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Optimization of thin layers of coated turmeric extract (*Curcuma longa* L) tablets using a dipping method

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ABSTRACT

Turmeric extracts have many benefits, such as an anti-oxidant, anti-inflammatory, and neuro-protector for dementia. The turmeric extracts can be prepared in the form of a thin layer of coated tablets through a dipping method using the dip coating and Simplex lattice design (SLD) methods. The quality of the thin layers of coated tablets is much related to the formulation in the coating process. This research aims to formulate and optimize the coating composition of HPMC, PEG-400, and dip time. Consequently, the TSLT meets the standard requirements. The core tablets were made by using the wet granulation method with the formulation of turmeric extract, erosol, lactose, gelatin, and aquades. Before the core tablets had been produced, the eligibility of granules was initially evaluated based on the standard requirements. Subsequently, the core tablets that meet the standard requirements were printed and replicated. The coating processes on core tablets were performed by dipping into the coating solution in the various duration of dipping times: 5, 30, and 60 seconds. The coating solution consists of HPMC, PEG-400, glycerine, sunset yellow, and distillate water. Then, produced TSLTs were evaluated based on the hardness, friability, and disintegration time. The best optimization process for the mixture of HPMC and PEG-400 indicates a more positive value of R (R = 0.2024).

1. Introduction

Curcumin (C21H20O6) is a phenol component in turmeric (*Curcuma longa* L) that has biological activities, such as antioxidant, neuroprotective, anti-inflammatory, and anti-aging (Singh & Kumar, 2017). The neuroprotector effect of curcumin has been proven in animals or in-vitro studies and developed into active clinical trials in neurodegenerative disorders (Molino et al., 2016). It is also proven that curcumin interacts with glutathione S-transferase and reduces glutathione (GSH) to produce reactive oxygen species (ROS) that lower as well as induce an antioxidant enzyme of heme oxygenase-1. Therefore, curcumin is believed to nourish the brain and play an important role as an anti-degenerative function to prevent Alzheimer's disease.

Turmeric extract has been formulated and made in the dosage form of tablets (Suyono & Nurhaini, 2016; Wijayanti, 2002). Some studies have reported the formulations of manufacturing coated tablets of meniran, gambir, fruit, mahogany seed, pomegranate peel, bitter melon, and papaya leave extracts. However, the formulation and provision of coated tablets from turmeric extract have not been investigated. Whereas, tablet coating, especially with the polymer, can protect sensitive materials from environmental influences, such as light and humidity, or eliminate bad tastes in the formulation (Englert et al., 2018). Curcumin will experience structure degradation or decomposition in the form

of curcumin cyclization; thus, its color becomes darker when exposed to light (Tensiska et al., 2012). Other studies have revealed that the natural pigment of turmeric (curcuminoids) can experience photodecomposition due to the influence of light, solvents, and oxygen (Price & Buescher, 1996). Curcumin would receive an adverse effect from the light stability (Wang et al., 1997).

The coating solution can be produced from multiple polymeric compounds, such as hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG). The HPMC compound is one of the gelling agents frequently used to coat drugs because it is water-soluble, does not affect the hardness of tablets, has no tastes or odors, and contains relatively low toxicity (Ardana et al., 2015). In addition, the HPMC bases have good drug releases with wide spreads (Madan & Singh, 2010). Meanwhile, the PEG is used for film-coating and hydrophilic polishing materials. PEG-coated tablets can increase water permeability so that body fluid can easily penetrate the tablets, and medicines can be absorbed by the body easily (Basri, 2009). This study aims to (1) modify the dosage of available tablets into coated tablets with thin layers by adding coating solution in the available tablet using the dip-coating method and (2) discover the optimum formulations of coating solutions using the Simplex lattice design (SLD) method. This study is believed to provide turmeric extract tablets with thin layers and levels of hardness, friability, and disintegration time that meet the required standards. In general, a tablet is considered good and meets the standard if its hardness is 4-8 kg (Parrot, 1970). A table hardness less than 4 kg is still acceptable as long as the tablet friability does not exceed the limit set. An ideal friability value of an uncoated tablet is not more than 1% (Lachman et al., 1994). Meanwhile, (Ansel, 1999) and (Voight, 1984) argue that the tablet friability should not exceed 0.8%. Pharmacopoeia edition V (2014) explains that the disintegration time of coated tablets is not more than 60 minutes. This standard is also stated in several studies (Hadisoewignyo & Fudholi, 2013; Setianto et al., 2014; Sugijanto, 2009).

2. Materials and Methods

2.1. Tools and Materials

This research employed several tools, such as hardness tester of Amtast brand, friability tester of Charles Ischi AG and Pharma Pruftechnik brands, and disintegration tester of Vanguard Pharmaceutical Machinery Inc.

The materials used in this research were turmeric extract from PT. Borobudur Semarang, Aerosil, lactose, gelatin, magnesium (Mg) stearate, HPMC, PEG-400, glycerin, and aquades from PT. Brataco Chemica Yogyakarta. Meanwhile, the sunset yellow was obtained from one grocery and pastry shop in Yogyakarta.

2.2. Working Procedures

1) Manufacturing Granules and Tablet Cores

The tablets were made by wet granulation with the composition of turmeric extracts (15.0 g), aerosols (35.0 g), lactose (12.8 g), gelatin (0.5 g), Mg stearate (1.0%), and aquades (200 ml). The total weight of each tablet was 630 mg. In granule manufacture, each formula contains 15 grams of turmeric extracts, 35 grams of aerosols, 12.8 grams of lactose, 0.5 grams of gelatin, and 200 mL of aquades. These substances were then mixed. Afterward, the mixture was sieved using the sieve mesh 12 and then dried in an oven at a temperature of 40 oC for 24 hours. After the mixture had been dried, the granules were removed from the oven then sieved again using the sieve mesh 14/30. The sieved granule was then added with 1.0% Mg-stearate of the granule weight retained on the sieve mesh 30. Then, the granule was printed using a tablet printer machine (single punch) to generate the tablet cores. Afterward, each produced tablet core was weighed and would be used in the next test.

2) Manufacturing Thin Layers of Coated Tablets

The coating solution was made by mixing HPMC, PEG-400, 1.5 grams of glycerin, and 7.0 grams of sunset yellow in a beaker glass. Then, these substances were added with aquades until the total weight of the mixture was 100 grams. The weight of HPMC and PEG-400 is presented in Table 1. Furthermore, the weighed tablet cores were dipped in a beaker glass containing a coating solution and then let rest for 5, 30, and 60 seconds. After that, the dipped tablet cores were removed and dried in an oven at a temperature of 40°C for 48 hours. The dried tablet cores were then stored in a desiccator and would be used in the next experiment.

Table 1. Coating Solution Formulations

Compositions	F1 (% weight)	F2 (% weight)	F3 (% weight)
HPMC	0.1	0.6	1.1
PEG-400	1.1	0.6	0.1
Glycerin	1.5	1.5	1.5
Sunset yellow	7	7	7
Aquades	Added until the solution weight of 100 g		

3) Determining Standard Test of Thin Layers of Coated Tablets

The standard test of thin layers of turmeric extract was determined by testing the friability, hardness, and disintegration time using the same tools and by testing the core tablets. The standard limit of friability of coated tablets is the value of friability <`1 %. Meanwhile, the acceptable hardness value refers to the hardness level ranging from 4 to 8 kg, and disintegration time should not exceed 15 minutes of the testing time. The quality of coated tablets of turmeric extract was analyzed referring to Standard Indonesian Pharmacopoeia (Anonim, 1979; Hadisoewignyo & Fudholi, 2013).

4) Optimizing Coating Solutions

The coating solution was optimized by using the Simplex lattice design (SLD) method for the two variables (HPMC and PEG-400) and varying the length of the dipping time for 5, 30, and 60 seconds. This design was created by selecting three combinations of a mixture of HPMC and PEG-400. Then, each combination was observed to gain responses. After the value of response [Y] had been obtained, the normalization (N) and weighted (P) were calculated. In this study, the weighting was set to 4:4:2 for friability, hardness, and disintegration time. The final result of this calculation was expressed in R. The value of R is the summation of each result of multiplying N with P of each variable. The result of the best optimization is a mixture of HPMC and PEG-400 with the highest R-value. (Armstrong, 1986).

2. Data Analysis

The data from the friability, hardness, and disintegration time tests of thin layers of coated tablets were analyzed using the normality and homogeneity tests. The next processes were ANOVA and the Kruskal-Wallis tests using SPSS 18.

3. Results and Discussion

The dip-coating method was employed to produce thin layers of coated tablets. This method has a drawback; for example, the tablets will easily be disintegrated in the coating solution if the dipping time is too long. However, this method can work well if the dipping time is controlled precisely. Moreover, this method is the simplest and easiest one to use (Lachman et al., 2012).

Coating process mechanisms for tablet cores are presented in Figure 1. These coating process mechanisms were modified from (Gaur et al., 2014), (Porter et al., 2017), and (Hadisoewignyo & Fudholi, 2013).

Figure 1(a) shows that polymer (HPMC), plasticizer (PEG-400), glycerin, and sunset yellow particles are dispersible in water. When the water begins to evaporate, the coating particles begin to precipitate on the tablet core surface (Figure 1(b)). The more water evaporates, the more coating particles settle on the tablet core surface (Figure 1(c)). Moreover, the more water evaporates, the more polymer particles will increasingly accumulate and close together; consequently, the solidification and deformation occur (Figure 1(d)). If the particle fusion (cohesion) has greater strength than the particle repulsion, the particles will start to merge and form bonds between the polymer molecules. The occurring merging is a complex process that depends on the conditions of the coating polymer, storage, molecular weight, particle size of the polymer, coating constituents, and liquid properties, such as viscosity (Gaur et al., 2014). Further evaporation causes most water to evaporate, the solution viscosity to increase (gelation), and the adjacent polymer chains to remain and sediment on the top of the previous polymer layer. The subsequent incorporation of polymer particles occurs through the polymer chain interdiffusion process (autohesion) on the particles' interfaces; thus, the coating surface is more homogeneous (Figure 1(e). A single chain polymer adjusts to form a film layer (Pamar et al., 2012). If the coating particle dispersed in water lasts longer, a gel from the reaction of PEG-400 will

form; moreover, HPMC PEG polymerization forms greater hydrogel than HPMC because the HPMC only constitutes a non-ionic polymer group that can only inflate smaller (Putri et al., 2016).

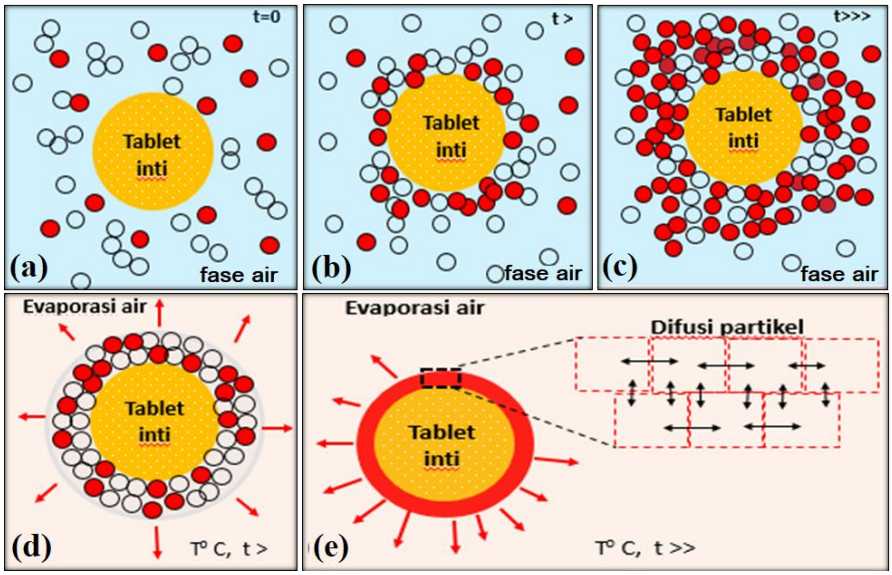

Fig. 1. The coating process for tablet cores was done by the polymer HPMC and PEG through several stages. First, the coating solution was dispersed in the water around the tablet cores. Second, the coating particles began to precipitate on the surface of the tablet cores. Third, the hydrogel polymerization was formed on the tablet core surfaces. Fourth, the coating particles were compacted and deformed on the surface of tablet cores. Fifth, homogeneous coating tablets were formed through particle diffusions

In this research, the coating tablet core process started with designing three formulations of dipping time: 5, 30, and 60 seconds. Then, the values of friability, hardness, and disintegration time of tablets were evaluated. The results of evaluating the friability, hardness, and disintegration time of thin layers of coated tablets in all formulations are presented in Table 2. The coating process for all samples was tested once; except the FI sample with a five-second dipping time was done in replication. The replication process was performed because the FI sample had met the qualification of friability, hardness, and disintegration time of the coated tablets.

Table 2. Results of testing coating solution formulations with various dipping times for the SLD calculation

Dipping time	Friability (%)			Hardness (kg)			Disintegration time (minutes)		
	FI (0, 1)	**FII (0.5, 0.5)**	**FIII (1, 0)**	**FI (0, 1)**	**FII (0.5, 0.5)**	**FIII (1, 0)**	**FI (0, 1)**	**FII (0.5, 0.5)**	**FIII (1, 0)**
5 seconds	0.73	3.73	1.9	4.05	4.53	4.52	33.18	31.37	38.57
30 seconds	13.85	13.67	24.29	4.14	3.44	3.49	37.59	47.90	41.92
60 seconds	0.159	0.058	6.31	3.59	3.60	3.7	56.57	95.64	48.33

The friability level is one of the important parameters to assess the quality of thin layers of coated tablets; the higher the friability value, the worse the quality is (Hadisoewignyo & Fudholi, 2013). In general, the highest friability level occurs on the 30-second dipping time. It is believed that a longer contact time between tablets and coating solution makes the water get into the tablet. Whereas the 60-second dipping time in fractions I and II obtains smaller friability values (better) because polymer (HPMC) and plasticizer (PEG-400) particles are attached to the surface of the tablet; thus, these particles block the water entry when the coating solution or water vapor is dispersed into the tablet during storage. A high friability value of thin layers of coated tablets indicates that more tablet surfaces are damaged, more flattened, or broken when the tablet experiences mechanical shock or erosion (Agoes, 2012). Therefore, the polymer used should sufficiently withstand mechanical pressures to prevent the breaking process (Bodmeier, 1997). Table II shows a positive correlation between the dipping time and the percentage of friability. This condition probably occurs because the tablet cores are already protected by the polymer particles.

The five-second dipping time in fraction I has obtained a prominent friability value. This condition is possibly caused by a very short dipping time and the influence of the coating solution formulation. The hardness value of thin layers of coated tablets on a five-second dipping process in all fractions has met test standard requirements. This indicates that a short dipping time and an increasing amount of HPMC and PEG-400 will produce a higher hardness value of thin layers of coated tablets. On the contrary, a longer dipping time and a decreasing amount of HPMC would reduce the level of violence thin layers of coated tablets. Table II shows that thin layers of coated tablets would have increasingly quicker disintegration time if the immersion time decreases. Thin layers of coated tablets with a five-second dipping time provide the fastest disintegration time among other times.

The coating process in this research employed two variables: HPMC [A] and PEG-400 [B]. The smallest percentage of weight is symbolized by X = 0, the largest by X = 1, and the moderate by X = 0.5. In the five-second dipping time, the results of the test on physical properties, such as hardness, friability, and disintegration time of the coated tablet from formulas I, II, and III, were used to calculate the coefficients a, b, and ab. The test has resulted in three equations with a pattern of Y = a [A] + b [B] + ab [A][B]. Similar results are also found in the 30-second and 60-second dipping times. The equations to calculate R-values are presented in Table 3.

Table 3. SLD equations to calculate R-values

Dipping time	Friability (%)
5 seconds	Y = 1.9 [A] + 0.73 [B] + 9.66 [A][B]
30 seconds	Y = 13.67 [A] + 13.85 [B] + 42.12 [A][B]
60 seconds	Y = 6.31 [A] + 0.159 [B] – 12.706 [A][B]
Dipping time	Hardness (kg)
5 seconds	Y = 4.52 [A] + 4.05 [B] + 0.98 [A][B]
30 seconds	Y = 3.44 [A] + 4.14 [B] – 1.2 [A][B]
60 seconds	Y = 3.7 [A] + 3.59 [B] – 0.18 [A][B]
Dipping time	Disintegration time (second)
5 seconds	Y = 38.57 [A] + 33.18 [B] -18.02 [A][B]
30 seconds	Y = 47.9 [A] + 37.59 [B] – 3.3 [A][B]
60 seconds	Y = 48.33 [A] + 56.57 [B] + 172.76 [A][B]

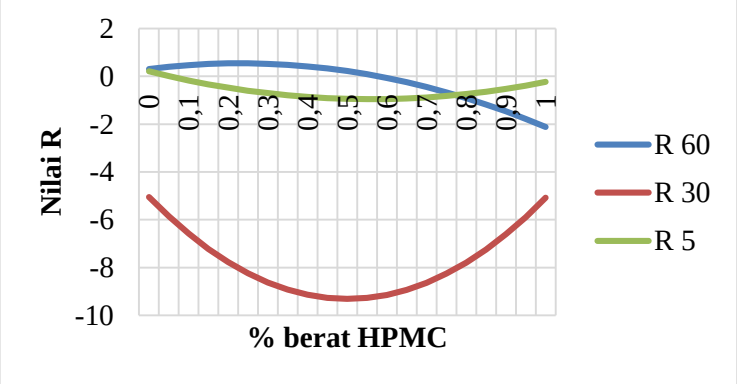

Fig. 2. Comparison between the R-values of SLD in 5-second, 30-second, and 60-second dipping times and the % of HPMC weight

Figure 2 denotes that the five-second dipping time has two positive R-values: R = 0.2024 from the coating solution I with SLD (0.1) and R = 0.004 from the coating solution with SLD (0.05 and 0.95). These two formulations have met the requirements of coated tablets because the friability value is < 1 %, the hardness value ranges from 4 to 8 kg, and the disintegration time is not more than 60 minutes. Since the value of R in the SLD for 0.1 is higher than that of R in the SLD for 0.05 and 0.95, the optimum coating solution formulation is the formulation in SLD for 0.1. In the 30-second dipping time, the optimum R-value is -5.051 from coating solution formulation I with 13.85% of friability, 4.14 kg of hardness, and 37.59 minutes of disintegration time. The negative R-value indicates that the SLD formulation does not meet the test standards of coated tablets. In the 60-second dipping time, the

optimum result of SLD (R) is 0.542 from coating solution formulations of 0.25 and 0.75. Although this R-value is positive, the tests on hardness and disintegration time do not meet the standard requirements of the coated tablets. Moreover, the formulation has obtained a friability value of -0.663 %, a hardness value of 3.58 kg, and a disintegration time of 86.9 minutes. Physical-coated tablets after the replication are presented in Figure 3.

Fig. 3. Physical-coated tablets from the replication that meets the test standards

The results of the 5-second dipping time for coating formulation I were then replicated three times; thus, the average value and standard deviation of the hardness are 4.443 ± 0.311 kg, those of friability are 0.067 ± 0.028%, and those of disintegration time are 47.3 ± 10.789 minutes. The results of the statistical test for a three-time replication show that the data have been normally distributed, are homogeneous, do not show significant differences at a 95% confidence level.

4. Conclusion

This study has found that the optimum disintegration time for thin layers of coated tablets using the dip-coating is 5 seconds, and the R-value of HPMC and PEG-400 fractions in the SLD value (0.1) is 0.2024. Meanwhile, the compositions of the coating solution consist of 0.1 g of HPMC, 1.1 g of PEG-400, 1.5 g of glycerin, 7 g sunset yellow, and aquades. These are the formulation of a coating solution that has met the friability value of 0.73%, hardness value of 4.05 kg, and disintegration time of 33.18 minutes. In this study, the weight percentages of HPMC, PEG, and disintegration time are the highly influential factors on the coating quality of thin layers of coated tablets.

Author Contributions: Adi Permadi conceived and designed the study. Adi Permadi performed all data analyses. Adi Permadi, Sapto Yuliani, Iis Wahyuningsih, Ibdal Satar interpreted the results and revised the paper. Adi Permadi wrote the manuscript. All authors read and approved the final manuscript.

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Competing Interests

The authors disclose no conflict.

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