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Original Article

DEVELOPMENT AND CHARACTERIZATION OF VORICONAZOLE-OXALIC ACID DIHYDRATE COCRYSTALS FOR ENHANCED PHARMACEUTICAL PERFORMANCE

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ABSTRACT

Pharmaceutical cocrystallization is a promising alternative for improving the solubility and dissolution rate or manipulating other physical properties of active pharmaceutical ingredients. The objective of this investigation was to study the effect of cocrystallization to improve physicochemical properties of voriconazole (VZ). Liquid assisted grinding method was attempted for preparation of cocrystals. Melting point, Fourier transformation infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), and differential scanning calorimetry (DSC) techniques were employed to investigate the hydrogen bonding interaction, crystallinity and thermal behaviour of prepared cocrystals respectively. The pharmaceutical cocrystals were successfully obtained with oxalic acid dihydrate (OAD) in 2:1 stoichiometric ratio. The physicochemical properties of VZ and corresponding cocrystals were assessed in terms of saturation solubility and dissolution performance. The VZ cocrystals showed enhanced solubility and dissolution rate as compared with VZ. The VZ cocrystals (4.179 mg/mL) showed higher solubility in 0.1 N hydrochloric acid than VZ (3.140 mg/mL). Cocrystals showed higher dissolution rate than VZ. The enhancement in dissolution rate of VZ cocrystal from OA was 2.28-fold within 10 min.

KEYWORDS: Cocrystals, liquid-assisted grinding, solubility, dissolution.

1. Introduction

Crystal engineering is the most widely used technique to modulate the physicochemical properties of drug substances. Pharmaceutical cocrystals are the multi-component system in which one of the components is an API and other is GRAS listed coformer [1-3]. VZ ((2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol) is a triazole anti-fungal drug belonging to BCS class II drugs (low solubility and high permeability) with prevalent solubility problem which results in poor absorption of VZ when administered through oral route [4]. VZ exhibits antifungal activity by inhibiting the cytochrome P450 (CYP)-dependent enzyme 14-alpha-sterol demethylase [5]. It has wide application against fungal infections caused by *Candida* spp., *Aspergillus* spp., and *Cryptococcus neoformans*, including those resistant to other commonly used antifungal agents [6]. The aim of this study is to enhance the solubility and dissolution behaviour of VZ by cocrystallization technique using GRAS listed coformers. Since cocrystals of VZ with fumaric acid, PABA, and PHBA have been documented, additional GRAS-listed coformers were explored to enhance the physicochemical properties of VZ like adipic acid, glutaric acid, oxalic acid dihydrate, maleic acid, salicylic acid, succinic acid, tartaric acid, citric acid, cinnamic acid, malonic acid, nicotinic acid [7,8]. Liquid assisted grinding method was used to prepare the cocrystals. The formulated co-crystals were characterized by melting point, FTIR, PXRD, DSC, solubility and dissolution studies.

2. Materials and Methods

VZ was provided by Hetero drugs Ltd, Hyderabad and coformers were purchased from S.D. Fine Chemicals Limited, Mumbai. All other chemicals were of analytical grade.

2.1. pKa

pKa serves as a basic estimate for predicting cocrystal formation, as illustrated in Table 1. Salt formation takes place when the pKa difference between the acid and base is greater than 3, while a pKa difference of less than 0 indicates the likelihood of cocrystal formation. The pKa value measures an acid's tendency to donate a proton; therefore, variations in pKa values indicate the potential for

proton transfer and the subsequent formation of either cocrystals or salts [9,10].

Table 1. pKa of drug and coformer

Sl. no	Name	pKa	ΔpK_a	Inference	Reference
1	VZ (pure drug)	1.76	-	-	11
2	Adipic acid	4.42	-2.66	Cocrystal	12
3	Glutaric acid	4.34	-2.58	Cocrystal	12
4	OAD	1.25	0.51	Cocrystal or salt	12
5	Maleic acid	1.93	-0.17	Cocrystal	12
6	Salicylic acid	2.97	-1.21	Cocrystal	12
7	Succinic acid	4.19	-2.43	Cocrystal or salt	12
8	Tartaric acid	3.2	-1.44	Cocrystal	12
9	Citric Acid	3.13	-1.37	Cocrystal	12
11	Cinnamic acid	4.4	-2.64	Cocrystal	12
12	Malonic acid	2.83	-1.07	Cocrystal	12
13	Nicotinic acid	4.8	-3.04	Cocrystal	12

2.2. Preparation of cocrystals by liquid assisted grinding technique

VZ and coformer were taken in 2:1 stoichiometric ratio and mixed in a mortar and pestle using 2-3 drops of ethanol. The mixture was triturated for 30-45 mins and stored in a desiccator. Various coformers used for the preparation of VZ cocrystals were presented in the Table 2. The formation of VZ cocrystals was confirmed by melting point determination, FTIR, PXRD, DSC [13,14].

Table 2. Cocrystals preparation using different coformers

Sl. no	Drug-coformer	Ratio	Solvent	Inference
1	VZ-Adipic acid	2:1	Ethanol	Product was found to be sticky in nature
2	VZ-Glutaric acid	2:1	Ethanol	Product was found to be sticky in nature
3	VZ-OAD	2:1	Ethanol	Cocrystals might have formed
4	VZ-Maleic acid	2:1	Ethanol	Cocrystals might have formed
5	VZ-Salicylic acid	2:1	Ethanol	Product was found to be sticky in nature
6	VZ-Succinic acid	2:1	Ethanol	Cocrystals might have formed
7	VZ-Tartaric acid	2:1	Ethanol	Product was found to be sticky in nature
8	VZ-Citric Acid	2:1	Ethanol	Product was found to be sticky in nature
9	VZ-Cinnamic acid	2:1	Ethanol	Product was found to be sticky in nature
10	VZ-Malonic acid	2:1	Ethanol	Product was found to be sticky in nature
11	VZ-Nicotinic acid	2:1	Ethanol	Product was found to be sticky in nature

2.3. Melting point of cocrystals

The melting point of a compound is a fundamental physical property determined for the purpose of characterization or purity identification of a compound. The melting points of the VZ and VZ-OAD cocrystal were determined by open capillary tube method [15,16].

2.4. FTIR

Solid samples of VZ, OAD and VZ-OAD cocrystal were prepared as KBr pellets and analysed using IR spectroscopy (Nicolet 6700, Waltham, MA, USA) [17,18].

2.5. PXRD

PXRD is a powerful technique for determining the presence of polymorphs, crystal habit modifications in drug crystals and/or generation of new crystal form during cocrystallization process. The generation of cocrystalline material was confirmed by X-ray Diffractometer (Bruker XRD-D8 Advance, Germany) recording diffractometry patterns of pure VZ, OAD and VZ-OAD cocrystal [19].

2.6. DSC

DSC measurements were conducted using TA Q200 DSC instrument (New Castle, DE, USA) at 10ºC/ min heating rate to characterize the integrity and purity of APIs. The bulk purity of the cocrystals were characterized by this technique to confirm the bulk purity of the formed VZ-OAD cocrystal [20].

2.7. Solubility studies of VZ cocrystals

Solubility of VZ-OAD cocrystal was determined by adding excess amount of samples to 10 mL of 0.1 N HCl and stirring at 100 rpm for 24 hrs at 25ºC. Samples were filtered and analysed by UV spectroscopy. [21].

2.8. Dissolution studies of VZ cocrystals

For the dissolution studies, 0.1 N HCl was selected as a dissolution medium and measurements were conducted using Dissolution Apparatus USP - Type II. VZ-OAD cocrystal equivalent to 50 mg of pure VZ was filled into capsules and added into 900 mL dissolution medium at room temperature [20]. The paddles were stirred at 50 rpm and the samples were withdrawn at different time intervals (10, 20, 30, 40, 50, 60 min). Absorbance was measured using UV spectrophotometer at 255 nm [22].

3. Results and discussion

3.1. Melting point of cocrystals

Among the prepared cocrystals, the VZ -OAD cocrystals have shown melting point lower than VZ and OAD as shown in Table 3. These observations clearly indicated the formation of cocrystals of VZ with OAD. The altered melting points in cocrystals as compared to VZ and coformer might be attributable to hydrogen bonding interaction between API and crystal forming agent, altered packing arrangement and change in the crystallinity of molecules in the cocrystals [23].

Table 3. Melting point of VZ and VZ-OAD cocrystal

Name of cocrystal	Melting point of drug/coformer (literature value)	Melting point of drug/coformer (observed value)	Melting point of drug/cocrystals (observed value)	Inference
VZ	127-130ºC	125-135ºC	-	-
OAD	101-102 ºC	102-105 ºC	-	-
VZ-OAD	-	-	118-125ºC	Cocrystals might have formed

3.2. FTIR

The possible interaction between the VZ and VZ-OAD cocrystal, coformer were studied by FTIR spectroscopy and IR spectra are depicted in Fig. 1. VZ structural characteristic bands at O-H - 3201.3 cm^{-1} (stretching), C=N - 1619.5 cm^{-1} (stretching), C=C - 1587.3 cm^{-1} (stretching), C-F 1277.4 cm^{-1} (stretching) are shown in Fig. 1. VZ-OAD cocrystals showed bands of O-H - 3203.5 cm^{-1} (stretching), C=N - 1588.3 cm^{-1} (stretching), C=C - 1644.5 cm^{-1} (stretching), C-F - 1248.4 cm^{-1} (stretching). It was noted that all significant bands corresponding to the functional groups of VZ are present in the cocrystal, along with some new bands. The results revealed considerable changes in IR bands of VZ in prepared OAD cocrystals when compared to pure drug, thereby indicating the presence of hydrogen bonding that had occurred in cocrystals [24].

3.3. PXRD

As shown in Fig. 2, unique PXRD reflection patterns distinguishable from the VZ (drug) and the OAD (coformer) were noted. It can be seen that the VZ-OAD cocrystal exhibited spectra with maximum intensity reflection at 23° which is different from maximum intensity of VZ (20°), indicating the generation of cocrystals. This was also strongly supported by the melting points and FTIR observed for the VZ-OAD cocrystal which were completely different from VZ and VZ-OAD crystals. Thus, co-crystal formation was dependent on the non-covalent intermolecular hydrogen bonding interactions, thereby confirming the formation of the co-crystal of VZ and OAD [25, 26, 27].

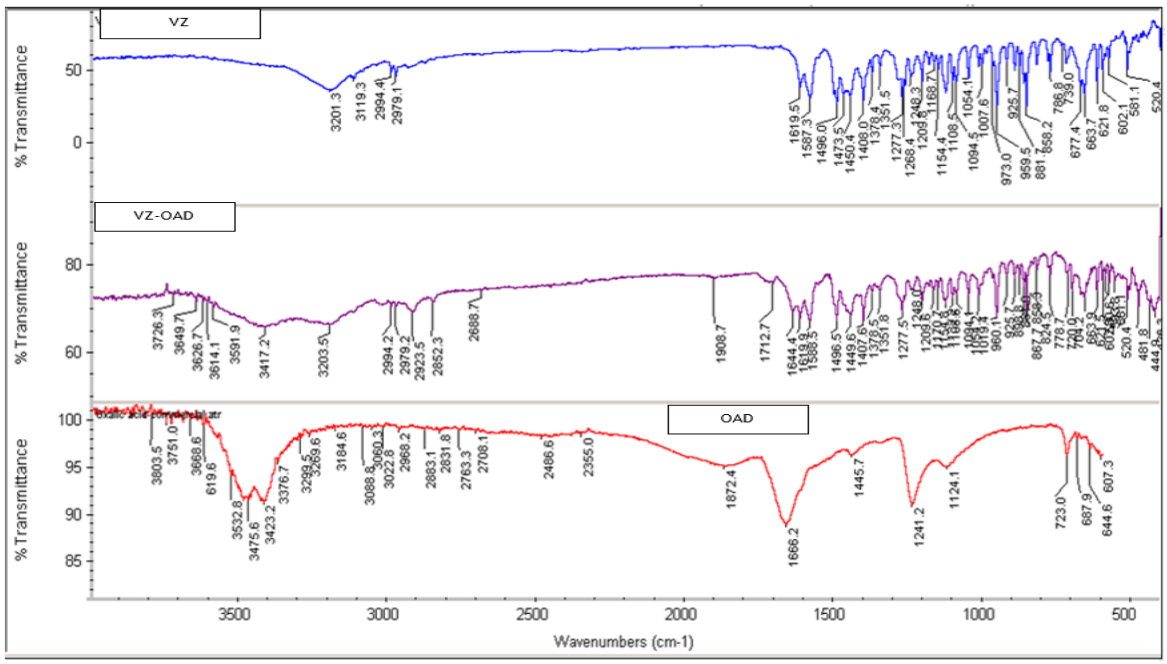

Fig. 1. FTIR spectral comparison of VZ and OAD (2:1) liquid assisted grinded mixture with its individual components.

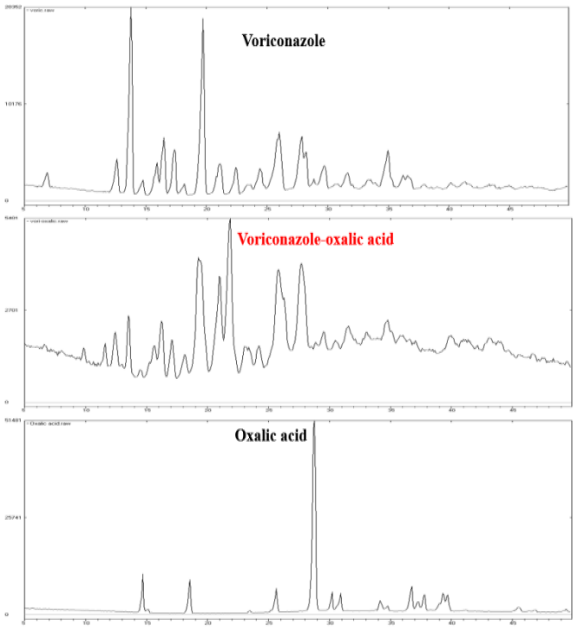

Fig. 2. Comparison of the PXRD reflection pattern of VZ-OAD cocrystals with its individual components shows difference in the peak positions.

3.4. DSC

The DSC thermogram of VZ and VZ-OAD cocrystals were obtained and and shown in Fig. 3. VZ-AD cocrystals showed sharp endothermic peak and lower melting point, i.e., 121.66°C, compared to VZ (138.86 °C) and OAD (102°C) [26].

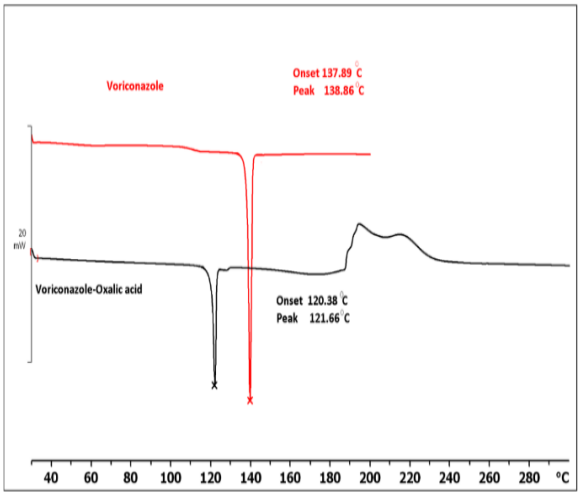

Fig. 3. DSC thermogram of VZ and VZ-OAD cocrystal.

3.5. Solubility studies of VZ cocrystals

The solubility of VZ in VZ-OAD cocrystals showed higher solubility, i.e., 4.179 mg/mL than VZ alone (3.14 mg/mL) as showed in Fig. 4. The enhanced solubility of VZ might be due to the formation of cocrystals. This indirectly supports the characterization of cocrystals. These findings are consistent with melting point studies, which indicated a successful interaction between VZ and the coformer, confirming the formation of cocrystals [27].

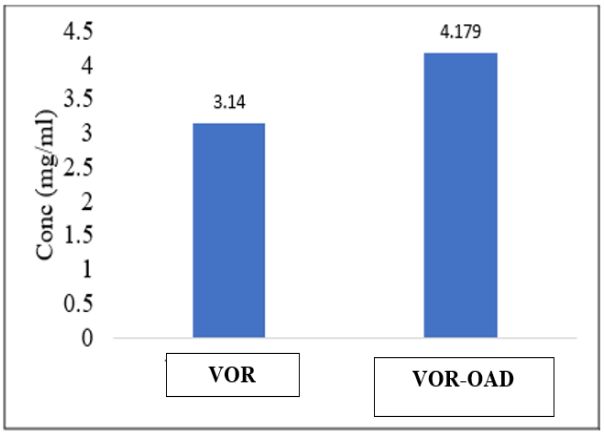

Fig. 4. Solubility of VZ and VZ-OAD cocrystal in 0.1N HCl.

3.6. Dissolution studies of VZ cocrystals

Fig. 5 presents the dissolution-time profile for VZ and the VZ-OAD cocrystal in 0.1 N HCl. The dissolution data for the VZ-OAD cocrystal indicated a drug release of 85.38 % within 60 minutes, demonstrating enhanced drug release compared to pure VZ, which showed a release of 61.03 %. The study indicated that the prepared cocrystal facilitated a faster and more complete release of the drug compared to VZ [28].

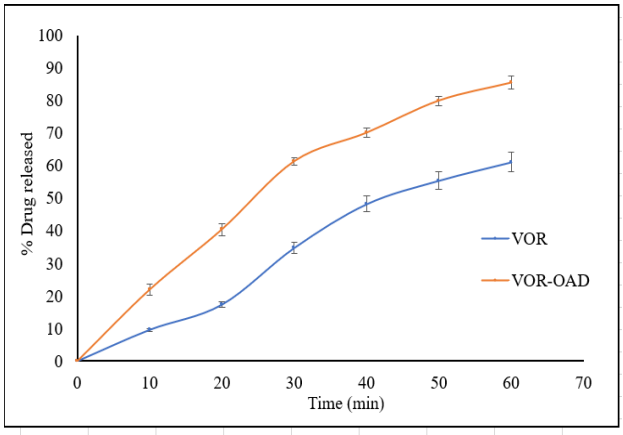

Fig. 5. Cumulative % drug dissolved-time profile of VZ and VZ-OAD cocrystals.

4. Conclusion

Crystal engineering approach was employed to alter the physicochemical properties of VZ. The liquid-assisted grinding method was utilized to prepare VZ cocrystals in a 2:1 stoichiometric ratio, eleven coformers being tested during the preparation. The drug exhibited changes only with the OAD, which was further characterized using FTIR, PXRD, melting point analysis, and DSC. The FTIR results indicated significant alterations and shifts in the frequencies of IR bands in the VZ-OAD cocrystals compared to VZ. The PXRD pattern of the VZ-OAD cocrystals displayed different peak positions than those of VZ and OAD. The results offer a promising strategy to improve the physicochemical properties of VZ through cocrystallization with OAD.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Guo, M.; Sun, X.; Chen, J.; Cai, T. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. *Acta Pharm. Sin. B.* **2021**, *11*(8), 2537-64. doi: 10.1016/j.apsb.2021.03.030
2. Panzade, P.; Shendarkar, G.; Shaikh, S.; Rathi, PB. Pharmaceutical cocrystal of piroxicam: design, formulation and evaluation. *Adv. Pharm. Bull.* **2017**, *7*(3), 399. doi: 10.15171/apb.2017.048
3. Singh, M.; Barua, H.; Jyothi, VG.; Dhondale, MR.; Nambiar, AG.; Agrawal, AK.; Kumar, P.; Shastri, NR.; Kumar, D. Cocrystals by design: a rational coformer selection approach for tackling the API problems. *Pharm.* **2023**, *15*(4), 1161.
4. Greer, ND. Voriconazole: the newest triazole antifungal agent. *Bayl Univ Med Cent.* **2003**, *16*(2), 241-8. doi: 10.1080/08998280.2003.11927910
5. Scott, LJ.; Simpson, D. Voriconazole: a review of its use in the management of invasive fungal infections. *Drugs.* **2007**, *67*(2), 269-98. doi: 10.2165/00003495-200767020-00009
6. Shah, MK.; Azad, AK.; Nawaz, A.; Ullah, S.; Latif, MS.; Rahman, H.; Alsharif, KF.; Alzahrani, KJ.; El-Kott, AF.; Albrakati, A.; Abdel-Daim, MM. Formulation development, characterization and antifungal evaluation of chitosan NPs for topical delivery of voriconazole in vitro and ex vivo. *Polymers.* **2021**, *14*(1), 135. doi: 10.3390/polym14010135
7. Sanphui, P.; Mishra, MK.; Ramamurty, U.; Desiraju, GR. Tuning mechanical properties of pharmaceutical crystals with multicomponent crystals: voriconazole as a case study. *Mol. Pharm.* **2015**, *12*(3), 889-97. Doi: 10.1021/mp500719t
8. Kumar, SS.; Thakuria, R.; Nangia, A. Pharmaceutical cocrystals and a nitrate salt of voriconazole. *CrystEngComm.* **2014**, *16*(22), 4722-31. doi: 10.1039/C3CE42324G
9. Savla, PP. The Selection and Screening of Conformers. The Bombay Technologist. **2021**. doi: 10.36664/bt/2021/v68i1/164061
10. Wathoni, N.; Sari, WA.; Elamin, KM.; Mohammed, AF.; Suharyani, I. A review of coformer utilization in

multicomponent crystal formation. *Mol*. **2022**, *27*(24), 8693. doi: 10.3390/molecules27248693

11. Mushtaq, M.; Fatima, K.; Ahmad, A.; Mohamed Ibrahim, O.; Faheem, M.; Shah, Y. Pharmacokinetic interaction of voriconazole and clarithromycin in Pakistani healthy male volunteers: a single dose, randomized, crossover, open-label study. *Front Pharmacol*. **2023**, *14*, 1134803. doi: 10.3389/fphar.2023.1134803

12. Marydele, J. The Merck index: an encyclopedia of chemicals, drugs and biologicals, 14th ed.; Whitehouse station (New Jeresy): Merck and Co. Inc, **2006**.

13. Buddhadev, SS.; Garala, KC. Pharmaceutical cocrystals—a review. *InProceedings*. **2021**, *62*(1), 14. doi: 10.3390/PROCEEDINGS2020062014

14. Nijhawan, M.; Godugu, M.; Saxena, T.; Farheen, T.; Dwivedi, K. Pharmaceutical co-crystals of posaconazole for improvement of physicochemical properties. *Braz. J. Pharm. Sci*. **2022**, *58*, e191024. doi: 10.1590/s2175-97902022e191024

15. Ammanage, A.; Rodriques, P.; Kempwade, A.; Hiremath, R. Formulation and evaluation of buccal films of piroxicam co-crystals. *Future J. Pharm. Sci*. **2020**, *6*, 1-1. doi: 10.1186/s43094-020-00033-1

16. Desai, H.; Rajadhyax, A.; Jaiswal, S.; Gulhane, N. Studies on Formulation and Evaluation of Clotrimazole Cocrystals. *World j. pharm. pharm. Sci*. **2022**, *11*(10). doi:10.20959/wjpps202210-23314

17. Nijhawan, M.; Santhosh, A.; Babu, PS.; Subrahmanyam, CV. Solid state manipulation of lornoxicam for cocrystals–physicochemical characterization. *Drug Dev Ind Pharm*. **2014**, *40*(9), 1163-72. doi: 10.3109/03639045.2013.804834

18. Madan, JR.; Waghmare, SV.; Patil, RB.; Awasthi, R.; Dua, K. Cocrystals of apixaban with improved solubility and permeability: formulation, physicochemical characterization, pharmacokinetic evaluation, and computational studies. *Assay drug dev techn*. **2021**, *19*(2), 124-38. doi: 10.1089/adt.2020.1052

19. Wu, N.; Zhang, Y.; Ren, J.; Zeng, A.; Liu, J. Preparation of quercetin–nicotinamide cocrystals and their evaluation under in vivo and in vitro conditions. *RSC advances*. **2020**, *10*(37), 21852-9. doi: 10.1039/D0RA03324C

20. Khan, FM.; Ahmad, M.; Idrees, HA. Simvastatin-nicotinamide co-crystals: formation, pharmaceutical characterization and in vivo profile. *Drug Des. Devel. Ther*. **2020**, *14*, 4303-13. doi: 10.2147/DDDT.S270742

21. Nijhawan, M.; Dhyagala, S.; Gunnam, S.; Aleti, R.; Saxena, T. Dipyridamole cocrystal tablets with enhanced solubility and dissolution at intestinal pH. *Fabad J. Pharm. Sci*. **2024**, *49*(1), 37-50. doi: 10.55262/fabadeczacilik.1318448

22. Naqvi, A.; Ahmad, M.; Minhas, MU.; Khan, KU.; Batool, F.; Rizwan, A. Preparation and evaluation of pharmaceutical co-crystals for solubility enhancement of atorvastatin calcium. *Polym. Bull*. **2020**, *77*, 6191-211. doi:10.1007/s00289-019-02997-4

23. Thimmasetty, J.; Shashank, NN.; Raheem, TA.; Shwetha, SK.; Tanmoy, G. Modafinil Cocrystals for Altered Physicochemical Properties. *Res J Pharm Technol*. **2021**, *14*(9), 4891-4896. doi: 10.52711/0974-360X.2021.00850

24. Nikam, VJ.; Patil, SB. Pharmaceutical cocrystals of nebivolol hydrochloride with enhanced solubility. *J. Cryst. Growth*. **2020**, *534*, 125488. doi: 10.1016/j.jcrysgro.2020.125488

25. Thenge, RA.; Patel, R.; Kayande, NA.; Mahajan, NI. Co-crystals of carvedilol: preparation, characterization and evaluation. *Int J Appl Pharm*. **2020**, *12*(1), 42-49. doi: 10.22159/ijap.2020v12i1.35640

26. Colmenero, F. Mechanical properties of anhydrous oxalic acid and oxalic acid dihydrate. *Physical Chemistry Chemical Physics*. **2019**, *21*(5), 2673-90. doi: 10.1039/C8CP07188H

27. Lalitha, P.; Arumugam, S.; Sinthiya, A.; Nivetha, C.; Muthuselvam, M. Oxalic acid incorporated acetamide single crystal growth dynamics, characterization, NLO and antimicrobial activities via shock wave treatment. *Results in Chemistry*. **2023**, *5*, 100790. doi: 10.1016/j.rechem.2023.100790

28. Dutt, B.; Choudhary, M.; Budhwar, V. Preparation, characterization and evaluation of fenofibrate: benzoic acid cocrystals with enhanced pharmaceutical properties. *Future J. Pharm. Sci*. **2021**, *7*(1), 170. doi: 10.1186/s43094-021-00320-5

29. Ahirrao, SP.; Sonawane, MP.; Bhambere, DS.; Udavant, PB.; Ahire, ED.; Kanade, R.; Kuber, D. Cocrystal formulation: a novel approach to enhance solubility and dissolution of etodolac. *Biosci. Biotechnol. Res. Asia*. **2022**, *19*(1), 111. doi: 10.13005/bbra/2971

30. Kulkarni, AL.; Shete, SW.; Hol, VI.; Bachhav, RI. Novel pharmaceutical cocrystal of telmisartan and hydrochlorothiazide. *Asian J Pharm Clin Res*. **2020**, *13*(3), 104-2. doi: 10.22159/ajpcr.2020.v13i3.36541