

Optimization cocrystal formation of furosemide with malic acid coformer using neat grinding method to improve solubility and dissolution

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ABSTRACT: Furosemide is a Biopharmaceutical Classification System (BCS) Class IV diuretic whose bioavailability is strictly limited by its poor solubility and low permeability. This study aimed to optimize the cocrystallization of furosemide with malic acid as a coformer using the neat grinding method to enhance its solubility and dissolution rate. Optimization was performed using a Simplex Lattice Design (SLD) in Design-Expert 13.0 software. Furosemide (A) and malic acid (B) served as variables ranging from 1 to 2 molar ratios across eight experimental trials. Numerical analysis of saturation solubility and percentage of drug dissolved at 60 minutes (Q60) was conducted to identify the optimal ratio. Cocrystal formation by neat grinding significantly improved both the solubility and dissolution rate of furosemide. The optimal molar ratio of furosemide to malic acid was determined to be 1.339:1.661, achieving a desirability value of 0.965. The resulting optimized capsule formulation fully complied with standard physical properties and dissolution release parameters. In conclusion, neat grinding cocrystallization with malic acid at the optimized ratio effectively enhances the solubility and dissolution profile of furosemide, offering a novel approach for improved drug delivery.

KEYWORDS: cocrystal; dissolution; furosemide; malic acid; neat grinding.

INTRODUCTION

The BCS IV diuretic furosemide has limited solubility, which limits its dissolution in gastrointestinal fluids and thus its bioavailability [1]. Therefore, many strategies have been developed to increase solubility and thereby to improve bioavailability [2]. The cocrystal formation showed good potential in this strategy. In the production of a cocrystal, drug molecules and coformers are combined by non-covalent intermolecular interactions, such as hydrogen bonds, Van der Waals contacts, and pi-pi interactions, without alteration of the chemical composition of the drug. This process reduced the crystal lattice energy, which made it easier for solvent molecules to penetrate the solid drug [3]. The key advantages of cocrystals are enhancement of drug solubility, rapid dissolution rate, improved stability and increased bioavailability without modifying the chemical structure of drug [4]-[5]. The formation of a furosemide cocrystal with a carboxylic acid coformer, such as nicotinamide, will enhance its photostability [6]. In the nicotinamide-catechin cocrystal, hydrogen bonds are formed between the hydroxyl groups and the amide groups [7].

The preparation of cocrystals can be done by various methods such as solid-state and solvent-based liquid-solid state techniques. The selection of an appropriate method is based on a complete evaluation of the thermal properties and solubility of the drug. For example, heat-sensitive drugs are more suited to solvent-based methods. Neat grinding is a fast process of grinding the drug and coformer together at a defined molar ratio. The advantages of the neat grinding method include the absence of solvent-related risks (eliminating the risk of residual solvent entrapment or the formation of unwanted solvates or hydrates); simplicity (involving only dry mixing without the need for precise measurement or the addition of liquid additives); and an environmentally friendly profile (a truly solvent-free preparation method that completely avoids volatile organic compounds). This method is simple and improves physicochemical properties and retains the stability of the drug [8]. Neat grinding improves the solubility by altering the crystal structure of the drug by cocrystallization, as well as by reducing the particle size to increase the surface area. The larger surface area

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gives better contact with the solvent. This mechanochemical process breaks down the crystal lattice of the drug and encourages the formation of new bonds with the coformer, producing a structure with higher solubility in body fluids [9].

Coformers are important agents for cocrystal formation, since they interact with the drug molecule. This interaction modifies or improves the physicochemical properties of the drug. Malic acid was selected as the coformer because of its stability, availability, and ability to form hydrogen bonds with furosemide. Thus, it is expected to improve the solubility and stability of furosemide. Malic acid has a hydrogen-bond donor group that is able to interact with the carboxylic acid group in furosemide [7]. The present work was undertaken to determine the optimum molar ratio of furosemide and malic acid for cocrystal formation by neat grinding so as to improve solubility and dissolution rate. The optimization was carried out using Simplex Lattice Design (SLD) in Design-Expert 13.0 software [10].

MATERIALS AND METHODS

Materials

Materials used in this study were furosemide (PT. First Medhiparma, Indonesia), malic acid (PT. Merck Chemicals, German), distilled water, sodium hydroxide (PT. Kimia Samarinda Raya) and potassium dihydrogen phosphate (PT. Kimia Samarinda Raya, Indonesia). The experimental work was performed with UV-Vis spectrophotometry (Shimadzu, Japan), Fourier Transform Infrared Spectroscopy (FTIR) (Shimadzu, Japan), dissolution tester (LABOAO, China), pH meter (Ohaus, United States of America), shaking waterbath (Kotterman, German), and analytical balance (Pioneer, United States of America).

Preparation of cocrystal

The cocrystal was optimized using the SLD technique in Design-Expert 13.0. The optimization was carried out on two variables i.e. furosemide and malic acid at two levels of concentration (low 1 M and high 2 M). Eight formulations were prepared as given in Table 1. Cocrystals were prepared by neat grinding, where furosemide and malic acid were mixed in the formulation and ground in a mortar for 30 min until separable crystals were observed [11].

Table 1. Experimental formulas of furosemide and malic acid cocrystals generated by Design-Expert 13.0 (SLD method).

Run	Furosemide		Malic acid	
	Molar	mg	Molar	mg
1	1.25	413.42	1.75	234.65
2	1	330.74	2	268.09
3	1.75	578.79	1.25	167.61
4	1	330.74	2	268.09
5	2	661.48	1	134.09
6	1.5	496.12	1.5	201.13
7	2	661.48	1	134.09
8	1.5	496.12	1.5	201.13

Note: Runs 2 & 4, 5 & 7, and 6 & 8 share identical furosemide:malic acid ratios – these are the built-in replicate points of the Simplex Lattice Design

Analytical method validation

UV-Vis spectrophotometry was used to determine the amount of furosemide cocrystal present in solubility and dissolution studies. Solubility test was performed with 0.1 N NaOH, dissolution test was performed with buffer at pH 5.8 [12]. The validation of each solvent was performed by the following methods:

Determination of the maximum wavelength

The absorbance of 10 ppm furosemide solution in the wavelength region of 200-400 nm was measured by UV-Vis spectrophotometry.

Preparation of the standard calibration curve

The absorbance of furosemide solutions of concentrations 8, 10, 12, 14, 16, and 18 ppm at the peak wavelength was studied. The standard curve equation was obtained via linear regression of absorbance (y) on furosemide concentration (x).

Precision evaluation

The intraday precision was assessed by determining the absorbance of 14 µg/ml furosemide solution in six repetitions using UV-Vis spectrophotometer and then computing the relative standard deviation (RSD). Interday precision was calculated by measuring the absorbance of furosemide solutions at 14, 16, and 18 ppm (each in duplicate) over 3 successive days and determination of the RSD.

Accuracy evaluation

The spiking method was used to determine the accuracy in which standard furosemide solution was added to the test solution of 80, 100, and 120 % of the active ingredient.

Limit of detection (LOD) and limit of quantification (LOQ)

The LOD and LOQ were calculated from the standard calibration curve. The calculations were performed using the equations: $LOD = 3.3 \times (SD/b)$ and $LOQ = 10 \times (SD/b)$, where SD is the standard deviation and b is the slope of the linear regression line $y = bx + a$.

Determination of furosemide cocrystal content

The cocrystal was accurately weighed (equivalent to 40 mg of furosemide), dissolved in 50 mL of NaOH, filtered, and diluted to 100 µg/mL. Next, 250 µl of the liquid was taken, diluted to 5 mL, and its absorbance was determined using a UV-Vis Spectrophotometer at the maximum wavelength [13].

Cocrystal solubility test

The cocrystal was accurately weighed (equivalent to 40 mg of furosemide), dissolved in 100 mL of phosphate buffer pH 5.8, filtered, and its absorbance was determined using a UV-Vis Spectrophotometer at the maximum wavelength [2].

Cocrystal dissolution test

Cocrystals equivalent to 40 mg of furosemide were encapsulated in hard gelatine capsule. Dissolution was performed using a type 2 paddle apparatus at 50 rpm in 900 mL of phosphate buffer (pH 5.8, 37 ± 0.5 °C). Samples of 5 mL were withdrawn at 5, 15, 30, 45, and 60 minutes. Furosemide concentrations were determined by UV-Vis spectrophotometry [14].

Characterization of the cocrystal optimal formula

Cocrystal powder flow rate

The powder flow rate was measured using the funnel method. Ninety grams of cocrystals were weighed and placed in a funnel. After the bottom cap was removed, the time required for complete discharge of the powder was recorded. The flow rate was then calculated in grams per second [14].

Weight Uniformity

Ten capsules were individually weighed in milligrams (mg). The contents were removed, and the empty shells were weighed. The net content weight of capsule was calculated by subtracting the weight of shell from the gross weight. The mean and standard deviation were subsequently calculated [14].

Disintegration time

Disintegration was evaluated using a disintegration tester. Each of six capsules was placed in a tube containing 900 mL of phosphate buffer solution (pH 5.8) at 37 ± 2 °C. The time required for capsule disintegration was recorded [14].

Fourier Transform Infrared (FTIR)

Fourier Transform Infrared (FTIR) spectroscopy was performed on the sample over the wavelength range of 4000 to 400 cm^{-1} [3].

Data analysis

The data were analyzed using Design-Expert 13.0 software to determine the effects of furosemide and malic acid on solubility and dissolution (Q_{60}) using the equation coefficient and contour plot. The optimum ratio of furosemide and malic acid was determined using a numerical method (Design-Expert 13.0) with the parameters listed in Table 2. Validation of the optimum cocrystal formula was tested statistically using SPSS with a one-sample t-test method.

Table 2. Optimization parameters.

Parameters	Goal	Weights	Importance	Requirements
Solubility (%)	Maximize	1	+++	> 80% [14]
Dissolution (Q_{60} , %)	Maximize	1	+++	> 80% [14]

RESULTS

Figure 1 shows the spectrum of furosemide in 0.1 N NaOH and in a phosphate buffer solution at pH 5.8. The validation parameters for the spectrophotometric method for the measurement of furosemide concentration, including the linear range of the standard curve, precision, accuracy, and limit of detection and quantification (LOD-LOQ), are shown in Table 3.

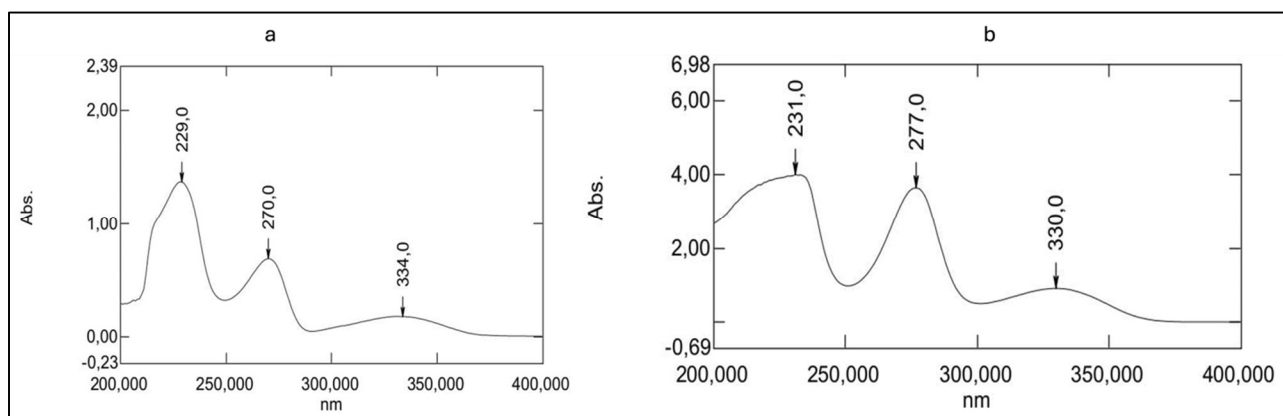


Figure 1. Spectrum of furosemide (10 ppm) in 0.1 N NaOH (a) and phosphate buffer solution at pH 5.8 (b).

Table 3. Validation parameters of the UV-Vis Spectrophotometer.

No.	Parameters	0.1 N NaOH solvent	Phosphate buffer solvent pH 5.8
1.	Standard curve	$y=0.0488x - 0.1513$ ($r=0.9934$)	$y=0.0486x - 0.0531$ ($r=0.9839$)
2.	Precision (n=6)		
	RSD (intraday)	0.13%	0.17%
	RSD (interday)	0.80%	0.16%
3.	Accuracy (mean $\pm$ SD) (n=3)		
	Recovery (80 %)	88.45 $\pm$ 0.20 %	80.50 $\pm$ 0.12 %
	Recovery (100 %)	86.93 $\pm$ 0.16%	81.98 $\pm$ 0.12 %
	Recovery (120 %)	88.58 $\pm$ 0.11 %	87.67 $\pm$ 0.15%
4.	LOD & LOQ		
	LOD	12 mg/L	12 mg/L
	LOQ	37 mg/L	38 mg/L

Table 4 shows the results of drug content, solubility, and dissolution (Q_{60}) of all cocrystal experimental formulas.

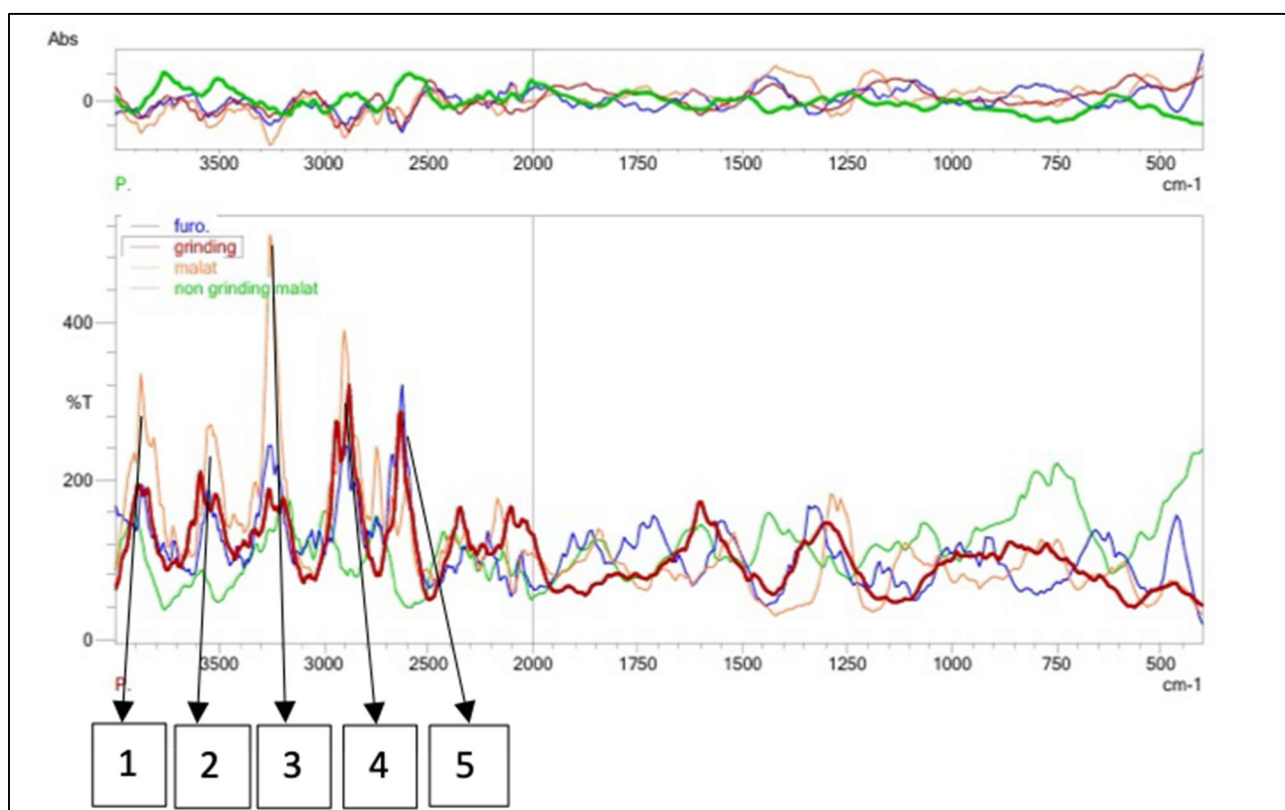
Table 4. Quality parameters of eight cocrystal experimental formulas.

Run	Parameters (mean±SD) (n=3)		
	Drug content (%)	Solubility (%)	Q ₆₀ (%)
1	90.75 ± 0.71	97.86 ± 0.96	98.41 ± 0.96
2	90.66 ± 0.42	90.52 ± 0.52	83.23 ± 0.55
3	94.71 ± 0.88	90.75 ± 0.41	90.74 ± 0.57
4	90.95 ± 0.66	90.52 ± 0.52	83.20 ± 0.57
5	97.25 ± 0.66	85.16 ± 0.98	89.74 ± 0.81
6	99.98 ± 0.59	98.73 ± 0.89	97.90 ± 0.29
7	92.98 ± 0.98	85.16 ± 0.39	89.34 ± 0.34
8	95.67 ± 0.53	97.18 ± 0.44	97.71 ± 0.75

The quality of the optimal furosemide-malic acid cocrystal formula was assessed based on powder flow rate, weight uniformity, disintegration time, solubility, and dissolution. The corresponding results are shown in Tables 5 and 6. The FTIR characterization results for the optimal formula are provided in Figure 2.

Table 5. Physical properties of the optimal cocrystal formula.

Parameters	Mean±SD
Flow rate (n=3)	15.44 ± 1.03 g/sec
Capsule weight (NP) (n=10)	89.92 ± 0.54 mg (1.44%)
Disintegration time (n=6)	11.78 ± 1.08 minutes
Solubility (n=3)	99.23 ± 0.58 %
Dissolution (Q ₆₀) (n=3)	99.60 ± 0.58%

**Figure 2.** FTIR overlay spectrum of furosemide-malic acid and optimal cocrystal formula.

DISCUSSION

Analytical method validation

The UV-Vis spectrophotometric method for the determination of furosemide was validated to prove its suitability for the intended purpose and its capability of providing reliable analytical data. Validation was done in two solvents, 0.1 N NaOH for assay analysis and phosphate buffer (pH 5.8) for solubility and dissolution analysis. Validation parameters comprising linearity, precision, accuracy, limits of detection (LOD) and quantification (LOQ) are given in Table 3. The analytical method was highly linear ($r > 0.95$), indicating a robust quantitative relationship between absorbance and analyte concentration [15]. Besides, good precision and repeatability were also established by the intra- and interday data with RSD values less than 2% for both solvents. Sensitivity and recovery were likewise good [16].

Figure 1 presents the spectral data of furosemide in two different solvents. Maximum absorbance of furosemide was obtained at 270.0 nm in 0.1 N NaOH and 277.0 nm in phosphate buffer (pH 5.8). These results are consistent with similar studies reporting maximum wavelengths for furosemide of 270.8 nm in 0.1 N NaOH and 277.60 nm in phosphate buffer (pH 5.8) [17]. The little difference in the maximum wavelength of furosemide is attributed to the solvent effects and the degree of ionization of drug molecules that are influenced by the change of acidities (pH). In a strong base solvent like NaOH, phenoxide ions or ionized groups are more stable because of more effective dipole-dipole solvation with the solvent. It increases the energy of transfer of electrons from the bonding orbital (π) to the anti-bonding orbital (π^*), resulting in a reduction in absorbed wavelength (hypsochromic shift) [18]. In phosphate buffer at pH 5.8, on the other hand, furosemide stays ionized, but ionic connections and the polarity of the medium are altered. In this environment, the energy needed for electron transfer is less than that in NaOH, which results in a slightly longer absorbance wavelength (bathochromic shift) [18]. Maximum sensitivity, accuracy, and minimum instrumental error are obtained by measuring a molecule at its maximum wavelength, which is the method of choice for quantitative UV-Vis spectrophotometry.

Physical and chemical properties of cocrystal capsules

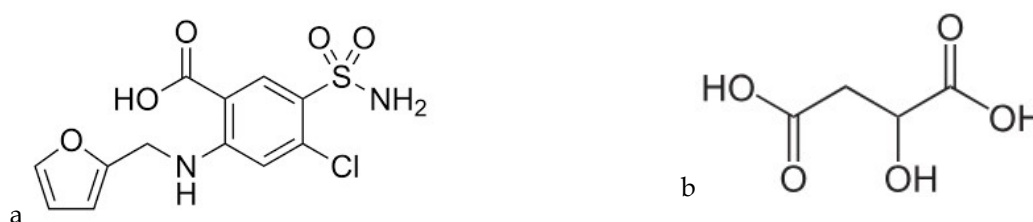
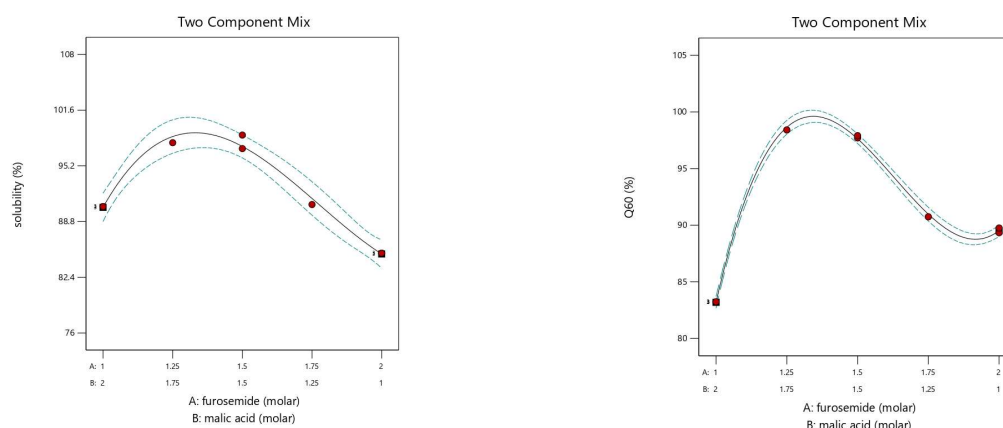
Eight experimental formulations of furosemide cocrystals were prepared using the neat grinding process. The newly formed cocrystal was then encapsulated in a hard gelatine capsule. The capsules were tested for furosemide content, solubility, and dissolution release. The furosemide content ranged from 90.66 to 99.98%, indicating that the physical properties of the freshly manufactured cocrystal were altered, but its chemical stability was preserved during neat grinding [14]. This is in agreement with previous reports in which mechanical grinding for a controlled time does not contribute to drug degradation [19]. The effect of this approach was mostly on the solubility and dissolution, as shown in Table 4. The effects were directly proportional to the molar ratio of furosemide to malic acid, as submitted to neat grinding.

The solubility and dissolution tests were used to investigate the changes in physical properties of the furosemide cocrystal. Table 6 presents the Analysis of Variance (ANOVA) for solubility and dissolution data using a cubic model (Design-Expert 13.0). The F values of solubility and dissolution models are 97.03 and 1305.81, respectively, which indicates the variance of the model is much higher than the error variance. The p-value < 0.05 indicates that the model term is statistically significant and is adequate for predicting outcomes [20]. The model has a high R^2 , and the difference between predicted and adjusted R^2 is about 0.2, indicating good stability and predictive reliability. Furthermore, the adequate precision value was over 4, which indicated the signal was robust to noise. The large amount of data helps the model to explain and predict the effect of the furosemide-malic acid molar ratio on cocrystal solubility and dissolution.

Table 6. ANOVA of quality parameters of furosemide-malic acid cocrystal capsules using the SLD method (Design Expert 13.0).

Parameters	Equation	P-value	R ²	adj R ²	pred R ²	adeq precision	Equation model
Solubility (%)	$Y_1 = 85.05 (A) + 90.43 (B) + 38.69 (AB) - 23.63(AB (A-B))$	0.0003	0.9864	0.9763	0.9317	22.8336	Significant (Cubic)
Dissolution (Q ₆₀) (%)	$Y_2 = 89.52 (A) + 83.19 (B) + 45.10 (AB) - 57.75 (AB (A-B))$	≤0.0001	0.9999	0.9982	0.9940	82.9283	Significant (Cubic)

Based on the Y_1 equation, the malic acid variable (+90.43) has a greater influence on solubility than the furosemide variable (+85.05) as an active ingredient. Malic acid is highly soluble in water, and when it comes in contact with water, it provides an environment for the dissolution of furosemide [21]. Interaction of furosemide with malic acid also enhanced the solubility of furosemide (+38.69). At the molecular level, furosemide cocrystallizes with malic acid through hydrogen bonds between the -NH and -SO groups of furosemide and the -COOH group of malic acid, as shown in Figure 3 [22]. It creates a new crystal structure, which is more stable and structured, and hence increases the solubility of furosemide. The non-covalent interactions, such as hydrogen bonds, enable the formation of co-crystals with modified crystal structures, which improve drug solubility and bioavailability [23]. Further, grinding reduces the particle size of furosemide and changes its crystalline structure to a less ordered, more amorphous state, which increases the solubility [21]. The solubility parameters are plotted in a convex contour plot in Figure 4, which shows that the cocrystal formation with the malic acid coformer increases the solubility of furosemide.

**Figure 3.** Molecular structure of (a) furosemide [24] and (b) malic acid [25].**Figure 4.** Contour plot of the effect of furosemide and malic acid on solubility and dissolution.

Dissolution is a test to determine the rate of release of drugs to a given medium over time. This is an important factor in assessing the biopharmaceutical properties of a medicinal product. It also investigates the effect of the altered physical properties of the cocrystal. All experimental formulation runs (1-8) showed acceptable release profiles that meet the specification of the Indonesian Pharmacopeia, version VI (2020), that the quantity of furosemide dissolved at 60 minutes (Q_{60}) is not less than 80% [14]. In the results, the neat grinding method for the cocrystal formation of furosemide using malic acid as a coformer considerably increases the solubility and release of furosemide. The interaction between furosemide and malic acid as a coformer promoted drug release (+45.10) in accordance with the effects on solubility parameters according to the Y_2 equation for the dissolving parameter (Q_{60}). It improved solubility and dissolution by forming hydrogen bonds, decreasing particle size, and converting to the amorphous state [21]. Figure 4 indicates that dissolution was promoted at a certain fraction combination. The highest curvature indicates the best formulation for maximal solubility.

Characteristics of the optimum cocrystal formula

The optimal molar ratio of furosemide-malic acid for the cocrystal formation was obtained by a computational method (Design-Expert 13.0) based on solubility and dissolution properties (Q_{60}), as shown in Table 2. The best molar ratio of the formula is 1.339:1.661 with a desirability value of 0.965. This ratio permits appropriate intermolecular interactions (including hydrogen bonds) between the functional groups of the drug and coformer in the crystal lattice [7]. Furosemide contains a carboxylic group (-COOH), a sulfonamide group (-SO₂NH₂), and an amine group (-NH-), which are all rich as donors and acceptors in hydrogen bonds. Meanwhile, malic acid is an effective hydrogen-bond donor, as a dicarboxylic acid consisting of two hydroxyl (-OH) and two carboxyl (-COOH) groups [7].

Table 7. Statistical analysis of predicted vs experimental optimum formula of furosemide cocrystal.

Parameters	Prediction	Experiment (n=3)	Sig (2-tailed)	T _{calculated}	Conclusion
Dissolution (Q_{60})	99.61	99.60 ± 0.58	0.667	0.500	Not Significant
Solubility (%)	98.99	99.23 ± 0.58	0.423	1.000	Not Significant

The results of the one-sample t-test indicated that the solubility and dissolution characteristics of the predicted optimal formula were not significantly different from the experimental optimal formula (Table 7). The results indicate that the equation models for Y_1 and Y_2 are effective in predicting the solubility and dissolution of the furosemide cocrystal. The best formulation showed 98.99% solubility and 99.61% drug release in 60 min. The suitable molar ratio of furosemide to malic acid coformer (1.339:1.661) was advantageous for solubility and optimal drug release.

Table 5 shows that the quality of the optimal formula is good. The optimal cocrystal formulation exhibits desirable flow properties with a flow rate > 10 g/sec. The flow properties are needed for a uniform filling of the capsule shell to maintain a constant weight of the capsule and content with an acceptance value (NP) less than 15% [14]. The optimum formula has a good disintegration time of less than 15 min. Disintegration time is used to evaluate drug release and improved solubility [26]. A decrease in disintegration time is beneficial for the rapid release of the drug as the capsule breaks into small grains or powders, which increases the surface area [27].

The interactions between the drugs and coformers are determined by FTIR (Fourier Transform Infrared) analysis, usually indicated by the shifts in vibrational frequencies and the presence or absence of particular bands [28]. Figure 2 represents the FTIR spectra overlay of furosemide, malic acid, and their cocrystal. The band shift in the optimal formulation of furosemide-malic acid cocrystal is shown in comparison with the pure furosemide or the physical mixture. The shift of the N-H band at about 3300 cm⁻¹ in the 3200-3600 cm⁻¹ region indicates the formation of a new hydrogen bond between the N-H group of furosemide and the -OH or -COOH group of malic acid. Furthermore, the hydrogen bonds are confirmed by changes in the O-H and N-H stretching bands in the region of 2800-2600 cm⁻¹ [29]. In contrast, the mixture of furosemide-malic acid without grinding does not reveal any notable changes in the spectrum. The spectra match the individual

compounds. Based on the observations, the formation of furosemide-malic acid cocrystals only occurs in samples prepared by the neat grinding method through intermolecular interactions in the form of hydrogen bonds.

CONCLUSION

The preparation of furosemide cocrystal with malic acid as a coformer by neat grinding method improves the solubility and dissolution of the active substance. The optimum molar ratio of furosemide and malic acid is 1.339:1.661 with a desirability value of 0.965. Capsules containing the optimum cocrystal formula exhibit good physical properties and dissolution release as required by the compendia.

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