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RESEARCH ARTICLE

Dissolution profile of Curcumin from solid dispersion prepared at a high drug load of Curcumin using Poloxamer 407 as the carrier

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Abstract

Introduction: Curcumin, a BCS II drug, suffers from poor bioavailability. Increasing curcumin dissolution is a way to increase its bioavailability. Solid dispersion formulation can be used to improve curcumin dissolution. However, the successful curcumin solid dispersion is limited to a relatively low drug load (< 20%). **Aim:** This study aimed to investigate the dissolution behaviour of curcumin at a higher drug load (27.9%, 42.3%, and 56.6%) using a surfactant carrier of poloxamer 407. **Methods:** The solvent evaporation method was employed to prepare high drug load solid dispersion of curcumin. A physical mixture of the corresponding solid dispersion formulation was prepared as a control. Drug load, dissolution behaviour in 180 minutes, and dissolution efficiency (DE180) were determined. **Results:** The results showed that incorporating curcumin into a poloxamer 407 solid dispersion significantly improves the dissolution rate of curcumin. In the solid dispersion formula, the dissolution behaviour of curcumin was found to be carrier-dependent.

Introduction

Curcuminoid, a mixture compound of curcumin, demethoxycurcumin, and bisdemethoxycurcumin, is widely known as a functional food and is obtained from the isolation of turmeric (*Curcuma longa*) rhizome and other species of Zingiberaceae. Extensive investigations revealed the beneficial effects of curcumin to cure several diseases with its main activities as antioxidant and anti-inflammation (Basnet & Skalko-Basnet, 2011; Abdollahi *et al.*, 2017). Although extensive *in vitro* and *in vivo* studies highlighted the potential activities of curcumin, a clear therapeutic benefit of curcumin in clinical studies remained questionable due to the poor bioavailability of curcumin after oral administration (Gupta, Patchva & Aggarwal, 2012). The poor bioavailability of curcumin has been attributed to the low aqueous solubility and dissolution; the solubility of curcumin in water was reported to be 11 ng/mL (Wang *et al.*, 1997).

An increased dissolution has been proposed to tackle the bioavailability problem of curcumin. Solid dispersion is one of the potential strategies to improve curcumin dissolution. Several factors enhance the dissolution rate of drugs, including increased surface area by reducing particle size, improvement of wetting, reduced agglomeration, and increased saturated concentration resulting from the amorphous form (Craig, 2002). Different types of carriers and methods are used to prepare solid dispersions (Leuner & Dressman, 2000). One of the carriers used in solid dispersion preparation is the poloxamer, a non-ionic triblock copolymer of polyoxyethylene-polyoxypropylene-polyoxyethylene, which has surfactant properties (Bodratti & Alexandridis, 2018). The dissolution enhancement rate of poloxamer

solid dispersion is achieved by improving the wettability and the ability of intermolecular interaction of poloxamer-drug to form a molecular dispersion (Ali, Williams & Rawlinson, 2010). This work aimed to investigate the dissolution behaviour of curcumin at a higher drug load (above 20% to less than 60%), using a surfactant carrier of poloxamer 407.

Material and Method

Material

Curcuma longa standardised extract (84.67% curcumin as detected by spectrophotometric method) was given by PT Phytochemindo Reksa, Bogor, Indonesia. Curcumin standard compound was purchased from Sigma. The poloxamer 407 was given by PT Konimex, Solo, Indonesia. Citric acid, methanol, ethanol, sodium dihydrogen phosphate dihydrate, and sodium lauryl sulfate (SLS) were purchased from Merck. Capsule shells of the size of 00 were purchased from Kapsulindo Nusantara, Indonesia. MiliQ water was supplied by our laboratory.

Method

1. Preparation of the solid dispersion formulation

The poloxamer 407 based solid dispersion (SD-PC) was prepared at 27.9%, 42.3%, and 56.6-wt % of the *C. longa* extract by a solvent evaporation method using a vacuum rotary evaporator. The formulas were coded as SD-PC 33, SD-PC 50, and SD-PC 67 assigned to each extract -wt. % of 27.9%, 42.3%, and 56.6-wt %, respectively in the solid dispersion formulations. Briefly, an accurate weight of *C. longa* extract and poloxamer 407 according to each code of formula was dissolved in ethanol at concentrations of 5 mg/mL and 45 mg/mL. Both solutions were stirred for 30 minutes to form a clear yellow solution. The ethanol was evaporated using a BUCHI vacuum rotary evaporator at 80^{o}C. The obtained viscous solution was then subsequently dried using a vacuum oven. The dried product was pulverized in a mortar and sieved using a 60-mesh size. Physical mixture formulations (PM-PC) were prepared at the drug load as that prepared in the SD-PC formulations. The extract and poloxamer 407 were gently mixed in a mortar using a spatula and sieved using a 60-mesh size. For the dissolution study, the SD powder was prepared into an approximately 500 mg capsule of size 00. The drug load of curcumin in the SD formulations was quantified using the calibration curve prepared from the serial concentrations of curcumin reference standard in methanolic solution. The linearity between the concentration and the absorption was confirmed with y=0.1349x + 0.0035 and a correlation coefficient of 0.9972.

2. Dissolution

The dissolution of the SD-PC or PM-PC prepared in capsules was evaluated using a SOTAX AT7 dissolution tester according to the USP type II dissolution method. For the dissolution study of lipophilic compounds like curcumin, 0.5% surfactant of SLS was added into 20 mM sodium phosphate buffer of pH 6.0. This pH value was chosen because the curcumin solution is highly stable at pH 6.0 (Wang *et al.*, 1997). The dissolution was carried out in 900 mL media with a paddle speed of 100 rpm and a temperature of 37±0.5°C. The samples of 2 mL were taken at predetermined time intervals of 0, 10, 15, 30, 45, 60, 90, 120, and 180 minutes. The withdrawn volume was replaced with the same volume of a fresh dissolution medium, maintained at 37° to keep the volume and sink condition constant. Curcumin in the dissolution sample was determined using the validated spectroscopic method at 430 nm against the blank sample of the dissolution medium. Curcumin concentrations were quantified based on the calibration curve at which the result shows linearity with a linear equation of y=0.1279x + 0.009 and a relation coefficient of 0.997.

3. Data analysis

The dissolution profile was determined by calculating the Dissolution Efficiency (DE) at 180 min, as in equations 1 and 2. The area under the curve of dissolved curcumin was calculated by the trapezoidal method, as shown in the following equations:

$$DE_t = \frac{\int_{t1}^{t2} y.\,dt}{y_{100}.t}) \times 100\% \qquad AUC = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})(y_{i-1} + y_i)}{2}$$

Equation 1 Equation 2

DE_t : Dissolution efficiency at time (t)

y : Area under the curve of dissolved drug at time t

y100.t : Rectangle area where 100% of drug dissolved at time t

Results

Table I shows the amount of curcumin content in the solid dispersion and physical mixture formulations. The % assay values, calculated based on the recovery at which the obtained curcumin contents were divided by the theoretical values and multiplied by 100%, were

between 94.33-99.48% for SD-PC and PM-PC formulations. The curcumin content for all SD and PM formulations was calculated for the relative standard deviation (RSD) values. The RSD values for all SD and PM formulations are between 0.12%-4.50%.

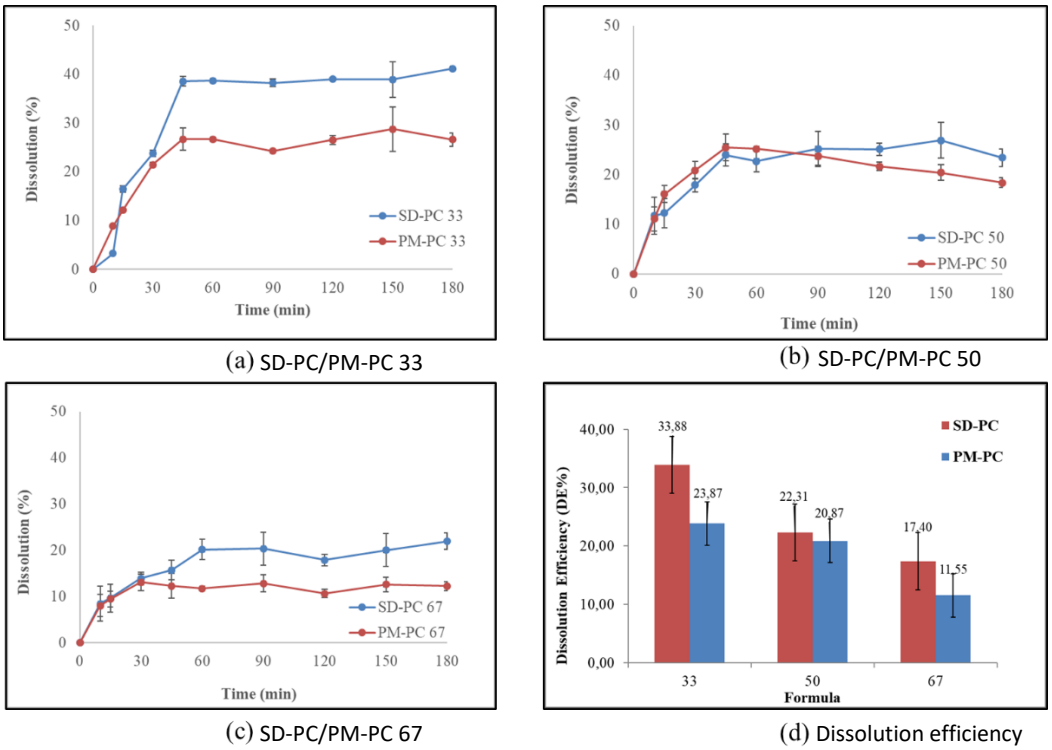
Table I: Curcumin content was observed in the solid dispersion (SD) and physical mixture

% weight of *C. longa* extract	Code	SD-PC			Code	PM-PC		
		% found	% assay	RSD		% found	% assay	RSD
27.9	SD-PC 33	27.59 ± 0.38	99.24	1.37	PM-PC 33	27.42 ± 0.32	99.48	1.16
42.3	SD-PC 50	40.87 ± 0.67	96.54	1.63	PM-PC 50	41.22 ± 0.71	96.38	1.72
56.6	SD-PC 67	56.29 ± 0.07	99.38	0.12	PM-PC 67	53.52 ± 2.41	94.33	4.50

Note: Data were presented as mean and SD of 3 assays. % assay was calculated by dividing the observed amount of curcumin by the theoretical amount of curcumin present in the formulation at the accordingly wt % of *C. longa* extract. The theoretical amount of curcumin was determined based on the curcumin content in the standardized *C. longa* extract.

The *in vitro* dissolution profile of the different solid dispersion formulations using poloxamer 407 and the respective physical mixture in 20 mM sodium phosphate buffer of pH 6.0 are shown in Figure 1 (a, b, and c). At the end of 180 minutes, 26.62%, 18.38%, 12.22%, 41.18%, 23.41%, and 21.92% were released from PM-PC 33, PM-PC 50, PM PC 67, SD-PC 33, SD-PC 50, and SD PC 67, respectively. The dissolution profile of SD and PM formulation show stagnant dissolution rate after 30 minutes (SD/PM-PC 33), 45 minutes (SD/PC-50), and 60 (SD/PC-PC 67).

DE_{180} was used to compare the dissolution profiles resulting from all SD and PC formulations and presented in Figure 1d, showing that all SD formulations increased the dissolution rate of curcumin compared to the physical mixture formulation as monitored in 180 minutes. It also revealed that the solid dispersion formulation increased the dissolution rate of curcumin as compared to the corresponding physical mixture formulation.



(a) SD-PC/PM-PC 33 (b) SD-PC/PM-PC 50

(c) SD-PC/PM-PC 67 (d) Dissolution efficiency

Figure 1: Dissolution behaviour of curcumin from SD and PM formulations

Discussion

As shown in Table I, the RSD values for SD and PM formulations are all below 5%. The data indicate that the solid dispersion and physical mixtures formulations are homogenous; independent assays of three samples taken from any dispersion showed an even drug distribution within each system. All formulas showed that % values between the founded curcumin content and the theoretical curcumin concentration were close, as reflected by a high % assay values of between 90 and 100%. Moreover, curcumin content in the SD-PC is quite close to the PM-PC, indicating that the curcumin remains preserved during the preparation processes of the solid dispersion formulations.

Surfactants can improve the hydrophobicity of poorly water-soluble drugs and increase the dissolution rate by increasing wettability. Solid dispersion formulation of *C. longa* extract using poloxamer 407 as carrier improves the dissolution profile of curcumin compared to the physical mixture formulation (Figure 1a, b, c) due to the improvement of wetting with the addition of poloxamer 407. A significant increase in dissolution rate was observed from the SD-PC 33 and SD-PC 67 compared to the corresponding physical mixture formulation (PM-PC 33 and PM-PC 67). The dissolution rate declined as higher extract concentration in the solid dispersion formulations was used (SD-PC 67). The release of curcumin during 180 minutes was about 40%; however, at higher extract concentration (SD-PC 67), the dissolution decreased to 20%. A lower dissolution rate at a higher drug load was also reported by other publications, suggesting that the dissolution mechanism is controlled by the carrier.

Dissolution efficiency (DE) is a dissolution parameter used to compare characteristics of the dissolution profile between formulas. The effect of increasing extract content in the solid dispersion formulation markedly reduced the dissolution rate of curcumin, as indicated by the DE values (Figure 1d). Lowering the dissolution rate by increasing the extracted content was observed in the solid dispersion formulation and demonstrated by the physical mixture formulation.

Conclusion

Poloxamer 407 is an effective carrier to increase the dissolution rate of curcumin during a 180-minute study in solid dispersion formulations containing C. longa standardized extract. An increased extracted content in the solid dispersion formulation results in reduced dissolution of curcumin dissolution. The highest dissolution rate of curcumin is found in the extracted content of 27.9 -wt% of curcumin of the SD-PC 33 formulation.

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