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The Drying Temperature Impact on Curcumin - Piperine Dissolution and Its Kinetic Release: Application of A Spray Dryer on the Preparation of Solid Dispersion-based Microparticle Containing Curcuma *longa* and Piper *Nigrum* Extracts

Siska Ayu PURNAMASARI [1], **Dewi SETYANINGSIH** [1*]

[1] Department of Pharmacy, Faculty of Pharmacy, Sanata Dharma University, Yogyakarta, Indonesia.
* Corresponding Author. E-mail: dewi@usd.ac.id (D.S.); Tel. +62-821-359 934 94.

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ABSTRACT: After oral administration, low water solubility and rapid pre-systemic metabolism contribute to curcumin's poor bioavailability. To solve the bioavailability issue, piperine, a natural bioenhancer, can be coupled with curcumin in a solid dispersion-based microparticle formulation (SD). This study's objective was to understand drying temperature's effect on the yield and dissolution behaviour of curcumin and piperine in the SD containing *C.longa* and *P.nigurm* extracts at a weight ratio of 3:1. The SD was prepared on a solvent method and used polyvinylpyrrolidone K30 as a carrier. Spray drying was operated at 105°C, 115°C, and 125°C to evaporate the solvent. The yield and dissolution behaviour of curcumin and piperine were their defining characteristics, and the dissolution efficiency (DE) was used to compare the dissolution profiles. The kinetic release model of curcumin and piperine was determined using DDsolver software. The results demonstrate that the SD's yield increases as inlet temperature increases, from 33.60% at 105°C to 35.75% at 115°C to 39.30% at 125°C. The dissolution of curcumin and piperine from the SD increases along with the rise in drying temperature. Variation in drying temperature provides a different kinetic model of curcumin and piperine release. The Weibull model describes the release kinetic of curcumin and piperine at almost used drying temperatures; however, the release of piperine from the SD prepared at 125°C fits the zero-order model.

KEYWORDS: Curcumin; ddsolver; dissolution; kinetic release; piperine; solid dispersion; spray drying

1. INTRODUCTION

Curcumin is a yellow pigment derived from the C.*longa* plant, is a principal component of turmeric, and is widely used as a spice and culinary color [1]. Antioxidant, chemopreventive, proapoptotic, anti-inflammatory, antifungal, anti-ischemic, hepatoprotective, antiparasitic, antimicrobial, and chemotherapeutic activity are all present [2,3]. Although curcumin has several advantages, it suffers from limited bioavailability after oral administration [4].

Curcumin belongs to the class II Biopharmaceutical Classification System (BCS). As a BCS II member, curcumin possesses low water solubility with high permeability membrane properties. Furthermore, a class II drug's solubility is the primary predictor of its oral bioavailability [5,6]. The challenges of curcumin becoming a therapeutic agent are its poor solubility and fast pre-systemic metabolism [4]. The aqueous solubility of curcumin was reported at only 11 ng/ml [7]. In addition to having weak water solubility, curcumin has a rapid metabolism[4,8]. In a study by Wahlstrom, it was discovered that 75% of curcumin administered orally to rats ended up in their feces [8].

A combination of turmeric and black pepper extract has been utilized in Indonesian traditional medicine to cure various ailments. Combining turmeric (*C.longa*) with black pepper (*P.nigrum*) extracts was thought to

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improve its effectiveness [9]. Piperine, the primary active component of *P.nigrum*, enhanced the bioavailability of curcumin by a fold of 20 through inhibition of glucuronidation in the liver and intestine [9–11]. Thus, it is conceivable that inhibiting the first-pass metabolism by combining curcumin and piperine may substantially improve bioavailability. However, piperine was sparingly soluble in water, about 40 mg/L at 18°C. Therefore, technological approaches must be pursued to increase curcumin and piperine water solubility.

Solid dispersion is a promising technique for improving the dissolution and oral bioavailability of l BCS II drugs [12–15]. Solid dispersion is the dispersion of one or more active hydrophobic drugs into a hydrophilic carrier while the mixture is still solid [16]. Spray drying is one of the solvent-evaporation techniques ideal for an SD preparation, resulting in a high level of stability with enhanced drugs' solubility and dissolution. Moreover, spray drying offers straightforward handling and storage [14,15,17–19]. The primary variables that must be optimized in spray drying are the air drying temperature and the feeding temperature [20].

No research has been published on the spray drying of a mixture of *C.longa* and. *C.nigrum* extracts, specifically on the effect of operating parameters on release characteristics. A study was conducted to determine the impact of drying temperature and pump rate on the qualities of spray-dried tomato powder. The author discovered that the percentage of the yield increases as the pump rate of compressed air and the temperature of the inlet air are increased [21]. Once the temperature of the air entering the system was high, the dry crust formed rapidly due to the high rate of water evaporation from the particles, as reviewed by Gharsallaoui [20].

Mathematical models are necessary to study the release mechanism of drug from the dosage form, as it describes the pattern of release of drug mathematically and helps to optimize the design of a therapeutic device to yield information on the efficacy of various release models [22]. Various mathematical models have been proposed to evaluate dissolution profiles to understand the drug release mechanism. A theoretical investigation of the process can deduce the mathematical models of a dissolving profile, but in most situations, no theoretical base exists due to the complexity of dosage forms. As a result, semi-empirical or empirical models must be utilized to fit dissolution data [23–27]**.** In order to evaluate the dissolution data, several mathematical models were developed, including the zero-order, first-order, Higuchi, Weibull, Korsmeyer-Peppas, Hixson- Crowell, Baker-Lonsdale, and Hopfenberg [28]. The mathematical models of the dissolution can be obtained using a DDSolver.

DDSolver is a contemporary tool that performs kinetic analysis of dissolution data using a non-linear regression methodology [28,29]. In various experiments, DDSolver successfully identifies the kinetics model of numerous active substances, including furosemide, aspirin, cefixime, and griseofulvin[28–32]. This study aimed to determine how drying temperatures affect curcumin and piperine dissolution behavior and define a suitable mathematical model to study the release profile of curcumin and piperine from the SD formulations.

2. RESULTS AND DISCUSSION

2.1 Yield

The yield of the SD formulations prepared at 105°C, 115°C, and 125°C were found to be 33.60%, 35.75%, and 39,30%, respectively. In this study, the yield of the SD increased as the temperature rose to 125°C. This finding was in line with a previous report that studied the impact of drying temperature between 110°C-150°C on the spray drying black mulberry extract; the yield of dried mulberry extract was obtained at more than 80% at a drying inlet temperature of 150 °C [33]. The appearance of the SD powders, as seen in Figure 1 shows the same color and odor; however, the SD obtained from the drying temperature of 125 °C looks more free-flowing.

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Figure 1. Spray Drying powder of solid dispersion at varying temperatures

2.2 Dissolution profile

The ability of a powder to fully reconstitute in water is measured using a dissolution tester. *In-vitro* dissolution has been recognized as a valuable method in pharmaceutical development. It can be used as a substitute for determining bioequivalence. Dissolution testing establishes long-term stability and the shelf life of pharmaceutical products.

Curcumin and piperine dissolution profiles from the SD formulation at 105°C, 115°C, and 125°C are shown in Figure 2. Dissolution Efficiency (DE) values obtained during 120 minutes of dissolution study were determined to compare the dissolution profiles. The DE_{120} values of curcumin and piperine are shown in Figure 2c. As seen in Figure 2 a,b, drying at 125°C resulted in curcumin and piperine dissolution rates of 88.49% ± 9.89% and 110.77 ± 13.6%, respectively. The drying temperature of 115°C produced powder with the dissolution of 53.74 ± 6.82% for curcumin and 64.96% ± 6.90% for piperine. However, drying at a lower temperature of 105°C resulted in the SD formulation with the dissolution of curcumin and piperine of 52.98% ± 4.31% and 63.92%±6.71%, respectively.

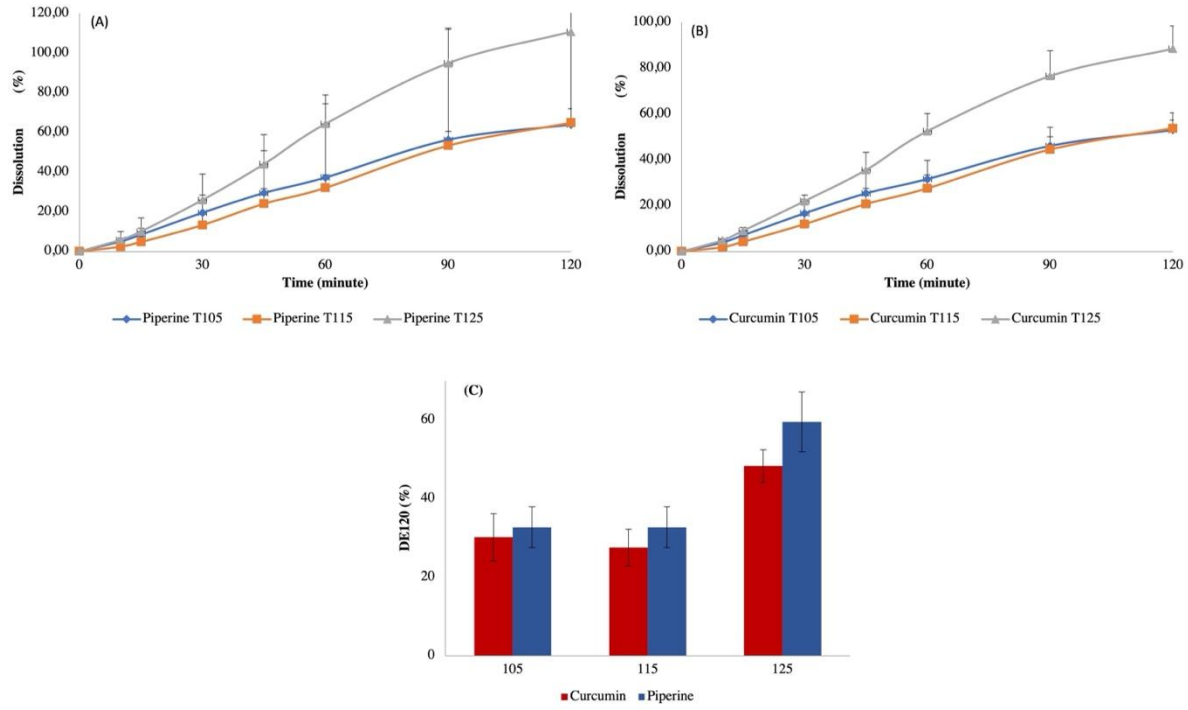

Figure 2. Dissolution profile of piperine (a), curcumin (b), and DE_{120} (c) (n = 3, mean ± SD).

This study found the highest dissolution rate of curcumin and piperine of more than 90% is demonstrated by the SD prepared at 125 °C. The DE_{120} of curcumin and piperine of the SD prepared at 125°C (48.31%± 4.15% for curcumin; 59.59%±7.63% for piperine) is significantly ($p<0.05$) higher than the DE_{120} of curcumin and piperine of the SD prepared at 115°C (30.17%±6.03% for curcumin; 36.19%±7.84% for piperine). However, raising the temperature from 105°C to 115°C (27.54%±4.66% for curcumin; 32.71%±5.16% for piperine) elicited a slight increase ($p>0.05$) in the DE_{120}.

The higher drying temperature of a spray dryer increased the dissolution rate was also observed by others. A study reported drying roselle-pineapple juice at various inlet temperatures of 140°C - 200°C enhanced the dissolution rate of roselle-pineapple as monitored by the reconstitution time in the water, at which the 140°C drying temperature resulted in the lowest dissolution rate. Moreover, the higher moisture content of the powder was demonstrated by the one drying at the lower drying temperature [34]. It implies that a slower evaporation rate is a result of drying at a lower temperature of the spray dryer. Due to the higher moisture content governed by the powder produced at the lower drying temperature, the particles tend to agglomerate,

which decreases the dissolution rate. Referring to the work of Osman and Endut [34], the lower dissolution of curcumin and piperine found in this study at 105°C and 115°C could be ascribed to particle agglomeration, as the SD formulations obtained at these temperatures demonstrated less free-flowing characteristic as depicted in Figure 1 compared to that obtained from the 125°C drying.

2.3 Kinetic Release of Curcumin and Piperine using DDSolver

Understanding the release kinetics of active pharmaceuticals is critical for developing drugs with the intended delivery and predicting the behavior of the created drug in vivo [23,35,36]. Several kinetic models and theories describe the drug dissolution profile relating to the amount of drug dissolved from a pharmaceutical dosage system as a function of time.

The dissolution profiles, as reported in the supplementary data in Table S1 and Table S2, were used to derive the mathematical model for describing the kinetic release of curcumin and piperine. DDSolver software [37] was employed to establish the kinetics models and to evaluate the goodness of fit of the resulting kinetic model of the drug release profiles. Among the models are the first-order, zero-order, Korsmeyer-Peppas, Higuchi, Hixson-Crowell, Hopfenberg, Weibull, and Baker-Lonsdale.

In order to obtain the model, the proportion of drugs dissolved and the dissolving time presented in the supplementary data in Table S1 and Table S2 are inputted into the DDSolver software [28]. The obtained mathematical models for describing the kinetic release of curcumin and piperine are summarized in Table *1*. The suitable mathematical model which can be used to predict the dissolution kinetics of curcumin and piperine was selected based on the values of $R2_{adjusted}$, Akaike Information Criterion (AIC), and Model Selection Criterion (MSC). The mathematical models with the lowest value of AIC, highest value of $R2_{adjusted}$, and greatest value of MSC were selected as the suitable kinetic model for describing the release of curcumin and piperine from the SD formulation [37].

Table *1*. *Statistical parameters of models to describe the release of curcumin and piperine SD*

SD	Model	Dissolution Model Parameters					
		R_2 adjusted		AIC		MSC	
		Piperine	Curcumin	Piperine	Curcumin	Piperine	Curcumin
105°C	Orde 0	0,97438	0,96304	38,10	35,38	3,41	3,27
	Orde 1	0,97105	0,98147	39,10	32,72	3,19	3,60
	Higuchi	0,85323	0,86891	52,67	48,57	1,49	1,62
	Hixson-Crowell	0,97868	0,98090	36,44	33,02	3,52	3,56
	Hopfenberg	0,98321	0,98760	35,05	29,41	3,70	4,01
	Weibull	0,98605	0,98893	35,05	28,11	3,70	4,18
	Korsmeyer-Peppas	0,97795	0,98059	35,05	31,50	3,70	3,75
	Baker-Lonsdale	0,81788	0,84274	35,05	50,15	3,70	1,42
115°C	Orde 0	0,97438	0,97623	38,10	35,12	3,41	3,41
	Orde 1	0,94238	0,95857	45,22	39,38	2,52	2,87
	Higuchi	0,78944	0,79993	55,99	52,58	1,18	1,22
	Hixson-Crowell	0,95733	0,96768	42,40	37,06	2,88	3,16
	Hopfenberg	0,97715	0,97777	38,12	35,26	3,41	3,39
	Weibull	0,98954	0,98765	31,23	30,19	4,27	4,02
	Korsmeyer-Peppas	0,98087	0,98023	36,37	34,20	3,63	3,52
	Baker-Lonsdale	0,75314	0,77129	57,33	53,71	1,01	1,08
125°C	Orde 0	0,97310	0,97065	47,30	44,86	3,32	3,18
	Orde 1	0,87663	0,93049	59,59	50,59	1,79	2,46
	Higuchi	0,82583	0,83537	63,17	59,02	1,34	1,41
	Hixson-Crowell	0,91581	0,95443	56,15	47,01	2,22	2,91

Hopfenberg	0,97151	0,98260	49,10	41,78	3,10	3,56
Weibull	0,96367	0,99104	50,75	34,13	2,89	4,52
Korsmeyer-Peppas	0,97164	0,97262	48,33	45,12	3,20	3,14
Baker-Lonsdale	0,74229	0,77821	66,30	61,45	0,95	1,10

From this study, it is demonstrated that the difference in the drying temperature of the spray dryer affects the release kinetic of curcumin and piperine from the SD containing *C.longa* and *P.nigurm*. As presented in Table *1*, based on the selection criteria of the mathematical model, the Weibull model is the accurate model to describe the release of curcumin and piperine from the SD formulation prepared at 105°C, 115°C, and 125°C drying temperatures. Moreover, the release kinetic of piperine from the SD formulations prepared at 105°C and 115°C follows the Weibull model. In contrast, the preparation of SD formulations at 125°C provided the release profile of piperine fits the Zero-order model. As follow the Zero-order model, the rate of piperine release from the SD formulation prepared at the highest temperature of 125°C is independent of drug concentration and remains constant over time. Furthermore, the zero-order model of piperine may explain that the drug does not disaggregate from the dosage form, and the dissolution process is slow [38].

The selected mathematical models for describing curcumin and piperine release from SD formulations are depicted in Figure 4. The β values of the selected Weibull model for curcumin and piperine release (Figure 4) are more than 1, demonstrating that the curve fits a sigmoidal shape with turning points. In addition, the β values of more than 1 reflect the curcumin and piperine transport method of the polymer matrix of PVP K30 during the dissolution study [39,40].

3. CONCLUSION

This experiment was conducted to determine the impact of drying temperature during the preparation of microparticle-based SD formulations containing *C.longa* and *P.nigrum* extracts using a spray dryer. The SD formulation prepared at 125^{o}C drying temperature obtained the highest dissolution rate and yield. Different release mechanisms are indicated as the experiment found that various drying temperature utilization elicits the different release kinetic models of curcumin and piperine, as demonstrated by the DDSolver. While the Weibull model described the release of curcumin at 105^{o}C, 115^{o}C, and 125^{o}C, that model was not applied to demonstrate the release kinetic of piperine at all utilized drying temperatures. Drying at 105^{o}C and 115^{o}C produced the SD formulations with the piperine release following the Weibull model, while the highest temperature at 125^{o}C provided the SD formulation with the piperine release following the zero-order model.

4. MATERIALS AND METHODS

4.1 Reagents and material

Reference standards of piperine and curcumin of purity of >98% were provided by Sigma Aldrich (St. Louis, USA). *C.longa* extract of high curcuminoid content (97.56%) was given by PT Phytochemindo Reksa, Bogor, Indonesia. *P.nigrum* extract was given by Dr.rer.nat Yosi Bayu Murti from the Faculty of Pharmacy Universitas Gadjah Mada, Yogyakarta Indonesia. The extraction was done according to the previous method [41,42]; it was further defined using the piperine standard (Sigma Aldrich) and the validated High-Performance Liquid Chromatography (HPLC) method [43]. Polyvinylpyrrolidone K30 (PVP K30) was donated by PT Konimex, Central Java, Indonesia. Methanol, ethanol, sodium lauryl sulfate (SLS), and sodium dihydrogen phosphate were purchased from Merck, Darmstadt, Germany. Water was prepared in the laboratory using a Milli-Q.

4.2 Methods

4.2.1 Preparation of solid dispersion formulation

SD formulation was made using dried extract containing *C.longa* in powder form, and *P. nigrum* extract in crystal form was prepared using PVP K30 as the carrier, as seen in Figure 3. The SD contained 30% w/w of *C.longa* and 10% w/w of *P.nigrum* extracts [44]. Drying was processed on a BUCHI B290 mini-spray dryer equipped with dehumidifier B-295 at different temperatures of 105 ^{o}C, 115 ^{o}C, and 125 ^{o}C. Under the nitrogen

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flow, the mixture of ethanolic solution of *C.longa* and *P.nigrum* extract was sprayed via a two-channel nozzle at 6 mL/min. The spray-dried powder was stored in a desiccator for further analysis.

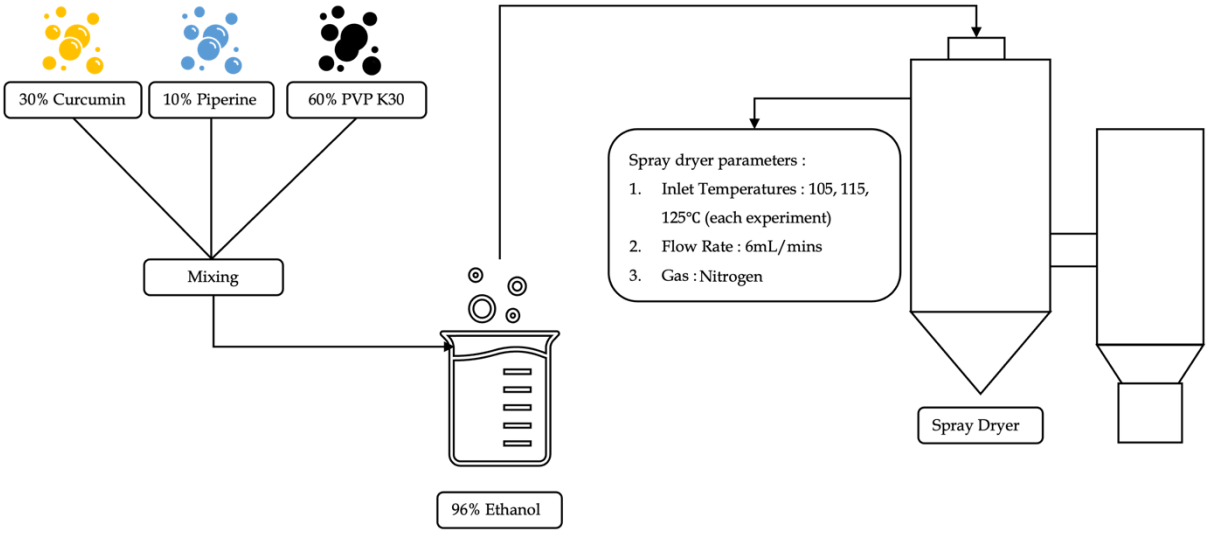

Figure 3. Flow Chart Process of Solid Dispersion Preparation Using Spray Dryer

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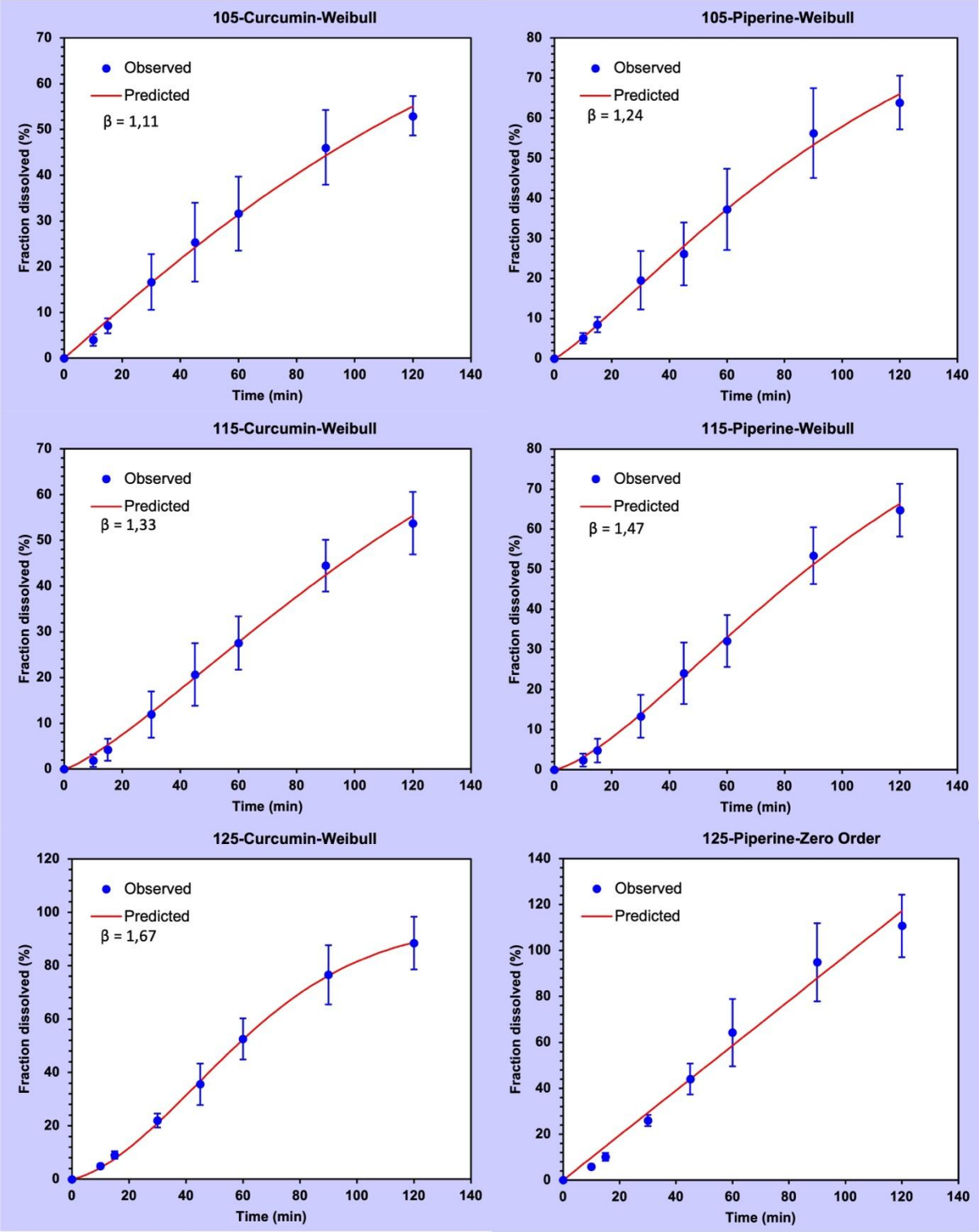

Figure 4. The selected mathematical model for describing curcumin and piperine release from SD formulation

4.2.2 Dissolution Test

The dissolution test was conducted using a USP Apparatus II in a 900 ml dissolution medium at 37 ± 0.5 ºC and a stirring speed of 75 rpm. The medium contained 0.5% SLS in a 20 mM sodium phosphate buffer of pH 6.00. A volume of 5.0 ml was sampled at predetermined time intervals and was replaced by a fresh dissolution medium to maintain sink condition. The dissolution test was performed for 120 minutes.

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The curcumin and piperine concentrations in the dissolution samples were determined based on the validated spectrophotometry method, as reported previously [44]. The absorptivity of compound E (1%, 1 cm) for each wavelength which is 344.4 nm (piperine) and 430.5 nm (curcumin), was determined by plotting the absorbance obtained at the accordingly wavelength into the calibration equation of y = 0.1606x + 0.0045 (curcumin) and y = 0.09x – 0.0088 (piperine). The concentrations of curcumin and piperine were determined simultaneously using Equation 1 and Equation 2

Simultaneous Equation (*Vierordt method*) :

$$Cp = \frac{(A1.ac2)-(A2.ac1)}{(ac2.ap1)-(ac1.ap2)} \qquad (Eq.\ 1)$$

$$Cc = \frac{(A2.ap1)-(A1.ap2)}{(ac2.ap1)-(ac1.ap2)} \qquad (Eq.\ 2)$$

Cp: Piperine concentration
Cc: Curcumin concentration
A1: Absorbance measured at wavelength 1
A2: Absorbance measured at wavelength 2
Ac1: Curcumin absorptivity at wavelength 1 in absorbance/(g/100ml)
Ac2: Curcumin absorptivity at wavelength 2 in absorbance/(g/100ml)
Ap1: Piperine absorptivity at wavelength 1 in absorbance/(g/100ml)
Ap2: Piperine absorptivity at wavelength 2 in absorbance/(g/100ml)

4.2.3 Data Analysis

The dissolution profile obtained in 120 minutes study was analyzed using an analysis of variance ANOVA with Real Statistic software add in Microsoft Excel. The dissolution efficiency values were calculated based on Equation 3.

Dissolution Efficiency:

$$\%DE = \frac{\int_{t1}^{t2} y.dt}{y100(t2-t1)} x100 \qquad (Eq.3)$$

DE : Dissolution efficiency at a time (t)
Ydt : Area under the curve of a dissolved drug at a time (t)
Y100.t : Rectangle area where 100% of the drug dissolved at a time (t)

The release profile of the SD product obtained for each inlet temperature was modeled using a DDSolver software in add in Microsoft Excel [37]. The following statistical characteristics were used to evaluate the release kinetics model: $R2_{adjusted}$, Akaike Information Criterion (AIC), and Model Selection Criterion (MSC).

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Author contributions: Concept – S.A.P., DS., ; Design – SAP., D.S.,.; Supervision – D.S.; Resources – D.S.; Materials – D.S.; Data Collection and/or Processing – S.A.P.; Analysis and/or Interpretation –S.A.P; Literature Search – S.A.P., D.S.; Writing – S.A.P.; Critical Reviews – D.S.
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REFERENCES

[1] Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol. 2007;595:105-125. https://doi.org/10.1007/978-0-387-46401-5_3.
[2] Abdollahi E, Momtazi AA, Johnston TP, Sahebkar A. Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades? J Cell Physiol. 2018;233:830–848. https://doi.org/10.1002/jcp.25778.
[3] Sufiawati I, Gunawan I, Wijaya I, Rusdiana T, Subarnas A. Reduction of salivary tumor necrosis factor alpha levels in response to magic mouthwash with *Curcuma xanthorriza* in cancer patients undergoing chemotherapy. J Res Pharm. 2018;23:55–61. https://doi.org/10.12991/jrp.2018.108.
[4] Wang R, Han J, Jiang A, Huang R, Fu T, Wang L, Zheng Q, Li W, Li J. Involvement of metabolism-permeability in enhancing the oral bioavailability of curcumin in excipient-free solid dispersions co-formed with piperine. Int J Pharm. 2019;561:9-18. https://doi.org/10.1016/j.ijpharm.2019.02.027.
[5] Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47-60. https://doi.org/10.1016/s0939-6411(00)00076-x.
[6] Wan S, Sun Y, Qi X, Tan F. Improved bioavailability of poorly water-soluble drug curcumin in cellulose acetate solid dispersion. AAPS PharmSciTech. 2012;13(1):159-166. https://doi.org/10.1208/s12249-011-9732-9.

[7] Kharat M, Du Z, Zhang G, McClements DJ. Physical and chemical stability of curcumin in aqueous solutions and emulsions: Impact of pH, temperature, and molecular environment. J Agric Food Chem. 2017;65(8):1525-1532. https://doi.org/10.1021/acs.jafc.6b04815.

[8] Wahlström B, Blennow G. A study on the fate of curcumin in the rat. Acta Pharmacol Toxicol (Copenh). 1978;43:86–92. https://doi.org/10.1111/j.1600-0773.1978.tb02240.x.

[9] Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Medica. 1998;64(4):353–356. https://doi.org/10.1055/s-2006-957450.

[10] Dudhatra GB, Mody SK, Awale MM, Patel HB, Modi CM, Kumar A, Kamani DR, Chauhan BN. A comprehensive review on pharmacotherapeutics of herbal bioenhancers. ScientificWorldJournal. 2012;2012:637953. https://doi.org/10.1100/2012/637953.

[11] Patil VM, Das S, Balasubramanian K. Quantum chemical and docking insights into bioavailability enhancement of curcumin by piperine in pepper. J Phys Chem A. 2016;120:3643–3653. https://doi.org/https:/doi.org/10.1021/acs.jpca.6b01434.

[12] Dwi S, Febrianti S, Zainul A, Retno S. PEG 8000 increases solubility and dissolution rate of quercetin in solid dispersion system. Marmara Pharm J. 2018;22:259–266. https://doi.org/10.12991/mpj.2018.63.

[13] Sakhare SS, Sayyad FJ. Studies on *Ocimum basilicum* mucilage based solid dispersions of indomethacin for enhancement of dissolution rate. J Res Pharm. 2019;23:832–838. https://doi.org/10.35333/jrp.2019.31.

[14] Szabó E, Záhonyi P, Brecska D, Galata DL, Mészáros LA, Madarász L, Csorba K, Vass P, Hirsch E, Szafraniec-Szczęsny J, Csontos I, Farkas A, Van denMooter G, Nagy ZK, Marosi G. Comparison of Amorphous Solid Dispersions of Spironolactone Prepared by Spray Drying and Electrospinning: The Influence of the Preparation Method on the Dissolution Properties. Mol Pharm. 2021;18(1):317-327. https://doi.org/10.1021/acs.molpharmaceut.0c00965.

[15] Ha E-S, Hyung Choi D, Baek I, Park H, Kim M-S. Enhanced oral bioavailability of resveratrol by using neutralized Eudragit E solid dispersion prepared via spray drying. Antioxidants (Basel). 2021;10(1):90. https://doi.org/10.3390/antiox10010090.

[16] Kumar B. Solid Dispersion-A Review. PharmaTutor. 2017;5:24–29.

[17] Robaina-Mesa M, López-Hernández OD, Rodríguez-Chanfrau CJE, Nogueira-Mendoza A. Spray dried aqueous extract of *Orthosiphon aristatus blume* (Java tea). Braz J Pharm Sci. 2017;53:1–5. http://dx.doi.org/10.1590/s2175-97902017000300015.

[18] Mustafa WW, Fletcher J, Khoder M, Alany RG. Solid dispersions of gefitinib prepared by spray drying with improved mucoadhesive and drug dissolution properties. AAPS PharmSciTech. 2022;23(1):48. https://doi.org/10.1208/s12249-021-02187-4.

[19] de Mohac LM, Raimi-Abraham B, Caruana R, Gaetano G, Licciardi M. Multicomponent solid dispersion a new generation of solid dispersion produced by spray-drying. J Drug Deliv Sci Technol. 2020;57:101750. https://doi.org/10.1016/j.jddst.2020.101750.

[20] Gharsallaoui A, Roudaut G, Chambin O, Voilley A, Saurel R. Applications of spray-drying in microencapsulation of food ingredients: An overview. Food Res Int. 2007;40:1107–1121. https://doi.org/10.1016/j.foodres.2007.07.004.

[21] Goula AM, Adamopoulos KG. Spray drying of tomato pulp in dehumidified air: I. The effect on product recovery. J Food Eng. 2005;66:25–34. https://doi.org/10.1016/j.jfoodeng.2004.02.029.

[22] Bötschi S, Rajagopalan AK, Morari M, Mazzotti M. Feedback control for the size and shape evolution of needle-like crystals in suspension. IV. Modeling and control of dissolution. Cryst Growth Des. 2019;19:4029–4043. https://doi.org/10.1021/acs.cgd.9b00445

[23] Kommavarapu P, Maruthapillai A, Palanisamy K, Koya RT. Effect of polymorphism and application of kinetic models for the evaluation of in vitro dissolution profiles of an eletriptan hydrobromide formulation. Dissolution Technol. 2015;22:30–37. https://doi.org/DOI:%2010.1023/A:1016020822093.

[24] Adams E, Coomans D, Smeyers-Verbeke J, Massart DL. Application of linear mixed effects models to the evaluation of dissolution profiles. Int J Pharm. 2001;226:107–125. https://doi.org/10.1016/s0378-5173(01)00775-x.

[25] Sathe PM, Tsong Y, Shah VP. In-vitro dissolution profile comparison: statistics and analysis, model dependent approach. Pharm Res. 1996;13(12):1799-1803. https://doi.org/10.1023/a:1016020822093.

[26] Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-133. https://doi.org/10.1016/s0928-0987(01)00095-1.

[27] Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol. 1975;27(1):48-49. https://doi.org/10.1111/j.2042-7158.1975.tb09378.x.

[28] Siswanto A, Fudholi A, Nugroho AK, Martono S. In vitro release modeling of aspirin floating tablets using Ddsolver. Indones J Pharm. 2015;26(2): 94-102. https://doi.org/10.14499/indonesianjpharm26iss2pp94

[29] Murtaza G, Ahmad M, Khan S, Hussain I. Evaluation of cefixime-loaded chitosan microspheres: Analysis of dissolution data using DDSolver. Dissolution Technol. 2012;19:13–19. https://doi.org/10.14227/DT190212P13

[30] Abali SO, Ekenna IC. Comparison of the use of kinetic model plots and DD Solver software to evaluate the drug release from griseofulvin tablets. J Drug Deliv Ther. 2022;12:5–13. https://doi.org/10.22270/jddt.v12i2-S.5402.

[31] Elmubarak EH, Osman ZA, Abdelrahman M. Formulation and evaluation of solid dispersion tablets of furosemide using polyvinylpyrrolidone K-30. Int J Curr Pharm Res. 2021;13:43–50. https://doi.org/https:/dx.doi.org/10.22159/ijcpr.2021v13i2.41554

[32] Raúl M-L, Sergio G-M, Marcela H. In vitro release studies of furosemide reference tablets: influence of agitation rate, USP apparatus, and dissolution media. ADMET DMPK. 2020;8:425–436. https://doi.org/10.5599/admet.801.

[33] Fazaeli M, Emam-Djomeh Z, Ashtari AK, Omid M. Food and bioproducts processing effect of spray drying conditions and feed composition on the physical properties of black mulberry juice powder. Food Bioprod Process. 2012;90:667–675. https://doi.org/10.1016/j.fbp.2012.04.006

[34] Osman AFA, Endut N. Spray drying of roselle-pineapple juice effects of inlet temperature and maltodextrin on the physical properties. 2nd International Conference on Environmental and Computer Science, ICECS 2009 2009:267–270. Https://doi.org/10.1109/ICECS.2009.91

[35] Dressman JB, Krämer J. Pharmaceutical dissolution testing. Taylor & Francis; 2005.

[36] U.S. Department of Health and Human Services. Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms. vol. 20857.

[37] Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, Xie S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J. 2010;12(3):263-271. https://doi.org/10.1208/s12248-010-9185-1.

[38] Huang W, Shi Y, Wang C, Yu K, Sun F, Li Y. Using spray-dried lactose monohydrate in wet granulation method for a low-dose oral formulation of a paliperidone derivative. Powder Technol. 2013;246:379–394. https://doi.org/10.1016/j.powtec.2013.05.042.

[39] Phaechamud T, Koizumi T, Ritthidej GC. Chitosan citrate as film former: compatibility with water-soluble anionic dyes and drug dissolution from coated tablet. Int J Pharm. 2000;198(1):97-111. https://doi.org/10.1016/s0378-5173(99)00460-3.

[40] Racz I, Dredan J, Antal I, Gondar E. Comparative evaluation of microcapsules prepared by fluidization atomization and melt coating process. Drug Dev Ind Pharm. 1997;23:583–587. https://doi.org/10.3109/03639049709149823.

[41] Shingate PN, Dongre PP, Kannur DM. New method development for extraction and isolation of piperine from black pepper. Int J Pharm Sci Res. 2013;4:3165–3170. https://doi.org/10.13040/IJPSR.0975-8232.4(8).3165-70.

[42] Saha KC, Seal HP, Noor MA. Isolation and characterization of piperine from the fruits of black pepper (*Piper nigrum*). J Bangladesh Agric Univ. 2013;11:11–16. https://doi.org/http:/dx.doi.org/10.3329/jbau.v11i1.18197.

[43] Setyaningsih D, Santoso YA, Hartini YS, Murti YB, Hinrichs WLJ, Patramurti C. Isocratic high-performance liquid chromatography (HPLC) for simultaneous quantification of curcumin and piperine in a microparticle formulation containing *Curcuma longa* and *Piper nigrum*. Heliyon 2021;7:e06541. https://doi.org/10.1016/j.heliyon.2021.e06541.

[44] Murti YB, Hartini YS, Hinrichs WLJ, Frijlink HW, Setyaningsih D. UV-VIS spectroscopy to enable determination of the dissolution behavior of solid dispersions containing curcumin and piperine. J Young Pharm. 2019;11:26–30. https://doi.org/10.5530/jyp.2019.11.6.