ORIGINAL ARTICLE

Influence of Nicotinamide in Solid Dispersion of Allopurinol-PEG 8000-Nicotinamide to Dissolution Rate of Allopurinol

Fera Ayu Dianovita[1], Achmad Radjaram[2], Siti Fauziyah Rahman[1,3]

[1] Division of Biomedical Engineering, Department of Electrical Engineering, Faculty of Engineering, Universitas Indonesia, Depok 16424, Indonesia
[2] Pharmaceutical Technology Laboratory, Department of Pharmaceutic, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[3] Research Center for Biomedical Engineering (RCBE), Faculty of Engineering, Universitas Indonesia, Depok 16424, Indonesia

ABSTRACT

Introduction: Allopurinol is commonly used to treat chronic gout or hyperuricemia, exhibiting effective permeability despite being practically insoluble in water. The dissolution rate becomes a crucial factor in drug absorption, influencing the bioavailability of orally administered medications. This study explores the physical attributes and in vitro dissolution profile of allopurinol-PEG 8000-nicotinamide ternary solid dispersion. **Materials and Methods:** Different ratios of allopurinol, PEG 8000, and nicotinamide (5:5:4.49) were employed to create the solid dispersion. Powder X-ray diffraction (PXRD) was utilized to characterize the solid dispersion. In-vitro dissolution tests were performed for allopurinol-PEG 8000-nicotinamide and compared with binary solid dispersion, physical mixture, and pure allopurinol. **Results:** The ternary solid dispersion of allopurinol-PEG 8000-nicotinamide displayed reduced crystal peak intensity compared to pure allopurinol, the physical mixture, and binary solid dispersion. This formulation significantly enhanced the dissolution rate of allopurinol. The order of dissolution rates among the ternary solid dispersion formulations was determined based on the dissolution efficiency at the 60th minute. Statistical analysis using the one-way ANOVA method (confidence level: 95%, $\alpha = 0.05$) revealed a significant difference in dissolution efficiency at the 60th minute, as evidenced by the calculated F value (103.746) exceeding the F table value (2.85). **Conclusion:** The current study demonstrated that incorporating nicotinamide into the allopurinol-PEG 8000-nicotinamide ternary solid dispersion markedly improves the dissolution rate of allopurinol.
Malaysian Journal of Medicine and Health Sciences (2025) 21(SUPP8):8-13. doi:10.47836/mjmhs.21.s8.2

Keywords: Allopurinol; PEG 8000; Nicotinamide; Solid dispersion; Dissolution

Corresponding Author:
Siti Fauziyah Rahman, S.T., M. Eng., Ph.D.
Email: fauziyah17@ui.ac.id
Tel : +62-81287867170

INTRODUCTION

Allopurinol, also known as [1H-pyrazolo [3,4-d] pyrimidin-4-ol], is an extensively prescribed medication that effectively treats gout by reducing uric acid levels in the body [1]. With an increasing prevalence of gout in the UK, the British Society for Rheumatology recommends pharmacological urate-lowering therapy (ULT), primarily xanthine oxidase inhibitors like Zyloprim (allopurinol) [2]. As a drug with low permeability and poor water solubility, allopurinol hinders its oral bioavailability, impacting the oral absorption of the drug [3]. The research on improving the bioavailability of allopurinol is one of the greatest challenges in drug development, as solubility is a crucial quality for the drug release mechanism [4].

Various methods, including particle size reduction, polymeric micelles, polymeric drug encapsulation and solid dispersions, aim to enhance dissolution rates [5]. Solid dispersion is the process of dispersing a more hydrophobic substance into an amorphous phase to enhance its Gibbs energy which will improve its dissolution rate [6,7]. This approach inhibits aggregation and facilitates particle size reduction, demonstrating potential progress for poorly water-soluble drugs as allopurinol [8]. PEG 8000 is a surfactant ingredient that was chosen as the solid dispersion matrix. It provides good wetting and is water-soluble, inert, and non-toxic, which leads to increased formulation stability

[9]. Extensive research has been conducted on solid dispersions involving the PEG matrix and gliclazide [10], griseofulvin-PEG 8000 [11], and nitazoxanide-PEG 8000[12]. However, for drugs requiring large doses, the use of matrices becomes impractical. To address this, our study integrates complex-forming materials, specifically nicotinamide, into a ternary system with the PEG matrix. Nicotinamide's hydrotropic effect improves drug solubility by disrupting water structure[13]. To address this limitation, the addition of nicotinamide can enhance dissolution rates. Nicotinamide is known for its hydrotropic effect and its ability to form complexes with poorly soluble drugs. Combining nicotinamide with PEG matrices improves drug solubility and is considered safe for use

This study aims to develop a composite matrix solid dispersion to enhance allopurinol's dissolution rate, utilizing a ternary system with nicotinamide to reduce dependence on the polymer matrix.

MATERIALS AND METHODS

Materials

All materials used in this study were pharmaceutical grade unless otherwise specified. These materials included allopurinol (Nanjing), polyethylene glycol (PEG 8000) (Fluka), nicotinamide (Western Drugs), absolute ethanol p.a (Merck), hydrochloric acid (Merck), and aqua demineralization (ultrapure water).

Preparation of Allopurinol-Nicotinamide Solid Dispersion in PEG 8000

Carefully weighing a specified amount of allopurinol, PEG 8000, and nicotinamide according to the planned ratios as listed in Table I. PEG 8000 was melted on a hot plate, followed by the addition of nicotinamide and stirring until fully dissolved. Allopurinol, along with 10 ml of absolute ethanol, was gently stirred until homogeneous. The solvent was evaporated on a hot plate at 70-80ºC. After drying, the solid dispersion was stored in a desiccator for 24-48 hours, then crushed in an agate mortar to a powdered form. Subsequently, it was sieved using a No. 70 mesh sieve and stored in an airtight glass container (Table I).

Preparation of Allopurinol-PEG 8000-Nicotinamide Physical Mixture

The allopurinol-PEG 8000-nicotinamide blend was prepared by accurately measuring PEG 8000 as specified in Table I and ground in an agate mortar. Simultaneously, nicotinamide was prepared in the designated amount as per the plan. These two components were combined and thoroughly mixed until a uniform blend was achieved. Allopurinol, previously measured following Table I, underwent sieving through a No. 70 mesh sieve. Subsequently, it was added to the pre-prepared polymer mixture (PEG 8000 and nicotinamide) and stirred until homogeneity was attained.

Table I. Distribution of allopurinol treatment groups

Material	PA	Solid Dispersion w/w			Physical Mix w/w		
		SD I	SD II	SD III	PM I	PM II	PM III
Allopurinol	5	5	5	5	5	5	5
PEG 8000	-	5	-	5	5	-	5
Nicotinamide	-	-	4.49	4.49	-	4.49	4.49

PA : Pure Allopurinol SD : Solid Dispersion PM : Physical mixture

Characterization with X-Ray Diffraction Analysis using PXRD

The sample was carefully loaded into a glass holder and inserted into an X-ray diffractometer (X'pert Philips, Netherlands) with a Ni-filtered Cu metal target, Kα X-ray radiation source, and a scintillation counter detector. Measurement settings included a voltage of 40 kV, a current of 30 mA, 0.5 divergence and scatter slits, and a 0.15 mm receiving slit. Observations were made over a 2θ angle range from 5º to 50º.

In-vitro dissolution test

The dissolution rate was assessed using an Erweka DT 700 dissolution tester with 900 mL 0.1 N HCl at 37 ± 0.5ºC, and a paddle rotation speed of 100 rpm. Samples, 5.0 ml each, were collected at 5-minute intervals (at 5, 10, 15, 20, 30, 45, and 60 minutes). Dissolved allopurinol at each time interval was calculated using both the allopurinol standard curve equation and the allopurinol-nicotinamide simultaneous equation. Dissolution efficiency values underwent statistical analysis using a one-way ANOVA (Analysis of Variance) with a Completely Randomized Design at a significance level (α) of 0.05.

RESULT

Characterization using Powder X-ray Diffraction Method (PXRD)

The peak intensity of allopurinol is observed at 2θ angles of 10.52º, 12.04º, and 17.30º. Using the peak intensity data (counts), the relative intensity of allopurinol was determined for each treatment. The calculation of the relative intensity involved comparing the peak intensity of each treatment with the peak intensity of pure allopurinol at the corresponding angle position.
(Figure 1)

To facilitate a comprehensive comparison of the relative

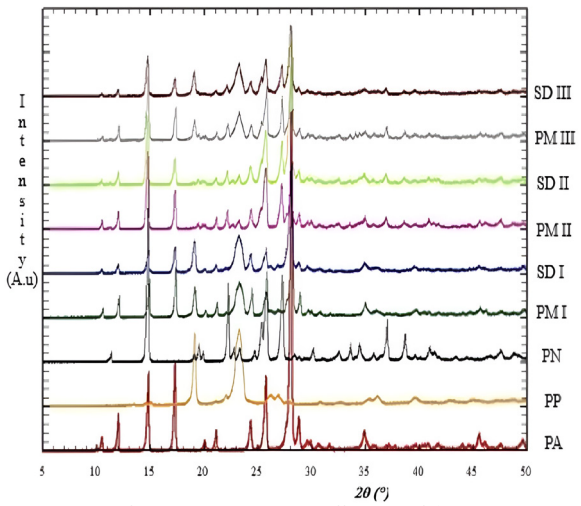

Figure 1: X-ray diffractogram of pure allopurinol (PA), pure PEG 8000 (PP), pure nicotinamide (PN), allopurinol-PEG 8000 physical mixture (PM I), allopurinol-PEG 8000 solid dispersion (SD I), allopurinol-nicotinamide physical mixture (PM II), allopurinol-nicotinamide solid dispersion (SD II), allopurinol-PEG 8000-nicotinamide physical mixture (PM III), allopurinol-PEG 8000-nicotinamide solid dispersion (SD III)

intensity of allopurinol across all treatments, we can compute the relative intensity of allopurinol at a specific angle, specifically 17.30 degrees. The necessary data for this calculation can be located in (Fig. 1).

Analyzing the data concerning the relative intensity of allopurinol, it becomes evident that the relative intensity of allopurinol within the solid dispersion system is noticeably lower when compared to the physical mixture at the same ratio. Specifically, for the allopurinol-PEG binary solid dispersion system, the calculated relative intensity is 25.65%, while the relative intensity for the binary physical mixture at the same ratio is 64.41%. Similarly, the ternary solid dispersion system also exhibited a decrease in peak intensity compared to the physical mixture. Specifically, it recorded an 18.08% relative intensity for the allopurinol-PEG 8000-nicotinamide ternary solid dispersion system, while the ternary physical mixture yielded a relative intensity of 22.90%.

In-vitro Dissolution Test

Analysis of the percent recovery revealed that the % recovery was as follows: 96.88% ± 0.49 for allopurinol-PEG 8000 solid dispersion, 96.52% ± 1.72 for allopurinol-nicotinamide solid dispersion, and 100.58% ± 0.22 for allopurinol-PEG 8000-nicotinamide solid dispersion. (Figure 2)

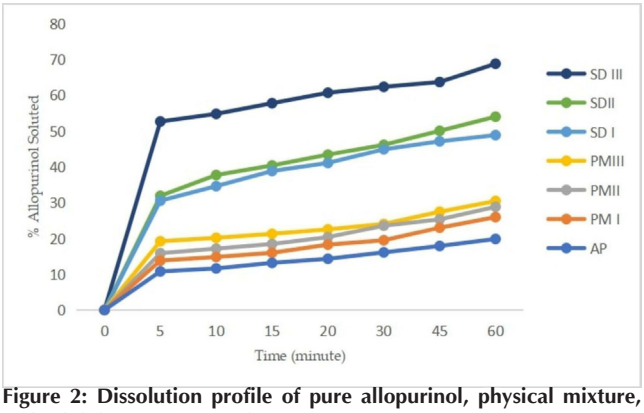

Figure 2: Dissolution profile of pure allopurinol, physical mixture, and solid dispersion in HCl 0.1 N at 37ºC ± 0.5, pH 1 ± 0.05

To identify variations in dissolution rates among different treatments, we computed the dissolution efficiency (DE) values (as presented in Table III). According to the DE60 values, the dissolution rate of allopurinol followed this trend: ternary solid dispersion > allopurinol-nicotinamide binary solid dispersion > allopurinol-PEG binary solid dispersion > ternary physical mixture > physical mixture allopurinol-nicotinamide > binary physical mixture allopurinol-PEG 8000 > pure allopurinol. (Table II)

Table II. Dissolution efficiency (DE) of allopurinol from each treatment group in 0.1 N HCl media at 37ºC ± 0.5, pH 1 ± 0.05

REPLICATION	DE_{60}						
	PA	PM I	PM II	PM III	SD I	SD II	SD III
1	15.27	20.42	25.55	19.05	41.17	43.63	57.89
2	17.68	18.78	18.30	29.08	40.84	37.76	59.65
3	12.22	17.95	21.20	22.52	41.16	47.85	59.11
MEAN	15.06	19.05	21.68	23.55	41.06	43.08	58.88
SD	2.74	1.26	3.65	5.09	0.19	5.07	0.90

Based on the aforementioned data, a one-way ANOVA test was conducted for each DE, and the calculated F value for DE (103.746) was found to be greater than the critical F table value (2.85). This leads to the conclusion that there is a significant difference among the treatments.

DISCUSSION

Figure 1 illustrates the diffractogram of allopurinol, showing a reduced peak intensity within the solid dispersion system at 2θ angles of 10.52 , 12.04 , and 17.30 , as indicated by previous research [14]. Despite variations in methodologies for creating solid dispersions compared to prior studies, such as solvent evaporation, co-grinding, kneading, co-precipitation,

and the melting method [15], consistent results were obtained, indicating a decline in peak intensity at 2θ in the allopurinol solid dispersion. In our study, allopurinol is dispersed within the hydrophilic matrix of PEG 8000, effectively enveloping the allopurinol particles. The reduction in relative intensity suggests the formation of a solid dispersion system, where allopurinol is dispersed within PEG 8000 [16]. The decreased intensity at each 2θ angle implies a reduction in the number of crystal lattice areas. This reduction in intensity at various 2θ angles signifies fewer crystal lattice regions due to the process of creating solid dispersions [17]. Active ingredients are dispersed onto the carrier, followed by rapid solvent evaporation, preventing full dispersion into the high molecular weight polymer. This hinders the arrangement of molecules into larger structures and the formation of smaller-sized drug particles. In this scenario, the drug substance doesn't transition into an amorphous form since, during manufacturing, the active substance doesn't completely dissolve. A eutectic mixture system is formed in this setup as the three-drug components remain in the solid dispersion system in particle form. Despite the intensity decrease, there's no change in peaks, leading to the conclusion that the solid dispersion formed is a simple eutectic solid dispersion [18].

Evaluating the dissolution profiles in Figure 2, it becomes apparent that the solid dispersion system yields a significantly higher dissolution rate compared to the physical mixture and pure allopurinol. The dissolution profile of the allopurinol-PEG 8000-nicotinamide ternary solid dispersion system shows an increased amount of allopurinol dissolved in the initial minutes. Within the first 5 minutes, the amount of pure allopurinol dissolved was only 10.79%. Notably, there was a substantial enhancement in the treatments: allopurinol-PEG 8000 binary solid dispersion, which dissolved 31.9% of allopurinol, allopurinol-nicotinamide solid dispersion, which dissolved 30.55%, and the ternary solid dispersion, which dissolved 52.68%. This indicates that during the initial 0 to 5 minutes, the solid dispersion system comes into contact with the dissolution medium. The hydrophilic polymer, PEG 8000, is the first component to be released from the system, subsequently dissolving in the dissolution medium, followed by the release of the drug substance with small particle sizes into the dissolution medium [19]. Moreover, the presence of the third ingredient, nicotinamide, also contributes to the increased dissolution rate of allopurinol through molecular interactions, although these interactions may not be as potent as those observed in the case of ornidazole-nicotinamide [20], theophylline-nicotinamide [21], and valsartan-nicotinamide [22]. This observation is corroborated by the X-ray diffractogram, which does not reveal any alterations in the peaks but rather a decrease in intensity, attributed to a reduction in the degree of crystal order in Figure 1. These circumstances facilitate the initial increase in the amount of drug substance dissolved within the first few minutes. However, subsequently, PEG 8000 and nicotinamide dissolve within the system, resulting in the dissolution profile of the system becoming more gradual, resembling the dissolution profiles of a physical mixture and pure allopurinol.

By examining the Dissolution Efficiency values at the 60th minute (DE60) of allopurinol, comparisons can be made between solid dispersions, physical mixtures, and pure allopurinol. In SD I, the dissolution of allopurinol increased by 2.15 times compared to PM I and 2.72 times compared to pure allopurinol. In SD II, it increased by 1.98 times compared to PM II and 2.85 times compared to pure allopurinol, while in SD III, it increased by 2.50 times compared to PM III and 3.90 times compared to pure allopurinol. Additionally, based on the DE60 values, a comparison can also be made between ternary solid dispersions and binary solid dispersions. In the ternary solid dispersion (5:5:4.49) system, allopurinol dissolution increased by 1.37 times compared to allopurinol-nicotinamide binary solid dispersion (5:4.49), while in the allopurinol-PEG binary solid dispersion (5:5), it increased by 1.43 times. Consequently, it can be concluded that the inclusion of a water-soluble and semi-polar PEG 8000 matrix enhances allopurinol's wetting and reduces the drug substance's particle size, directly leading to an increase in allopurinol dissolution within the solid dispersion system [23]. Furthermore, the addition of nicotinamide as a third ingredient in the allopurinol-PEG 8000 (5:5) solid dispersion system has a positive impact on enhancing the dissolution rate of allopurinol.

The Indonesian Pharmacopoeia specifies that allopurinol in pharmaceutical formulations must achieve a dissolution rate of 75% within 45 minutes [24]. Comparative analysis at the 45th minute reveals the following dissolution extents for allopurinol: 63.70% in the ternary solid dispersion system, 47.15% in the allopurinol-PEG binary solid dispersion, and 17.88% as pure allopurinol. This suggests an improvement in the dissolution of allopurinol as a raw material for pharmaceutical preparations. Consequently, further research is imperative to explore the use of excipients in solid preparations to ensure compliance with the stipulations outlined in the Indonesian Pharmacopoeia.

CONCLUSION

The present study demonstrates that the formulation of a ternary solid dispersion system comprising allopurinol, PEG 8000, and nicotinamide can significantly improve the dissolution rate of allopurinol. This enhancement is attributed to the reduction in the particle size of allopurinol, as it is dispersed within PEG 8000, facilitating efficient wetting and accelerating the dissolution rate. Additionally, the interaction between allopurinol and the third component, nicotinamide,

contributes to an increased solubility of allopurinol, further boosting its dissolution rate. Consequently, the ternary solid dispersion system shows great potential for development in dosage formulations.

ACKNOWLEDGMENTS

We gratefully acknowledge the funding from Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi through Penelitian Kerjasama - Dalam Negeri 2023 No. NKB-1159/UN2.RST/HKP.05.00/2023

REFERENCES

[1] Schlesinger N, Brunetti L. Beyond urate lowering: Analgesic and anti-inflammatory properties of allopurinol. Semin Arthritis Rheum 2020;50:444–50. https://doi.org/10.1016/j.semarthrit.2019.11.009.

[2] FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken) 2020;72:744–60. https://doi.org/10.1002/acr.24180.

[3] Rajpoot K, Tekade M, Sreeharsha N, Sharma MC, Tekade RK. Recent advancements in solubilization of hydrophobic drugs. The Future of Pharmaceutical Product Development and Research, Elsevier; 2020, p. 109–44. https://doi.org/10.1016/B978-0-12-814455-8.00004-9.

[4] Chinh NT, Manh VQ, Hoang T, Ramadass K, Sathish CI, Trung VQ, et al. Optimizing the component ratio to develop the biocomposites with carrageenan/collagen/allopurinol for the controlled drug release. J Drug Deliv Sci Technol 2022;68:102697. https://doi.org/10.1016/j.jddst.2021.102697.

[5] Kumar R, Thakur AK, Chaudhari P, Banerjee N. Particle Size Reduction Techniques of Pharmaceutical Compounds for the Enhancement of Their Dissolution Rate and Bioavailability. J Pharm Innov 2022;17:333–52. https://doi.org/10.1007/s12247-020-09530-5.

[6] de Rezende SC, Ferreira O, Santamaria-Echart A, Dias MM, Barreiro MF. Evaluating the potential of natural polymers for water-dispersible curcumin-based solid dispersion colourant systems for food applications. J Food Eng 2024;371:111986. https://doi.org/10.1016/j.jfoodeng.2024.111986.

[7] Samsoen S, Dudognon Й, Le Fer G, Fournier D, Woisel P, Affouard F. Impact of the polymer dispersity on the properties of curcumin/polyvinylpyrrolidone amorphous solid dispersions. Int J Pharm 2024;653:123895. https://doi.org/10.1016/j.ijpharm.2024.123895.

[8] Bhalani D V., Nutan B, Kumar A, Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines 2022;10:2055. https://doi.org/10.3390/biomedicines10092055.

[9] Tresia Butar-Butar ME, Wathoni N, Ratih H, Wardhana YW. Solid Dispersion Technology for Improving the Solubility of Antiviral Drugs. vol. 10. 2023. https://doi.org/10.7454/psr.v10i1.1292.

[10] Febriyenti F, Rahmi S, Halim A. Study of gliclazide solid dispersion systems using PVP K-30 and PEG 6000 by solvent method. J Pharm Bioallied Sci 2019;11:262. https://doi.org/10.4103/jpbs.JPBS_87_18.

[11] Wani RJ, Sharma P, Zhong HA, Chauhan H. Preparation and Characterization of Griseofulvin Solid Dispersions. Assay Drug Dev Technol 2020;18:109–18. https://doi.org/10.1089/adt.2019.965.

[12] Sood S, Maddiboyina B, Rawat P, Garg AK, Foudah AI, Alam A, et al. Enhancing the solubility of nitazoxanide with solid dispersions technique: formulation, evaluation, and cytotoxicity study. J Biomater Sci Polym Ed 2021;32:477–87. https://doi.org/10.1080/09205063.2020.1844506.

[13] Ainurofiq A, Putro D, Ramadhani D, Putra G, Do Espirito Santo LC. A review on solubility enhancement methods for poorly water-soluble drugs. Journal of Reports in Pharmaceutical Sciences 2021;10:137. https://doi.org/10.4103/jrptps.JRPTPS_134_19.

[14] Barbosa TWL, Talmeli RMS, Junior H de O, Doriguetto AC, de Araьjo MB, Bonfilio R. Solid state characterization, solubility, intrinsic dissolution and stability behavior of allopurinol hydrochloride salt. Drug Dev Ind Pharm 2021;47:799–808. https://doi.org/10.1080/03639045.2021.1934872.

[15] Tekade AR, Yadav JN. A Review on Solid Dispersion and Carriers Used Therein for Solubility Enhancement of Poorly Water Soluble Drugs. Adv Pharm Bull 2020;10:359–69. https://doi.org/10.34172/apb.2020.044.

[16] Sood S, Maddiboyina B, Rawat P, Garg AK, Foudah AI, Alam A, et al. Enhancing the solubility of nitazoxanide with solid dispersions technique: formulation, evaluation, and cytotoxicity study. J Biomater Sci Polym Ed 2021;32:477–87. https://doi.org/10.1080/09205063.2020.1844506.

[17] S'ari M, Blade H, Cosgrove S, Drummond-Brydson R, Hondow N, Hughes LP, et al. Characterization of Amorphous Solid Dispersions and Identification of Low Levels of Crystallinity by Transmission Electron Microscopy. Mol Pharm 2021;18:1905–19. https://doi.org/10.1021/acs.molpharmaceut.0c00918.

[18] Chaturvedi K, Shah HS, Nahar K, Dave R, Morris KR. Contribution of Crystal Lattice Energy on the Dissolution Behavior of Eutectic Solid Dispersions. ACS Omega 2020;5:9690–701. https://doi.org/10.1021/acsomega.9b03886.

[19] Nair AR, Lakshman YD, Anand VSK, Sree KSN, Bhat K, Dengale SJ. Overview of Extensively Employed Polymeric Carriers in Solid Dispersion Technology. AAPS PharmSciTech 2020;21:309. https://doi.org/10.1208/s12249-020-01849-z.

[20] Agrawal GP, Garg A. Polymorphic transformation of ornidazole with nicotinamide in solid dispersion to enhance solubility and dissolution rate. ACTA Pharmaceutica Sciencia 2020;58:259. https://doi.org/10.23893/1307-2080.APS.05815.

[21] Srinivasan P, Almutairi M, Dumpa N, Sarabu S, Bandari S, Zhang F, et al. Theophylline-nicotinamide pharmaceutical co-crystals generated using hot melt extrusion technology: Impact of polymeric carriers on processability. J Drug Deliv Sci Technol 2021;61:102128. https://doi.org/10.1016/j.

jddst.2020.102128.

[22] Turek M, Ryżycka-Sokołowska E, Koprowski M, Marciniak B, Bałczewski P. Role of Hydrogen Bonds in Formation of Co-amorphous Valsartan/Nicotinamide Compositions of High Solubility and Durability with Anti-hypertension and Anti-COVID-19 Potential. Mol Pharm 2021;18:1970–84. https://doi.org/10.1021/acs.molpharmaceut.0c01096.

[23] Hu C, Yan Q, Zhang Y, Yan H. Influence Mechanism of Drug–Polymer Compatibility on Humidity Stability of Crystalline Solid Dispersion. Pharmaceuticals 2023;16:1640. https://doi.org/10.3390/ph16121640.

[24] Kementerian Kesehatan Republik Indonesia. Disolusi Tablet Allopurinol. Farmakope Indonesia. 2020 [cited 2024 Jul 3];6:86-7. Available from: https://farmalkes.kemkes.go.id/2020/11/farmakope-indonesia-edisi-vi.