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RESEARCH ARTICLE

Solubility improvement of gallic acid in water through cocrystal formation with the solvent-drop grinding method and tartaric acid as co-former

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Abstract

Background: Quality, safety, and efficacy are required in pharmaceutical preparations on the market. The role of tested active substances and additives in producing a product formula that is stable, consistent, and meets standards. Solubility is an important parameter for achieving systemic drug concentration and pharmacological response. Cocrystals, for example, have been studied extensively to increase their solubility. Solvent-drop grinding is used to combine active pharmaceutical substances with co-formers into a single crystal unit. Gallic acid is an antioxidant, antimicrobial, anti-inflammatory, anticancer, cardioprotective, gastroprotective, and neuroprotective chemical compound. It is soluble in water thus used to make cocrystals. Also, tartaric acid is crystallised, inert, and easily soluble in water, so it is a natural choice as a co-former. **Objectives:** Solvent-drop grinding was used to characterise the gallic acid cocrystal formation with tartaric acid co-former, and the effect of gallic acid cocrystal formation with tartaric acid as a co-former was tested using Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD). **Method:** The ratios of gallic acid cocrystals to tartaric acid co-formers were 1:0, 1:1, and 2:1. After crushing gallic and tartaric acids for four minutes, a few drops of ethanol solvent were added until the mixture was homogeneous. **Result:** There was an increase in the cocrystal solubility test. The presence of hydrogen bonds between the co-formers of gallic and tartaric acids is indicated by a wavenumber shift in the cocrystal's infrared spectrum. Furthermore, each cocrystal creates a new peak in the X-ray pattern, indicating that hydrogen bonds formed cocrystals. **Conclusion:** The co-crystallisation method can increase the solubility of gallic acid in water by 1.21 times.

Introduction

Solubility is one of the parameters to achieve drug concentration in systemic circulation to obtain the required pharmacological response. A substance that has low solubility will be absorbed more slowly, causing low bioavailability of drug inside the body and affecting its pharmacological effect. About 40% or more of available drug candidates have low solubility in water (Dara & Husni, 2017).

One method to increase the solubility of an active substance is the solvent-drop grinding method. Solvent-drop grinding consists of grinding then adding a small amount of solvent. The solvent-drop grinding technique can control polymorphs formation, promote better crystallisation, and increase the selectivity of co-crystallisation (Vitthalrao *et al.,* 2013).

Gallic acid is slightly soluble in water, where 1 gram of gallic acid is soluble in 87 ml of water (Budavari *et al.,* 1996). It is unstable at extreme temperatures and in the presence of oxygen or light (Jacques *et al.,* 2010). Pharmacologically, gallic acid has several properties, i.e. antioxidant, antimicrobial, anti-inflammatory, anticancer, with cardioprotective, gastroprotective, and neuroprotective effects (Choubey *et al.,* 2015).

Tartaric acid was chosen as a co-former is because of its carboxyl group and physical properties: crystal, inert and easily soluble in water (FI ed III, p. 653). Hence, this research was conducted to form gallic acid cocrystals using tartaric acid as a co-former. The crystals formed

were evaluated, then characterised by the X-Ray Diffraction (XRD) test to investigate and identify gallic acid cocrystals compared to the pure gallic acid. Fourier Transform Infra-Red (FTIR) and solubility tests were carried out to determine the presence of functional groups in cocrystals and solubility improvements of the gallic acid cocrystal, compared to the pure gallic acid.

Significance of the study

The significance of this research is to provide solubility data and information about cocrystals of gallic acid and tartaric acid co-formers using the solvent-drop grinding method. Information about the cocrystal was carried out using Fourier Transform Infra-Red (FTIR) and X-Ray Diffraction (XRD) instruments.

Methods

Gallic acid cocrystal formation with the solvent-drop grinding method

The tools used in this research were X-Ray Diffraction (XRD) D8 Advance, FTIR, analytical balance (OHAUS PAJI003), orbital shaker, measuring pipette, mortar, pestle, vials, and glassware commonly used in the laboratory. The materials used in this study were gallic acid (Merck), tartaric acid (Merck), 96% ethanol (Brataco), aqua dest. The preparation of gallic acid cocrystals using tartaric acid co-formers was carried out with three different ratios, i.e. 1:0, 1:1, and 2:1. Gallic acid and tartaric acid were mixed in a mortar and crushed for four minutes, then a few drops of ethanol solvent were added until the mixture was homogeneous.

Tests with Fourier Transform Infra-Red (FTIR)

Tests were carried out on gallic acid cocrystals with tartaric acid co-formers. The infrared spectrum of samples was recorded using an infrared spectrophotometer. The instrument was turned on, software opened, the measure was clicked until a green status icon appeared, the background was tested first, then the sample was measured and smoothing, performed, and the data obtained were recorded.

Tests with X-Ray diffraction

Two grams of the analysed gallic acid cocrystal samples were crushed, then placed on a plate that was inserted into the XRD instrument (D8 ADVANCE) at the Bandung Geology Centre Laboratory. This analysis was carried out at an angle range of 2θ 4-45º with a shift speed of 0.800º/second using Cu-Kα1 radiation = 1.54060 nm; Kα2 = 1.54439 nm, at 40kV voltage and current of 30mA.

Solubility test method of gallic acid cocrystal

A sample of 50 mg was dissolved in 50 mL of distilled water, then shaken for 24 hours in a rotary flask shaker or orbital shaker. After 24 hours, the sample was filtered and diluted, and the concentration was measured using a UV spectrophotometer at a wavelength of 765nm.

Results

Gallic acid cocrystal diffractogram with X-Ray Diffraction (XRD)

The characterisation of cocrystals with X-ray diffraction aimed to compare the crystal shape before and after the crystallisation process, marked by the emergence of new peaks when compared to pure gallic acid, indicating the formation of cocrystals. Figure 1 shows the results of the X-ray diffraction characterisation.

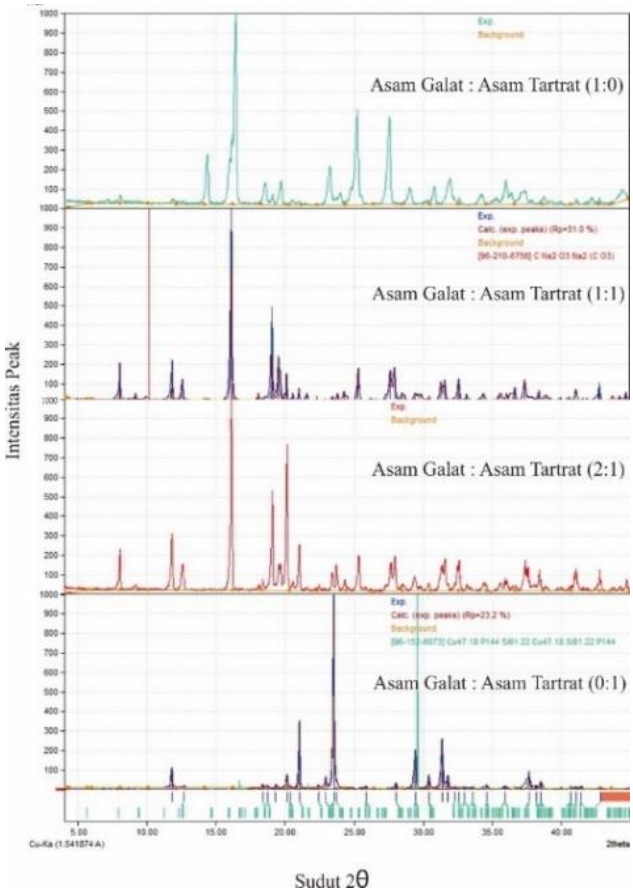

Figure 1: Sample test results using XRD

At 2θ 326,049 ± 0.5 and cocrystal ratio of 1:1, the relative intensity value was 15.08, while at a 2:1, it was lower, 14.82. Additionally, at 2θ 326,049 ± 0.5, several other peaks can be seen (Table I).

Table I: Comparison of the relative intensity between gallic acid and tartaric acid (1:1 and 2:1)

Gallic acid : Tartaric acid (1:1)		Gallic acid : Tartaric acid (2:1)	
Pos. [°2Th.]	**Rel. Int. [%]**	**Pos. [°2Th.]**	**Rel. Int. [%]**
215,955	4.80	215,514	1.23
242,955	5.82	242,905	5.47
285,869	4.48	285,292	3.53
326,049	15.08	326,237	14.82
331,873	3.96	331,371	3.11
344,293	4.97	344,548	3.89
356,685	5.57	355,969	4.86
366,764	8.81	366,505	3.09

Gallic acid cocrystal infrared spectrum with FTIR

The functional group analysis using FTIR spectroscopy was carried out on gallic acid, tartaric acid, and gallic acid-tartaric acid cocrystals at ratios of 1:1 and 2:1, respectively. The infrared (IR) spectrum can be seen in Figure 2.

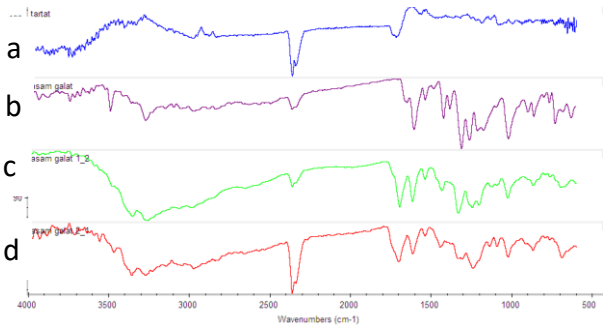

Figure 2: IR spectrum of (a) Tartaric acid, (b) Gallic acid, (c) Crocrystal gallic acid 1:1, (d) Cocrystal gallic acid 2:1

Solubility test results of Gallic acid cocrystal

The absorbance data obtained after the measurement using a UV spectrophotometer were converted into mg/ml solubility units and presented in Table II. The results indicated an increase in solubility.

Table II: Solubility test results

Ratio	Solubility (mg/10mL)	Solubility improvement
1:0	0.1662 mg/ 10mL	-
1:1	0.2012 mg/ 10mL	1.21 times
2:1	0.1753 mg/ 10mL	1.054 times

Discussion

The characterisation of cocrystals by X-ray diffraction aimed to compare the shape of crystals before and after the crystallisation process. It revealed the appearance of new peaks compared to pure gallic acid, indicating the presence of new crystal forms, i.e., the formation of cocrystals. As seen in Table I, the intensity was higher at the 1:1 ratio of gallic acid cocrystals with tartaric acid co-formers than at 2:1. Moreover, the cocrystal crystallinity was better at the ratio of 1:1.

The results of the infrared spectra of cocrystals showed several typical peaks corresponding to the peaks in standard gallic acid and tartaric acid, which indicates a shift in the OH hydroxyl group from a wavelength of 3488 cm-1 up to 3256 cm-1, the C=C group of alkenes from 1647 cm-1 to 1614 cm-1, and the CO carboxylic acid functional group from 1260 cm-1 to 1243 cm-1. The existence of a shift at several points of this wavelength indicates the formation of cocrystals.

In this study, both cocrystal solubility tests indicated an increase in solubility likely due to the presence of hydrogen bonds between gallic acid and tartaric acid co-formers. These hydrogen bonds cause tartaric acid to stick with gallic acid, which helps the dissolution process of gallic acid in water. Indeed, tartaric acid can attract water, thereby increasing the contact between gallic acid and water and the solubility of gallic acid in water. The highest solubility was shown in the 1:1 gallic acid cocrystal, with an increased solubility of 1.21 times, compared to pure gallic acid and 2:1 gallic acid cocrystal.

Conclusion

This study results indicate that the co-crystallisation method at a ratio of 1:1 can increase the solubility of gallic acid in water by 1.21 times.

Reference

Budavari, S. (ed). (1996). The Merck Index – An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station. Merck.Co.Inc. USA

Choubey, S., Varughese, L.R., Kumar, V., & Beniwal, V. (2015). Medicinal importance of gallic acid and its ester derivatives: a patent review. *Pharmaceutical patent analyst,* **4**(4), 305–315. https://doi.org/10.4155/ppa.15.14

Dara, A.I., & Husni, P. (2017). Teknik Meningkatkan Kelarutan Obat. *Farmaka,* **15**(4), 49-57. https://doi.org/10.24198/jf.v15i4.14684

Farmakope Indonesia, Ed III, p. 653

Jacques, A.C., Pertuzatti, P.B., Barcia, M.T., Zambiazi, R.C., & Chim, J.F. (2010). Estabilidade de compostos bioativos em polpa congelada de amora-preta (Rubus fruticosus) cv. Tupy. *Química Nova.* **33**(8), 1720–1725. https://doi.org/10.1590/S0100-40422010000800019

Vaghela, P., Tank, H.M., & Jalpa, P. 2014. Cocrystals: A novel approach to improve the physicochemical and mechanical properties. *Indo American Journal of Pharmaceutical Research,* **4**(10), 5055–5065

Vitthalrao, M.A., Kumar, F.N., & Radheshyam, B.K. (2013). Cocrystalization: an alternative approach for solid modification. *Journal of Drug Delivery and Therapeutics,* 3(4), 166–172. https://doi.org/10.22270/jddt.v3i4.555