J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 47(3): 853-863, 2023
Doi: 10.33483/jfpau.1253561

ORIGINAL ARTICLE / ÖZGÜN MAKALE

EFFECTS OF DRYING TEMPERATURE ON CURCUMIN AND PIPERINE DISSOLUTION AND THE RELEASE KINETICS OF SOLID DISPERSION-BASED MICROPARTICLES: A PRELIMINARY STUDY

KURUTMA SICAKLIĞININ KURKUMİN VE PİPERİN ÇÖZÜNMESİNE VE KATI DİSPERSİYON BAZLI MİKROPARTİKÜLLERİN SALINIM KİNETİĞİNE ETKİLERİ: BİR ÖN ÇALIŞMA

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ABSTRACT

Objective: *One of the major challenges in developing curcumin as a pharmaceutical agent is its low bioavailability after oral administration. Co-administration of curcumin-piperine combined with employing solid dispersions (SD) approach has been shown to enhance curcumin dissolution and bioavailability. Understanding the influence of the processing temperature during spray drying is crucial in SDs preparations; the purpose of this study is to inquire the effect of inlet temperature spray-dryer on dissolution behavior and the best-fit kinetic model of dissolution itself.*

Material and Method: *The SD powder was prepared using a spray-drying method by varying the inlet temperature (105°C; 115°C; 125°C) and involved polyvinyl alcohol (PVA) as a carrier. The SD were prepared at 30% Curcuma longa and 10% Piper nigrum extracts. Yield (%) of the dried powder resulted from the spray drying process was monitored, and dissolution behavior of curcumin and piperine were analyzed using a dissolution efficiency (DE) value. Furthermore, mathematical model describing the release mechanism of curcumin and piperine from the dissolution were evaluated using a DDSolver software.*

Result and Discussion: *The variation of drying temperature on the spray dryer affects the dissolution behavior and the % yield of the PVA-based SD containing C. longa and P. nigrum extract. The most ideal mathematical model of kinetic release for curcumin and piperine were the Quadratic model, indicating that the mechanism of dissolution is diffusion through a gap between the PVA particle and the surrounding medium.*

Keywords: *Curcuma longa, DDSolver, dissolution, Piper nigrum, solid dispersion*

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Submitted / Gönderilme : 20.02.2023
Accepted / Kabul : 25.07.2023
Published / Yayınlanma : 20.09.2023

ÖZ

Amaç: *Kurkuminin farmasötik bir ajan olarak geliştirilmesindeki en büyük zorluklardan biri, oral uygulamadan sonra düşük biyoyararlanımıdır. Kurkumin-piperin'in katı dispersiyon (KD) yaklaşımı kullanılarak birlikte uygulanmasının kurkumin çözünmesini ve biyoyararlanımını artırdığı gösterilmiştir. Püskürtmeli kurutma sırasında işlem sıcaklığının etkisinin anlaşılması, KD preparatlarında çok önemlidir; bu çalışmanın amacı, püskürtmeli kurutucunun giriş sıcaklığının çözünme davranışı ve çözünmenin en uygun kinetik modeli üzerindeki etkisini araştırmaktır.*

Gereç ve Yöntem: *KD tozu, giriş sıcaklığı değiştirilerek (105°C; 115°C; 125°C) ve taşıyıcı olarak polivinil alkol (PVA) kullanılarak püskürtmeli kurutma yöntemi ile hazırlanmıştır. KD, %30 Curcuma longa ve %10 Piper nigrum ekstraktları kullanılarak hazırlanmıştır. Püskürtmeli kurutma işleminden elde edilen kurutulmuş tozun verimi (%) izlenmiş ve kurkumin ve piperinin çözünme davranışı, çözünme etkinliği (ÇE) değeri kullanılarak analiz edilmiştir. Ayrıca, kurkumin ve piperinin çözünmeden salınım mekanizmasını tanımlayan matematiksel model bir DDSolver yazılımı kullanılarak değerlendirilmiştir.*

Sonuç ve Tartışma: *Püskürtmeli kurutucuda kurutma sıcaklığının değişimi, C. longa ve P. nigrum ekstresi içeren PVA bazlı KD'nin çözünme davranışını ve % verimini etkilemektedir. Kurkumin ve piperin için kinetik salınımın en ideal matematiksel modeli, çözünme mekanizmasının PVA partikülü ile çevreleyen ortam arasındaki bir boşluktan difüzyon olduğunu gösteren Kuadratik modeldir.*

Anahtar Kelimeler: *Curcuma longa, çözünme, DDSolver, katı dispersiyon, Piper nigrum*

INTRODUCTION

Herbal secondary metabolites have proved to be valuable sources that play an essential role in Indonesian traditional medicine for maintaining health and curing various diseases. In the community, herbal preparation is often found as combining two or more plant extracts for more health benefits [1]. One of the natural polyphenols found in the rhizome of *Curcuma longa* Linn is curcuminoids, with curcumin being the most prominent component among the curcuminoids. The polyphenolic compound curcumin plays an essential role as an antioxidant with several pharmacological activities, such as anti-inflammation and anticancer properties. Although curcumin has many beneficial properties, the clinical application of curcuminoids as pharmaceutical agents is limited due to their low bioavailability after oral administration. Curcumin is classified as Biopharmaceutics Classification System (BCS) II which is less soluble in water (11 ng/ml) but has high membrane permeability. The low bioavailability of curcumin is due to its sensitivity to phase II metabolism in the gastrointestinal tract, where it is known to be a substrate for uridine 5′-diphosphate-glucuronosyltransferase (UGT) enzymes, presenting a significant barrier to its development as an active pharmaceutical ingredient [2,3].

One way to overcome low bioavailability is the use of bioenhancer. Piperine, the main active ingredient of P. nigrum, showed effective results in increased bioavailability of curcumin in combination dosage [4,5]. Co-administration of piperine with curcumin (1:100) enhanced serum curcumin concentration by 154% for 1-2 hours after the onset. At the dosages used in the study, piperine appears to increase plasma concentrations, absorption rate, and curcumin bioavailability in rats and human subjects with no adverse effects [3]. Another study discovered that when curcumin was co-administered with piperine, the absorption was increased and remained in the body tissues for significantly longer (maximum 48 hours) [6]. However, piperine is also classified as BCS II because of its poor water solubility (40 mg/L) [4]. In contemplation of overcoming the poor aqueous solubility the SD method of *C. longa* and *P. nigrum* extracts is suggested.

Spray drying is a common SD method for increasing the dissolution rate by evaporating liquid into microscopic droplets. This technique uses atomization in hot water to remove the solvent from the dispersion of the target compound in the matrix solution, resulting in a powder. The final product quality and drying yield of spray-dried product is affected by manufacturing parameters such as feed flow rate, inlet and outlet air temperatures, atomization speed or pressure, feed concentration, etc [7]. Inlet temperature is the primary variable besides the feed flow rate in spray drying that needs to be optimized [8]. Several studies have published the effect of operating parameters and drying conditions on the physical properties of spray-dried powders, such as inlet drying yield, moisture content (MC) [9-12],

and wettability [9,11,12]. Neither report studied the impacts of the spray-drying operating parameters on the dissolution rate of spray-dried powder properties.

Prior research on the bioavailability of curcumin encapsulation in different ratios with varied carriers using SD has been conducted by Hu et al. [13]. Meanwhile, Wang et al. [14] investigated the bioavailability of curcumin SD co-formed with piperine without an excipient/carrier. Meanwhile, other studies, including the investigations by Jumah et al. [15], Kumar and Muzaffar [16], and Fujita et al. [17] have observed the effects of spray-drying method operating parameters on the powder characteristics. Nonetheless, the effect of inlet spray-drying temperature on the functional properties of curcumin piperine encapsulation using PVA has not yet been investigated. Hence, in this study inlet temperatures varied from 105°C to 125°C were applied to dry the PVA-based SD containing *C. longa* and *P. nigrum* extract.

In order to estimate curcumin and piperine absorption, it is also necessary to discover the kinetics and mechanism of dissolution. To determine the mechanism of drug release, various mathematical models for assessing dissolution profiles have been proposed. A theoretical investigation of the process can produce mathematical models of a dissolution profile, but due to the variety of dosage forms and its complexity, no theoretical base exists in most situations. As a result, empirical models must be used to fit dissolution data [18,19]. For that reason, a quantitative assessment of dissolution profile character is required.

DD Solver is a valuable software that involves a non-linear regression approach to perform kinetic analysis of dissolution profile [20]. DDSolver can be used as a predominant tool for monitoring drug product reliability and stability, as well as a quick and low-cost technique for predicting *in vivo* drug absorption. To the best of our knowledge, the application of mathematical models in evaluating the curcumin piperine release from SD is limited. Therefore, in addition to investigating the temperature of the inlet spray-drying on the functional properties of curcumin piperine, this study also presents empirical mathematical models to simulate and predict *in vivo* drug absorption of SD curcumin piperine.

MATERIAL AND METHOD

Material

C. longa extract of 97.56% curcuminoid content was given by PT. Phytochemindo Reksa, Bogor, Indonesia. *P. nigrum* extract was given by Dr.rer.nat Yosi Bayu Murti, Faculty of Pharmacy, Universitas Gadjah Mada Yogyakarta, Indonesia. The piperine standard (Sigma Aldrich) and the validated reversed phase High-Performance Liquid Chromatography (RP-HPLC) method were used to extract and further define the sample (validity recovery 91.14% with >0,999 correlation coefficient) [21]. PVA was donated by PT Konimex Solo, Central Java, Indonesia. Ethanol 96%, methanol, Sodium dihydrogen phosphate, and Sodium Lauryl Sulfate (SLS) were purchased from Merck, Darmstadt, Germany. Dissolution medium consisting of sodium phosphate buffer of pH 6.0 and Milli-Q water were prepared in the laboratory.

Preparation of Spray Dried Curcumin-Piperine

The SD of *C. longa* and *P. nigrum* extract were prepared by spray drying using PVA as a carrier. The SD contained 30% w/w *C. longa* extract; 10% w/w *P. nigrum* extract: 60% w/w PVA. In brief, *C. longa*, and 0.6 mg of *P. nigrum* extracts were diluted in 600 ml ethanol, and 3.6 mg PVA was diluted in 20 ml hot water (80-90°C). The resulting solution was loaded through a two-way nozzle into a BUCHI B-290 mini spray dryer installed with a B-290 dehumidifier under the following operating conditions: feed pump rate of 8%, aspirator rate of 100%, nozzle cleaner of 2%, and inlet temperature varied 105, 115, and 125° (not exceed 180°C) [22,23]. The spray-dried powder obtained was precisely weighed for drying yield calculation (33.50%; 33.76%; 37.01%) and placed in a desiccator for further evaluation.

Dissolution Test

The dissolution test was performed in 900 ml of 0.5 w/v % SLS (0.5 gram of SLS is used to make up a total volume of 100 ml) in a 20 mM phosphate buffer solution with a pH of 6 (USP Apparatus II). The study was conducted for 120 minutes under a stirring speed of 75 rpm (37 ± 0.5ºC). To maintain

the sink condition, at predetermined time intervals, the sample (5.0 ml) was removed and replaced with a fresh dissolution medium at the same temperature.

Curcumin and piperine concentrations in dissolution samples were determined using validated spectrophotometry and Vierordt's method for simultaneous determination of curcumin and piperine (equations 1 and 2) [24]. The compound absorptivity for each wavelength was determined by plotting the absorbance obtained at the respective wavelength into the calibration equation of y = 0.1606x + 0.0045 (curcumin) and y = 0.09x – 0.0088 (piperine) (piperine).
Simultaneous Equation (Vierordt's Method):

$$Cc = \frac{(A2.ap1)-(A1.ap2)}{(ac2.ap1)-(ac1.ap2)} \quad (1)$$

$$Cp = \frac{(A1.ac2)-(A2.ac1)}{(ac2.ap1)-(ac1.ap2)} \quad (2)$$

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

The curcumin-piperine concentrations of the samples were measured using a verified method UV spectrophotometer at 430,5 and 344,4 nm. The dissolution data were expressed as a percentage (%) dissolved and dissolution efficiency at 120 min (DE120).

$$DE_t = \int_0^t \left(\frac{Ydt}{Y100t}\right) x100\%)$$

Statistical Analysis

All experiments were experiments were performed in triplicate, and statistical tests were carried out using one-way ANOVA Test for more than two data (obtained to describe the closeness of dissolution profiles). Statistically significant data was accepted if the p-value was less than 0.05. *In-vitro* dissolution data were fitted to the mathematical kinetics model in DD Solver with (1) statistical parameters-based evaluation of the release kinetics model: $R^2_{adjusted}$, Akaike Information Criterion (AIC), and Model Selection Criterion (MSC).

RESULT AND DISCUSSION

Drying Yield

Drying yield is the most important criterion when evaluating the viability of the spray-drying process in SD methodology. Table 1 shows the drying yields for spray-dried curcumin-piperine at different temperature of the inlet. The drying yield was increased along with the increasing temperature, and the highest yield was attained when the inlet temperature reached 125°C. In a study, the authors observed that increasing inlet temperature from 130°C–180°C led to increased process yield of microsized maltodextrin (MDX) (6.75 – 40.25%) [25]. Our findings were similar to this result. Another study reported an increase in the drying yield of waxy rice starch, from 74.83% to 88.66%, when the temperature on inlet spray drier was elevated from 40°C to 80°C. However, because of the sticking problem, the drying yield of waxy rice starch decreased at 100°C, indicating that when the drying temperature exceeds the gelatinization onset temperature, the droplets become drier and stick to the cyclone wall [26,27]. The inlet temperature positively affects the drying yield, with higher inlet air

temperatures increasing the effectiveness of mas and heat transfer processes while reducing the risk of inadequate drying particles hitting and forming crust on the drying chamber wall [28].

Table 1. Drying yield of spray-dried curcumin-piperine at different temperatures

	Formula 1 (105°C)	Formula 2 (115°C)	Formula 3 (125°C)
Curcumin (30%)	2.3995 g	1.8002 g	1.8001 g
Piperine (10%)	0.7998 g	0.6001 g	0.6000 g
PVA (60%)	4.8003 g	3.6001 g	3.6001 g
Total weight	7.9996 g	6.0004 g	6.0002 g
Yield calculation	33.50%	33.76%	37.01%

In-Vitro Dissolution Study

An *in-vitro* dissolution is an essential approach in the pharmaceutical sector for drug development and estimating a drug product's *in vivo* performance as a quality control test. A dissolution study can be used in place of determining bioequivalence (biowaiver). An *in-vitro* dissolution study also can be used to identify pharmaceutical products' long-term stability and shelf life [29].

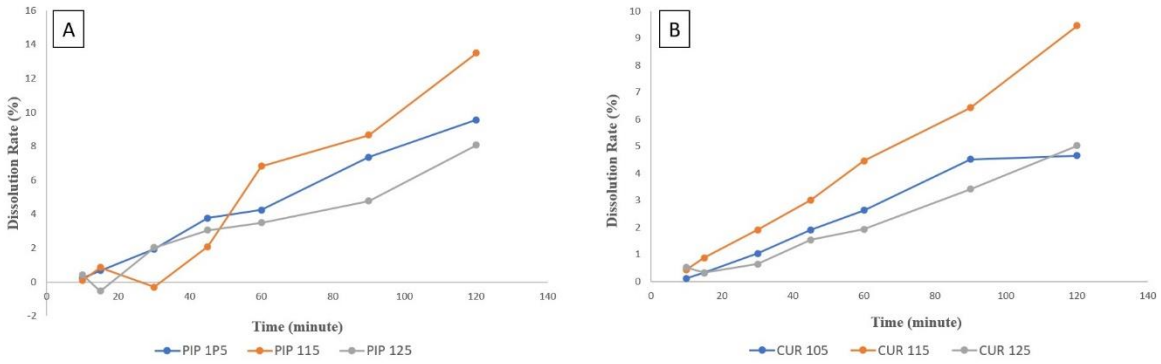

Figure 1. The dissolution rate of Curcumin (A); and Piperine (B) in sodium phosphate buffer (pH 6.0) at temperature 37±0.5°C

The dissolution profiles represented as percentage dissolution rate versus time dilution of SD at various inlet temperatures are illustrated in Figure 1. The percent dissolution value was also calculated as the Area Under the Curve (AUC) and Dissolution Efficiency (DE) values at 120 minutes. Figure 2 depicts the DE120 values of curcumin and piperine which were calculated to compare the dissolution profile. The data from the three formulas were found to be normally distributed by the normality test results, hence the ANOVA test was carried out. The ANOVA test revealed that piperine and curcumin had significantly different dissolution rates amongst the SD formulations obtained ($p>0.05$). The dissolution rate of curcumin and piperine increased from 105°C to 115°C, but then slightly decreased when the temperature of the inlet was raised to 125°C. The slight decreased dissolution rate obtained at 125°C could be explained by the crust formation which prevents water penetrasion during the dissolution study. The crust was formed to due rapid moisture evaporation occurring at 125°C drying temperature [16,30]. Thereby, the crust formation during drying in a spray dryer can be prevented by conducting it at lower temperatures. However, if the temperature of the inlet is defectively lower, the particle will retain moisture for a longer period of time and shrinks resulting in a smaller particle size which can affect the dissolution rate [17]. Shi et al. [10] reported similar dissolution behaviors in the

dried watermelon SD which was processed at varied inlet temperatures from 120°C to 150°C. The particle size decreased from 21.64 nm (120°C drying temperature) to 13.44 nm (140°C drying temperature). Then, the particle size increased to 21.21 nm when the inlet temperature was raised to 150°C, resulting in a lower dissolution rate. Another study by Santhalakshmy et al. [11] obtained similar results, analyzing the production of spray-dried jamun fruit juice powder at 140°C to 160°C. Furthermore, Figure 1 was shown that the highest dissolution rate only reached 13.49% ± 4.07% at 115°C. This is most likely due to the PVA carrier. The dissolution results in the three formulas where the remaining capsules are not dissolved at 120 minutes show that PVA can form a gel layer, making it difficult to dissolve. The formation of the gel layer causes the diffusion layer to thicken, affected in delaying dissolution [31]. Water molecules are prevented from penetrating through the particles due to the surface layer. By decreasing the particle's wettability, the dissolution powder and transfer rate provided an enormous force for evaporation, allowing powders with lower water content to be formed [32,33]. In addition, due to the formation of the gel layer, the PVA carrier also increased the viscosity of a preparation which affected the course of dissolution. Viscosity is inversely proportional to dissolution rate, so as viscosity increases, the dissolution profile in a medium will presumably decrease [34,35].

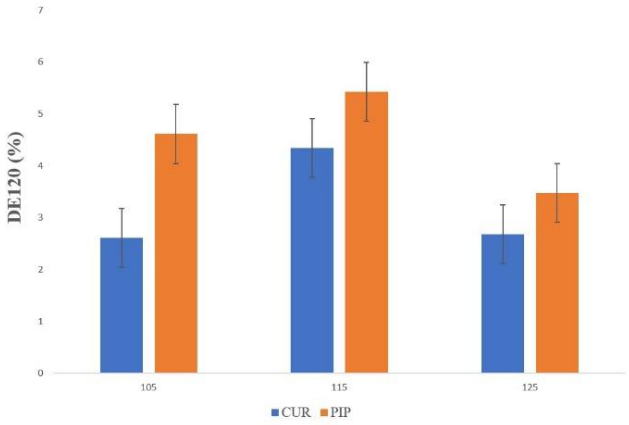

Figure 2. Dissolution Efficiency (DE120) of curcumin and piperine at 120 minutes

Dissolution Study of Curcumin-Piperine Kinetic Release using DDSolver

Mathematical models of kinetics drug release are useful for predicting the exact transport mechanism that affects a drug's *in vivo* dissolution profile [34]. Dissolution profiles of curcumin-piperine in various inlet temperatures were analyzed using drug release kinetic models. The obtained dissolution profiles of curcumin-piperine were fitted onto several mathematical models conducted by a non-linear regression approach using the DDSolver. The DDSolver was used to plot the dissolution profile data, which included the dissolution time (minutes) and the percentage of drug dissolved.

DDSolver offers a few statistical metrics to assess the dissolution model, including adjusted coefficient of determination, correlation coefficient, and coefficient determination. The most well-known and extensively used of these criteria for identifying *in vitro* drug release data modeling are $R^2_{adjusted}$, AIC, and MSC [36]. The $R^2_{adjusted}$ was considered the most acceptable parameter to compare the dissolution models [19]. As shown in Table 2, the result revealed that the prepared curcumin and piperin SD at all temperatures exhibited Quadratic model tendencies, with $R^2_{adjusted}$ values of 0.98427, 0.98787, and 0.95503 for curcumin and 0.97992, 0.96202, and 0.87643 for piperin. However, the results showed a high similarity between models at different temperatures. As a result, other statistical criteria, AIC and MSC were applied using DDSolver.

Table 2. Results of statistical parameters to describe the release of SD curcumin and piperine by each model

SD	Model	Dissolution Model Parameters (mean)					
		$R^2_{adjusted}$		MSC		AIC	
		Curcumin	Piperine	Curcumin	Piperine	Curcumin	Piperine
105	Zero-order	0.95864	0.95839	2.79162	2.91618	2.55799	11.57415
	First-order	0.95912	0.95643	2.79969	2.81064	2.49343	12.41852
	Higuchi	0.79417	0.77688	1.18165	1.11619	15.43776	25.97409
	Hixson-Crowell	0.95899	0.95716	2.79756	2.84498	2.51046	12.14375
	Hopfenberg	0.95235	0.95275	2.55256	2.68150	4.47048	13.45165
	Weibull	0.86903	0.92924	1.50097	3.01295	12.88314	10.80005
	Quadratic	0.98427	0.97992	2.64386	4.03150	3.74001	2.65158
	Korsmeyer-Peppas	0.84935	0.91540	1.53594	2.24456	12.60343	16.94712
	Gompertz	0.96055	0.96712	2.79172	3.32432	2.55720	8.30906
115	Zero-order	0.95973	0.91568	2.92895	2.07868	3.45045	13.89547
	First-order	0.95625	0.91392	2.83752	2.05761	4.18193	14.06399
	Higuchi	0.73873	0.77688	0.96011	1.11619	19.20115	25.97409
	Hixson-Crowell	0.95743	0.91454	2.86762	2.06493	3.94110	14.00548
	Hopfenberg	0.95302	0.90180	2.67895	1.83021	5.45045	15.88320
	Weibull	0.92859	0.88359	2.26581	1.60994	8.75560	17.64536
	Quadratic	0.98787	0.96202	4.05118	2.95320	5.52737	14.89926
	Korsmeyer-Peppas	0.96224	0.91540	2.96048	2.24456	3.19825	16.94712
	Gompertz	0.92975	0.90005	2.22296	1.81909	9.09839	15.97214
125	Zero-order	0.88825	0.84292	1.88969	1.54995	18.23976	27.37747
	First-order	0.88563	0.83605	1.85928	1.49783	18.48306	27.79443
	Higuchi	0.70210	0.63066	0.82793	0.64051	26.73386	34.65304
	Hixson-Crowell	0.88657	0.83848	1.86973	1.51559	18.39942	27.65239
	Hopfenberg	0.86974	0.81676	1.64046	1.30003	20.23357	29.37687
	Weibull	0.78403	0.73191	1.06917	0.86727	24.80395	32.83897
	Quadratic	0.95503	0.87643	2.50284	2.39663	13.33454	20.60408
	Korsmeyer-Peppas	0.61860	0.80884	0.60494	1.35567	28.51776	28.93170
	Gompertz	0.87629	0.82748	2.43229	1.43095	13.89894	28.32953

The ideal model is the one with the lowest AIC value, while the most accurate model has the highest MSC value. MSC is a modified opposite form of the AIC that has been validated to be independent of the underlying point scaling. The appropriate MSC value is greater than 2 or 3 [19,36]. Thus, the MSC and AIC values for all the kinetic dissolution models of varied temperatures were evaluated. From the kinetic model parameters as depicted in Table 2, the quadratic model is the most appropriate model to explain the phenomenon of curcumin piperine SD dissolution reverse to the result of AIC, MSC, and $R^2_{adjusted}$ value. Curve fitting results also indicated that the quadratic model is the best model for explaining the behavior of curcumin and piperine dissolution profiles at all inlet temperatures (Figure 3).

The Quadratic model is based on this equation $F = 100 (k_1.t^2 + k_2.t)$ [36]. A study by Delfour and Garon explained how a quadratic model could be applied in the case of this study. It was revealed that the quadratic model can be applied not only in time-dependent or nonlinear diffusion but also through a circumstance of the polymer-medium interface [37]. From those findings, the dissolution kinetic of curcumin-piperine from the PVA based microparticle containing *C. longa* and *P. nigrum* extracts in this study can be assumed that the PVA polymer might form tiny holes or cracks at which the drug curcumin-piperine could diffuse through the gap between the PVA particle and the medium.

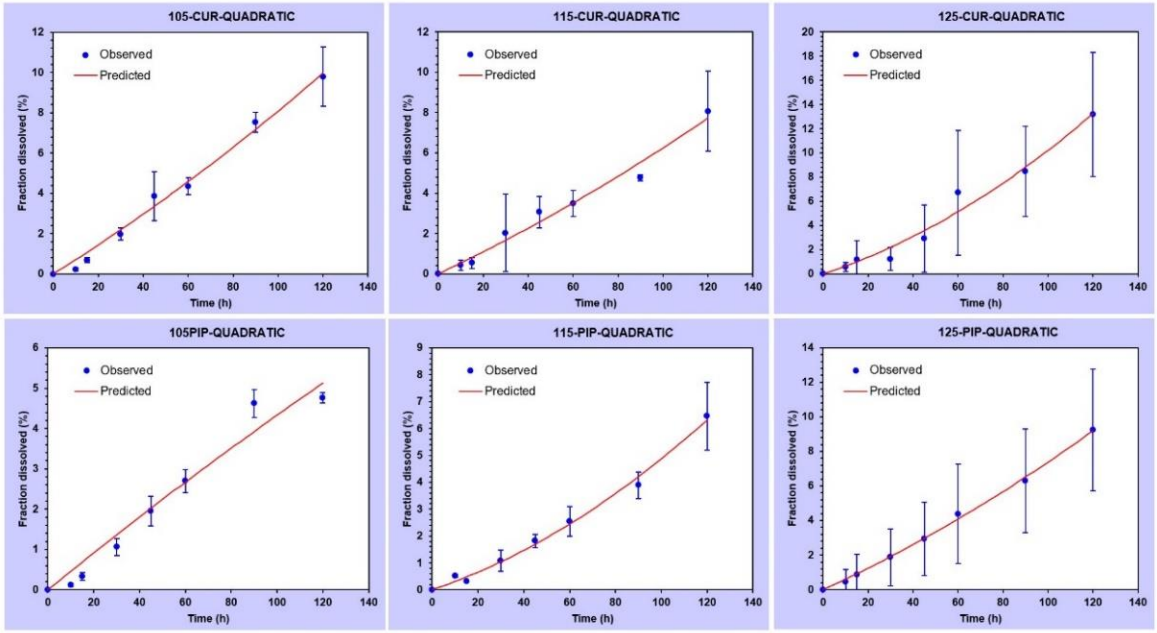

Figure 3. The most precise model prediction of the kinetic release of curcumin (CUR) and piperine (PIP)

Understanding the mechanism of oral drug absorption is important for efficacy and safety. Drug disintegration and dissolution, degradation, stomach emptying, intestinal transit, intestinal permeation and transport, intestinal metabolism, and hepatic metabolism are all possible phases in oral drug absorption. Dosage form, physicochemical and biological properties of the active pharmaceutical ingredient, and gastrointestinal (GI) tract physiology are all factors that may influence the rate and extent of drug absorption [37]. The kinetic modeling dissolution is known to be essential for estimating the absorption process. The absorption process itself is also a major challenge to control and maintain in oral administration. However, dissolution kinetic modeling cannot always illustrate the complex relationship between formulation attributes and oral absorption *in vivo*. The absorption modeling method is also considered necessary to investigate the effect of formulation attributes on oral absorption [19]. A study by Stillhart et al. [38] observed the beneficial effect of combining absorption modeling and in vitro dissolution tests of Basmisanil rather than only dissolution test to identify the rate-limiting processes in oral drug absorption. Therefore, predictive absorption modeling is required for further evaluation in future studies to demonstrate the compatibility between dissolution testing and the absorption process for finding the best strategy of formulation development.

ACKNOWLEDGEMENTS

The research was supported by Sanata Dharma University of Center for Research and Community Services under contract number 007 Penel./LPPM-USD/II/2022.

AUTHOR CONTRIBUTIONS

Concept: D.S.; Design: D.S.; Control: D.S.; Sources: D.S.; Materials: D.S.; Data Collection and/or Processing: M.O.T.D.; Analysis and/or Interpretation: M.O.T.D.; Literature Review: M.O.T.D.; Manuscript Writing: M.O.T.D.; Critical Review: D.S.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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