal formulations (T1–T8) were prepared and evaluated comparatively for saturation solubility and in vitro dissolution performance. The prepared systems were further characterized using appropriate analytical and solid-state characterization techniques to assess co-crystal formation. All co-crystal systems demonstrated improved aqueous solubility compared with pure VCZ (0.47 mg/mL). Among the investigated formulations, the VCZ–SA system prepared at a 1:2 w/w ratio by SE (T8) exhibited the highest solubility of 3.204 mg/mL, corresponding to an approximately 6.82-fold enhancement compared with pure VCZ. T8 also demonstrated superior dissolution performance, with 92.877% drug release at 60 min compared with 23.39% for pure VCZ. Formulation T8 exhibited the most favorable dissolution characteristics, with the lowest T_{50} and highest DE_{10} , DE_{30} , DE_{60} and RDR_{30} values. FTIR analysis confirmed that the characteristic functional groups of VCZ remained intact after co-crystallization, indicating the absence of any chemical degradation. The findings demonstrate that cofomer selection, drug-to-coformer ratio, and preparation method substantially influence the solubility and dissolution behaviour of VCZ. The VCZ–SA co-crystal prepared by SE therefore represents a promising approach for enhancing the aqueous solubility and dissolution of VCZ.

Keywords: Voriconazole; Pharmaceutical Co-Crystal; Succinic Acid; Nicotinic Acid; Solubility Enhancement; Solvent Evaporation

1 INTRODUCTION

Oral drug delivery is the most preferred route of drug administration due to its convenience, cost-effectiveness, patient compliance, and ease of large-scale manufacturing. However, the oral delivery of many therapeutic agents is limited by poor aqueous solubility, which can adversely affect dissolution, gastrointestinal absorption, and oral bioavailability¹. According to the Biopharmaceutical Classification System (BCS), Class II drugs exhibit low aqueous solubility and high intestinal permeability, making their absorption primarily dissolution-rate limited. Therefore, enhancement of solubility and dissolution of poorly water-soluble drugs remains an important objective in pharmaceutical formulation

development². Various techniques, including particle size reduction, micronization, salt formation, nanosuspensions, lipid-based formulations, cyclodextrin complexes, amorphous solid dispersions, self-emulsifying drug delivery systems, and nanotechnology-based approaches, have been employed to overcome solubility-related limitations^{3,4}. However, these approaches may be associated with limitations such as physical instability, recrystallization, complex manufacturing processes, scalability issues, and restricted applicability. Consequently, the development of alternative solid-state approaches, such as polymorphs, solvates, salts, and pharmaceutical co-crystals, has gained considerable attention. Pharmaceutical co-crystal engineering is an effective solid-state modification strategy for improving the physicochemical and pharmaceutical properties of drug molecules without altering their molecular structure or pharmacological activity⁵. The FDA defines pharmaceutical co-crystals as crystalline materials composed of two or more different molecules, typically an active pharmaceutical ingredient (API) and a coformer, present within the same crystal lattice^{6,7}. Co-crystals are formed in a definite stoichiometric ratio and are stabilized by non-covalent intermolecular interactions such as hydrogen bonding, π - π interactions, and van der Waals forces. Unlike salt formation, co-crystallization does not require the drug to be ionizable, thereby allowing its application to a broader range of drug molecules^{8,9}. Appropriate selection of coformers can modify crystal packing and improve important properties such as aqueous solubility, dissolution rate, chemical and physical stability, mechanical properties, tablet ability, and oral bioavailability while preserving the therapeutic activity of the parent drug^{10,11}.

Voriconazole (VCZ), a second-generation triazole antifungal agent, was selected as the model drug for the present investigation. It is widely used in the treatment of life-threatening invasive fungal infections owing to its broad-spectrum antifungal activity¹². However, VCZ belongs to BCS Class II and exhibits poor aqueous solubility despite having high intestinal permeability. In addition, extensive first-pass metabolism, dose-dependent adverse effects, and a relatively short biological half-life of approximately 6 hours result in variable oral bioavailability and necessitate frequent dosing^{13,14}. Hence, the present investigation was planned to develop VCZ co-crystals using nicotinic acid (NA) and succinic acid (SA) as coformers to improve the aqueous solubility and dissolution characteristics of the drug.

2 MATERIALS

Voriconazole (VCZ) was supplied by Hetero Drugs Ltd., Hyderabad. Nicotinic acid (NA) was obtained from Central Drug House (P) Ltd., Delhi, and succinic acid (SA) was procured from New India Chemical Enterprises. All other reagents, solvents used were of analytical grade (SD Fine Chemicals, Bengaluru, India). Double distilled water was used throughout the experiment.

2.1 UV spectrophotometric method

The absorption maximum of VCZ in pH 6.8 buffer was determined by scanning from 200 to 400 nm and was found to be 257.50 nm. A calibration curve was prepared over 4–20 $\mu\text{g/mL}$ in pH 6.8 buffer. The reported calibration data showed a correlation coefficient of 0.999.

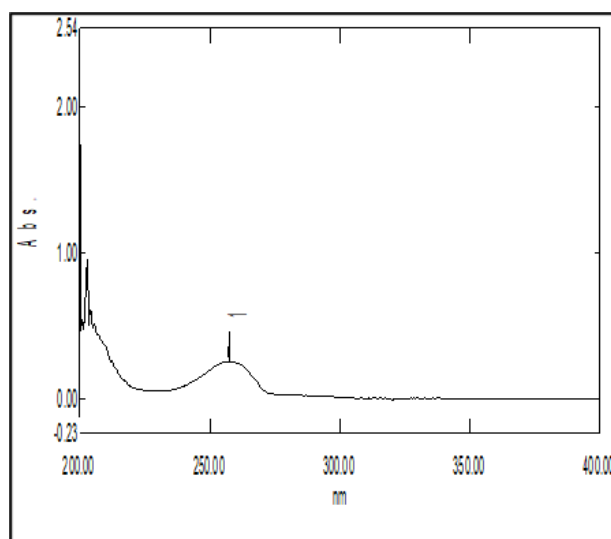


Figure 1: Absorption maxima of VCZ in pH 6.8

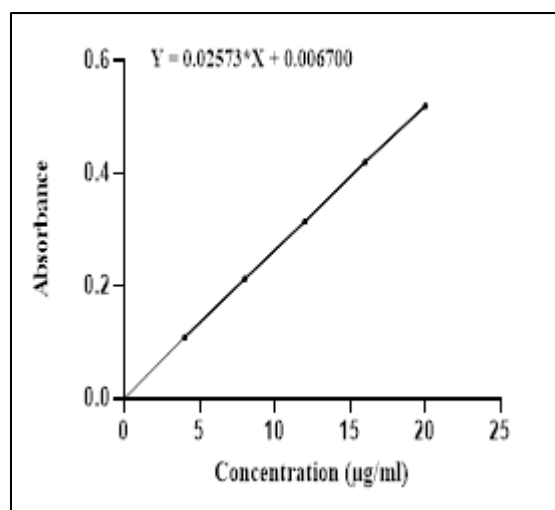


Figure 2: Calibration curve of VCZ

2.2 Phase-solubility study¹⁵

Excess VCZ was added to 10 mL of aqueous NA or SA solutions at 0, 1, 2, 3, 4 and 5% w/v. The suspensions were stirred continuously for 48 h at room temperature to attain equilibrium, filtered through a 0.45 µm membrane filter, suitably diluted and analyzed spectrophotometrically at 257.50 nm. Phase-solubility plots were generated by relating coformer concentration to VCZ solubility.

2.3 Preparation of VCZ co-crystals¹⁶⁻¹⁷

VCZ co-crystals were prepared with NA and SA at 1:1 and 1:2 (w/w) drug-to-coformer ratios using LAG and SE, producing eight batches (T1–T8). For SE, the components were dissolved in a minimum quantity of ethanol (approximately 10 mL) or an ethanol–acetone (1:1) mixture and stirred at 40°C until a clear homogeneous solution was obtained. The solvent was removed by slow evaporation at room temperature or 40°C, or by rotary evaporation under reduced pressure, followed by vacuum desiccation for 24 h. The dried mass was pulverized and passed through a #60 sieve. For LAG, the weighed components were mixed and wetted with 2–3 drops of ethanol or methanol, followed by manual grinding for 45–60 min. The ground mass was dried at 40°C for 24 h and passed through a #60/100 mesh sieve. Prepared co-crystals were stored in airtight amber containers under desiccated conditions.

Table 1: Preparation of VCZ co-crystal batches

Batch	Drug-coformer	Method	Ratio (w/w)
T1	VCZ–NA	LAG	1:1
T2	VCZ–NA	LAG	1:2
T3	VCZ–SA	LAG	1:1
T4	VCZ–SA	LAG	1:2
T5	VCZ–NA	SE	1:1
T6	VCZ–NA	SE	1:2
T7	VCZ–SA	SE	1:1
T8	VCZ–SA	SE	1:2

2.4 Characterization and evaluation¹⁸

Percentage yield was determined for the prepared co-crystals. Drug content was measured after dissolving co-crystals equivalent to 10 mg VCZ in methanol, followed by filtration and spectrophotometric analysis at 257.50 nm. FTIR spectra of pure VCZ and the co-crystals were obtained by the potassium bromide disc method over 4000–400 cm^{−1}. Saturation solubility was determined by adding pure VCZ (20 mg) or co-crystals equivalent to 10 mg VCZ to 15 mL of pH 6.8 medium and shaking for 24 h in a rotary flask shaker. Aliquots were filtered through 0.45 µm membrane filters and analyzed at 257.50 nm; measurements were performed in triplicate.

In vitro dissolution was evaluated using USP dissolution apparatus II. Samples equivalent to 20 mg VCZ were placed in 900 mL pH 6.8 phosphate buffer maintained at $37 \pm 0.5^\circ\text{C}$ and 50 rpm for 60 min. 5 mL samples were withdrawn at specified intervals, filtered and replaced with an equal volume of buffer to maintain sink conditions. Absorbance was measured at 257.50 nm, and dissolution data were analyzed using PCP DISSO V3.

3 RESULTS AND DISCUSSION

Pharmaceutical co-crystal engineering was employed as a unique approach to address the poor aqueous solubility of VCZ without altering its chemical structure or pharmacological activity. VCZ co-crystals were prepared and characterized using NA and SA as pharmaceutically acceptable cofomers, selected for their favorable hydrogen-bonding ability, safety, and potential to improve the solubility and dissolution characteristics of VCZ.¹⁹⁻²¹

3.1 Phase-solubility study

The phase-solubility study showed a concentration-dependent increase in the apparent solubility of VCZ in the presence of both cofomers. VCZ solubility increased from 0.55 to 2.82 mg/mL with NA from 1 to 5% w/v, whereas SA increased solubility from 1.13 to 3.42 mg/mL over the same concentration range. The reported linear relationships between cofomer concentration and VCZ solubility were $r = 0.9646$ for NA and $r = 0.9800$ for SA. SA produced the higher apparent solubility at every concentration studied.

Table 2: Phase-solubility study of VCZ in NA and SA solutions

Cofomer concentration (% w/v)	VCZ solubility in SA (mg/mL)	VCZ solubility in NA (mg/mL)
1	1.13	0.55
2	1.71	1.05
3	2.23	1.66
4	2.55	1.86
5	3.42	2.82

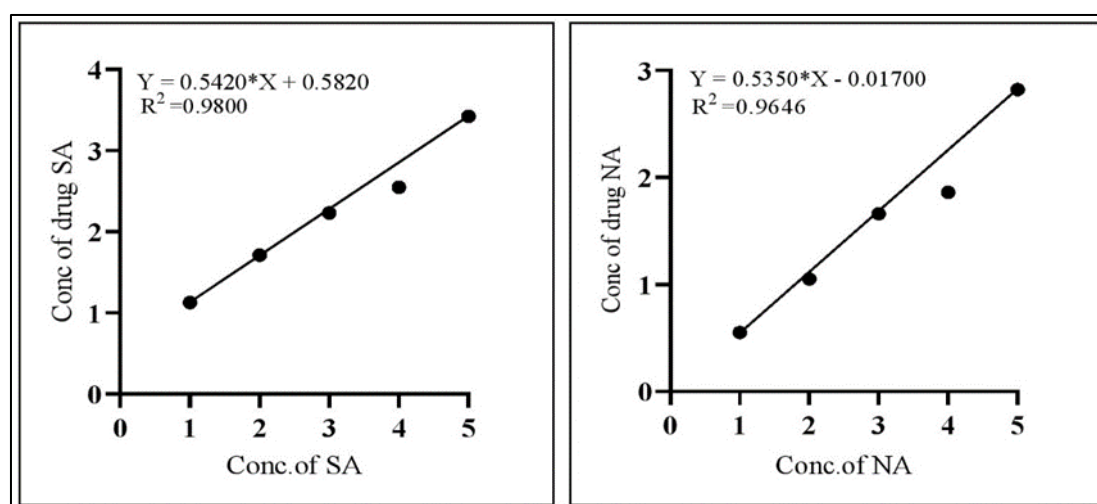


Figure 3: The phase-solubility plots between cofomer concentration and VCZ solubility.

3.2 Percentage yield and drug content

The percentage yield of eight co-crystal batches was found in the range of 96–99%. Drug content ranged from 96.46 to 97.78%, with low standard deviations, indicating uniform drug distribution among the prepared batches.

3.3 FTIR characterization

FT-IR spectroscopy was performed to investigate the possible intermolecular interactions between voriconazole (VCZ) and the selected coformers and to confirm the structural integrity of VCZ following co-crystallization. The FT-IR spectra of pure VCZ and the prepared co-crystals obtained by liquid-assisted grinding (LAG) and solvent evaporation (SE) methods are shown in Figures 4 and 5 respectively. The spectrum of pure VCZ exhibited characteristic absorption bands at 3200–3300 cm^{-1} corresponding to O–H stretching, 3060–3000 cm^{-1} and 2920–2850 cm^{-1} corresponding to aromatic and aliphatic C–H stretching, respectively, and 1600–1500 cm^{-1} corresponding to aromatic C=C and C=N stretching vibrations. The bands observed at 1270–1030 cm^{-1} were attributed to C–O and C–N stretching, while the bands below 900 cm^{-1} were associated with aromatic C–H bending and C–F stretching vibrations. These characteristic absorption bands confirmed the structural integrity of VCZ.

The VCZ–NA co-crystals prepared by the LAG and SE methods retained the characteristic absorption bands of VCZ, with slight shifts and changes in peak intensity, particularly in the O–H stretching and C=O/C=N stretching regions. These changes suggested the formation of intermolecular hydrogen-bonding interactions between the carboxylic acid group of NA and the nitrogen-containing heterocyclic groups of VCZ. Similarly, the VCZ–SA co-crystals exhibited broadening and shift in the O–H and carbonyl stretching regions, indicating hydrogen-bond formation between VCZ and SA. The spectral changes were more pronounced in the VCZ–SA co-crystals than in the VCZ–NA co-crystals, suggesting stronger intermolecular interactions and improved molecular organization. Among the investigated formulations, the VCZ–SA co-crystal prepared by the SE method (T8) exhibited the most distinct spectral changes, particularly broadening of the O–H stretching band and shifts in the carbonyl stretching region. These observations indicated stronger intermolecular hydrogen-bonding interactions and were consistent with the higher aqueous solubility observed for T8. The absence of new characteristic absorption bands in the co-crystals indicated that no chemical modification or degradation of VCZ occurred during the co-crystallization process. Overall, the observed spectral shifts, broadening, and changes in intensity were attributed to intermolecular hydrogen-bond formation rather than the formation of new covalent bonds, supporting the successful formation of VCZ–NA and VCZ–SA co-crystals. These findings were further supported by the DSC and dissolution studies.

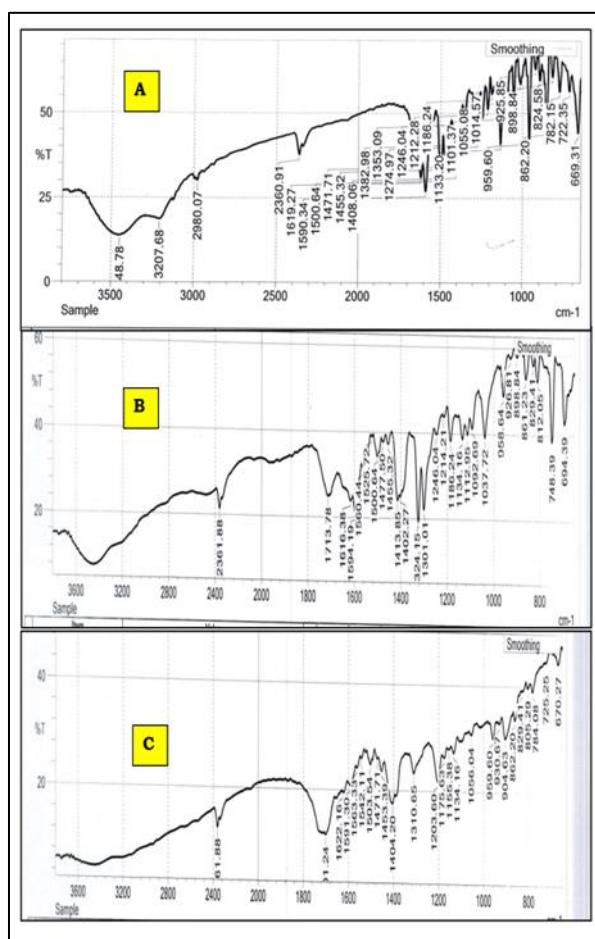


Figure 4: FTIR spectra of A) VCZ, B) VCZ:NA, C) VCZ:SA (LAG method)

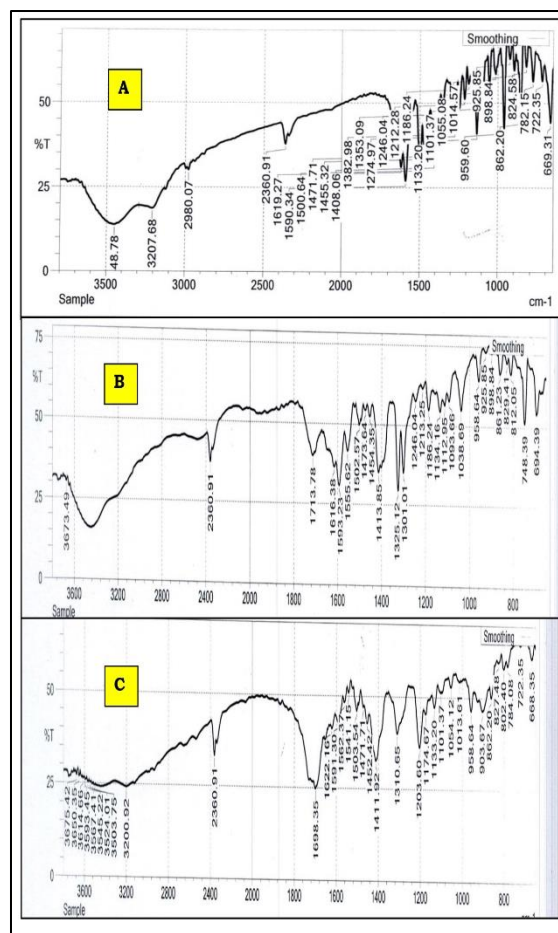


Figure 5: FTIR spectra of A) VCZ, B) VCZ:NA, C) VCZ:SA (SE method)

3.4 Saturation solubility of VCZ co-crystals

The aqueous solubility of pure VCZ and its co-crystals was determined at 25 ± 0.5 °C in pH 6.8 buffer, and the results are presented in Table 3. Pure VCZ exhibited a solubility of 0.47 ± 0.05 mg/mL. In comparison, all VCZ co-crystal formulations demonstrated a marked increase in solubility, indicating that co-crystal formation effectively improved the aqueous solubility of VCZ.

Among the VCZ–NA co-crystals, increasing the drug-to-coformer ratio from 1:1 to 1:2 (w/w) resulted in an increase in solubility for both preparation methods. For the LAG method, the solubility increased from 1.592 ± 0.06 mg/mL (T1) to 1.853 ± 0.03 mg/mL (T2), whereas for the SE method, it increased from 1.938 ± 0.05 mg/mL (T5) to 2.061 ± 0.04 mg/mL (T6). The SE-prepared VCZ–NA co-crystals exhibited slightly higher solubility than their corresponding LAG formulations.

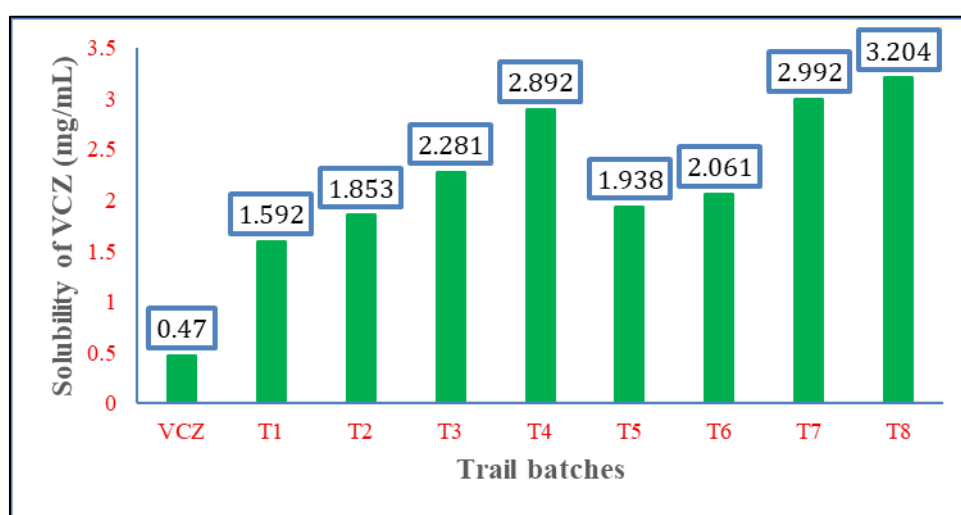
A greater enhancement in solubility was observed for the VCZ–SA co-crystals. The solubility increased from 2.281 ± 0.05 mg/mL (T3) to 2.892 ± 0.07 mg/mL (T4) with the LAG method and from 2.992 ± 0.05 mg/mL (T7) to 3.204 ± 0.02 mg/mL (T8) with the SE method. Among all formulations, T8 (VCZ–SA, 1:2 w/w, SE) exhibited the highest solubility (3.204 ± 0.02 mg/mL), corresponding to an approximately 6.8-fold increase compared with pure VCZ. The solubility enhancement followed the order:

$T8 > T7 > T4 > T3 > T6 > T5 > T2 > T1 > \text{Pure VCZ}$

The improved solubility of the VCZ co-crystals may be attributed to alterations in the crystal lattice and favourable intermolecular interactions between VCZ and the respective coformers, which can modify the physicochemical properties of the drug and facilitate dissolution. The greater solubility observed with SA compared with NA suggests that the choice of coformer plays an important role in determining the solubility enhancement of VCZ. Furthermore, the 1:2 drug-to-coformer ratio consistently produced higher solubility than the corresponding 1:1 ratio, irrespective of the preparation method. Overall, the findings demonstrate that co-crystallization, particularly with SA at a 1:2 ratio using the SE method, substantially enhanced the aqueous solubility of VCZ.

Table 3: Saturation solubility of pure VCZ and VCZ co-crystals

Batch	Drug-coformer	Method	Ratio (w/w)	Solubility (mg/mL)
Pure VCZ	—	—	—	0.47 ± 0.05
T1	VCZ-NA	LAG	1:1	1.592 ± 0.06
T2	VCZ-NA	LAG	1:2	1.853 ± 0.03
T3	VCZ-SA	LAG	1:1	2.281 ± 0.05
T4	VCZ-SA	LAG	1:2	2.892 ± 0.07
T5	VCZ-NA	SE	1:1	1.938 ± 0.05
T6	VCZ-NA	SE	1:2	2.061 ± 0.04
T7	VCZ-SA	SE	1:1	2.992 ± 0.05
T8	VCZ-SA	SE	1:2	3.204 ± 0.02

**Figure 6: Solubility profile of pure VCZ and T1-T8 co-crystals.**

3.5 In vitro dissolution

The dissolution profiles of pure VCZ and its co-crystals with NA and SA are presented in Table 4 and Figure 7. Pure VCZ showed poor dissolution, with only 23.394% drug release after 60 min. In comparison, all co-crystal formulations exhibited markedly improved dissolution. The VCZ-NA co-crystals T1, T2, T5, and T6 showed 66.150%, 68.346%, 62.424%, and 75.683% drug release, respectively, whereas the VCZ-SA co-crystals T3, T4, T7, and T8 showed 71.301%, 86.130%, 79.114%, and 92.877% release, respectively, at 60 min. The 1:2 (w/w) formulations generally exhibited higher drug release than the corresponding 1:1 formulation. Among all formulations, T8 showed the highest dissolution (92.877%), followed by T4 (86.130%).

Table 4: In vitro dissolution data of pure VCZ and T1-T8 co-crystals

Time (min)	VCZ	T1	T2	T3	T4	T5	T6	T7	T8
10	3.725	17.835	19.584	24.366	25.065	20.167	19.468	25.182	25.415
20	7.244	33.327	35.786	45.841	47.128	25.177	37.301	48.294	49.695
30	10.783	38.759	43.214	52.159	54.968	34.412	49.752	57.075	59.416
40	15.623	50.168	53.481	56.295	63.085	43.115	60.872	64.853	68.490
50	19.091	57.091	62.871	64.650	77.775	54.197	66.804	69.174	83.093
60	23.394	66.150	68.346	71.301	86.130	62.424	75.683	79.114	92.877

The improved dissolution of the co-crystals may be attributed to enhanced wettability and modification of the crystal lattice through favorable intermolecular interactions between VCZ and the coformers. Overall, SA produced a greater enhancement in VCZ dissolution than NA, with T8 prepared by the SE method showing the most pronounced improvement.

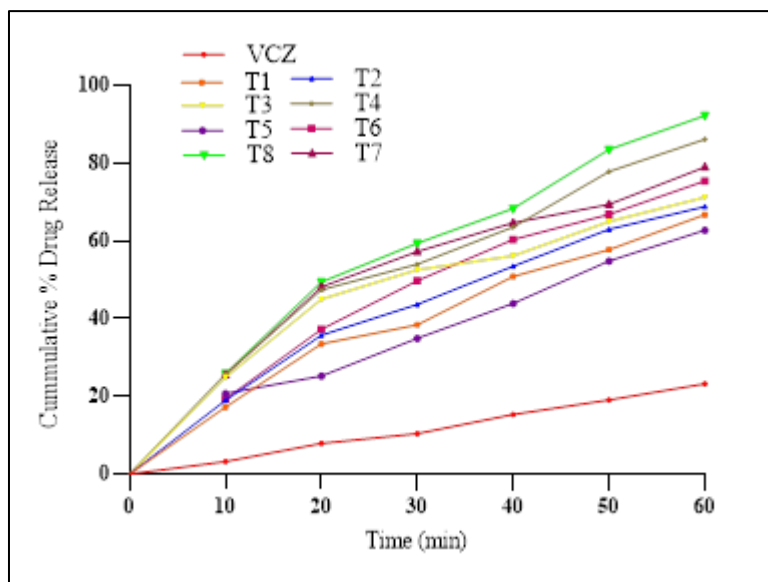


Figure 7: Comparative in vitro dissolution profiles of pure VCZ and T1–T8 co-crystals.

Table 5: Various dissolution parameters of VCZ and T1 to T8 co-crystals

Dissolution parameters	VCZ	T1	T2	T3	T4	T5	T6	T7	T8
T ₅₀ (min)	126.2	39.4	35.6	29.5	26.2	45.2	30.1	24.5	22.6
DE ₁₀ (%)	1.86	8.92	9.79	12.18	12.53	10.08	9.73	12.59	12.71
DE ₃₀ (%)	5.45	23.51	25.66	32.10	33.43	20.85	27.21	34.00	34.94
DE ₆₀ (%)	11.36	38.38	41.52	46.49	51.85	34.71	45.34	50.69	55.42
RDR ₃₀	1	4.31	4.70	5.88	6.13	3.82	4.99	6.23	6.41

Where, DE = Dissolution efficiency after 10, 30 and 60 min ; RDR₃₀ = Relative dissolution rate at 30 min. ; T₅₀ = time necessary to dissolve 50% drug

The dissolution parameters clearly demonstrated the superior dissolution behaviour of the co-crystal formulations compared with pure VCZ. Pure VCZ exhibited a T₅₀ of 126.2 min, whereas all co-crystal formulations showed substantially lower T₅₀ values, ranging from 22.6 to 45.2 min, indicating faster drug dissolution. The lowest T₅₀ was observed for T8 (22.6 min), followed by T7 (24.5 min) and T4 (26.2 min).

The dissolution efficiency (DE) values further supported the improved dissolution of the co-crystals. Pure VCZ exhibited DE₁₀, DE₃₀ and DE₆₀ values of only 1.86%, 5.45% and 11.36%, respectively. In comparison, T8 showed the highest values of 12.71%, 34.94% and 55.42%, respectively, indicating substantially greater drug dissolution over the respective time intervals. The RDR₃₀ values were markedly higher for the co-crystal formulations, with the highest value observed for T8 (6.41), followed by T7 (6.23) and T4 (6.13), indicating a higher dissolution rate during the initial 30-min period. Among all formulations, T8 (VCZ–SA, 1:2 w/w, SE) exhibited the most favorable dissolution characteristics, with the lowest T₅₀ and highest DE₁₀, DE₃₀, DE₆₀ and RDR₃₀ values.

4 CONCLUSION

The present study demonstrated that pharmaceutical co-crystallization can effectively enhance the aqueous solubility and dissolution of VCZ. Among the investigated coformers, ratios, and preparation methods, the VCZ–SA co-crystal prepared at a 1:2 w/w ratio by solvent evaporation (T8) exhibited the highest solubility, with an approximately 6.82-fold enhancement compared with pure VCZ, along with improved dissolution performance. These findings highlight the influence of coformer selection, drug-to-coformer ratio, and preparation method on the physicochemical performance of VCZ co-crystals. Thus, optimized VCZ–SA co-crystals may therefore serve as a promising groundwork for further development of VCZ dosage forms.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The Authors declare no conflict of interest.

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