

**Original Article**

**STUDY ON CAUSE-EFFECT RELATIONS AND OPTIMIZATION OF TABLETS CONTAINING  
AQUILARIA CRASSNA SPRAY-DRIED EXTRACT**

**BUI THI THU HUONG<sup>1</sup>, BOONYAPHAT MONSATTA<sup>2</sup>, NGUYEN DUC HANH<sup>1\*</sup>, PHAN HOANG DOAN PHUONG<sup>1</sup>,  
DO QUANG DUONG<sup>1</sup>**

<sup>1</sup>Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam, <sup>2</sup>Faculty of Pharmacy, Mahidol University, Thailand

Email: duchanh@ump.edu.vn

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**ABSTRACT**

**Objective:** The aim of this study was to develop and optimize the formulation of tablets containing *Aquilaria crassna* extract using the direct compression method.

**Methods:** D-optimal design based on three independent variables was applied to evaluate the cause-effect relations and optimize the *A. crassna* tablet formulation. The weight variation ( $Y_1$ ), disintegration time ( $Y_2$ ), hardness ( $Y_3$ ) and friability ( $Y_4$ ) were investigated with respect to three independent variables including % dicalcium phosphate anhydrous (DCPA) in filler ( $X_1$ ), % filler ( $X_2$ ) and % croscarmellose sodium (CCNa) ( $X_3$ ). The dissolution study of the optimized *A. crassna* tablets were investigated in simulated gastric fluid (SGF) (pH 1.2) using a validated high-performance liquid chromatography (HPLC) method for mangiferin analysis.

**Results:** All investigation factors were found to have significant effects on the physical properties of *A. crassna* tablet. The tablet hardness and the disintegration time increased in positive relations with the ratios of DCPA. The results exhibited the negative relations between disintegration time and the percentages of CCNa. The optimized *A. crassna* tablet formulation which included 35 % (w/w) DCPA in filler, 60 % (w/w) filler and 7% (w/w) CCNa possessed the weight variation of 1.38 % (w/w), the disintegration time of 6.29 min, the hardness of 85.63 N and the friability of 0.41 % (w/w). The optimized *A. crassna* tablet formulation was experimentally examined which demonstrated a good agreement between the experimental and predicted values. Mangiferin was found to release completely from the optimized *A. crassna* tablets within 30 min.

**Conclusion:** The cause-effect relations and optimization of *A. crassna* tablet formulation were investigated and reported for the first time. The *A. crassna* spray-dried extract could be formulated into tablet by direct compression method with good mechanical properties and acceptable release profile.

**Keywords:** *Aquilaria crassna*, Spray-dried extract, Direct compression, Optimization, Herbal formulation, Oral tablet

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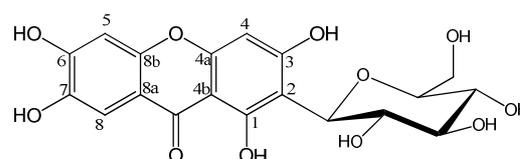
**INTRODUCTION**

*Aquilaria crassna* has been traditionally used in Asia countries for the production of incense, perfumes and traditional medicines [1]. The leaves of *A. crassna* have been reported to possess antipyretic, analgesic, laxative and antimicrobial activities [2]. The daily recommended dose of *A. crassna* leave extract ranges from 300 mg to 600 mg as traditional use in Vietnam. Mangiferin (fig. 1) is one of the active xanthone components of *A. crassna* leaves [3, 4]. Mangiferin has been reported to exhibit antioxidant, anti-diabetic, anti-hyperuricemic, antiviral, anticancer and anti-inflammatory activities [5, 6].

Direct compression is the simplest and most cost-effective tablet manufacturing technique by which the tablets are directly compressed from a blend of ingredients without a preliminary granulation or agglomeration process [7, 8]. Despite only a few steps in the manufacturing process, the product design in direct compression can be challenged due to some competing objectives [9]. The use of poorly controlled or inadequately specified raw materials may lead to the poor flowability of the powder and inconsistent tablet weight, the lack of content uniformity, unsatisfactory tablet strength or segregation and dissolution failure [10, 11]. *A. crassna* spray-dried extract is an active ingredient possesses the poor flowability property which needs to be overcome while preparing *A. crassna* tablets by direct compression method. In this study, the fillers were added into the formulation to improve the flowability of *A. crassna* spray-dried extract so that *A. crassna* tablets could be produced by direct compression method.

The aim of this study was to investigate the cause-effect relations between independent variables (% DCPA in filler, % filler and % CCNa) and dependent variables (weight variation, disintegration

time, hardness and friability of *A. crassna* tablet) and optimize the formulation of *A. crassna* tablet from *A. crassna* spray-dried extract for oral administration using direct compression method.



**Fig. 1: Chemical structure of mangiferin**

**MATERIALS AND METHODS**

**Materials**

*A. crassna* spray-dried extract was a gift from Evergreen Forest JSC (Vietnam). Silicified microcrystalline cellulose (SMCC) (Prosolv® SMCC 90) and croscarmellose sodium (Vivasol®) were received from JRS Pharma (Germany) via Sapharchem Co., Ltd (Vietnam). Magnesium stearate was a gift from Brenntag (Denmark). Dicalcium phosphate anhydrous (A-Tab®) was received from Innophos (Chicago Heights, IL, USA) via Asia Shine Trading and Service Co. Ltd. (Vietnam).

**Morphology of *A. crassna* spray-dried extract**

The shape and size of *A. crassna* spray-dried extract were investigated by scanning electron microscope (SEM) (JSM-IT100,

JEOL, Tokyo, Japan). The sample was mounted on a SEM stub using double-sided adhesive tape and then sputter-coated with gold particles [12]. SEM micrograph of *A. crassna* spray-dried extract was then photographed.

### Preparation of tablets

A direct compression method was used for the preparation of tablet formulations. Ingredients were weighed and pass through 40 mesh sieve. Powder blends of all formulations were mixed by tumbling action and then compressed using a single punch tableting machine (Riva Minipress MII, Riva, Germany) with a concave punch of 11 mm diameter.

### Experimental design and data analysis

The constituents of the tablet formulations included *A. crassna* spray-dried extract as active compounds, mixtures of DCPA and SMCC as the filler, CCNa as the supper disintegrant and magnesium stearate (1 %) as lubricant.

A total of 14 experimental runs according to the D-optimal design were generated by Design Expert software (version 6.0.6, Stat-Ease Inc., Minneapolis, USA) to study the effects of independent variables

on dependent variables. Percentages of DCPA in filler ( $X_1$ ), % filler ( $X_2$ ) and % croscarmellose sodium ( $X_3$ ) were selected as three independent variables whereas weight variation ( $Y_1$ ), disintegration time ( $Y_2$ ), hardness ( $Y_3$ ) and friability ( $Y_4$ ) were chosen as four dependent variables. Percentage of DCPA in filler ( $X_1$ ) and % CCNa ( $X_3$ ) were studied at three levels and % filler ( $X_2$ ) was studied at two levels (table 1). The experimental range for each independent variable was selected based on the results of initial trials. The compositions of 14 formulations are given in table 2. All formulations were conducted in triplicate and data were exhibited as mean±standard deviation.

The results of experimental design were analyzed using BCPharSoft OPT software (Vietnam). The best fitting model was chosen. In order to achieve a better understanding of the cause-effect relations between the independent and dependent variables, the 3D diagrams of the fitted models were depicted. D-optimal design employed for the study is shown in table 2.

The optimized formulation was performed in triplicate for further validation. The observed response data of the optimized formulation were compared with their predicted data created by BCPharSoft OPT software using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA).

**Table 1: Variables in experimental design**

	Levels		
	Low	Medium	High
<b>Independent variables</b>			
$X_1$ : % DCPA in filler (w/w)	10	30	50
$X_2$ : % filler (w/w)	40	60	
$X_3$ : % CCNa (w/w)	0	4	8
<b>Dependent variables</b>			
$Y_1$ : weight variation (% w/w)			
$Y_2$ : disintegration time (min)			
$Y_3$ : hardness (N)			
$Y_4$ : friability (% w/w)			
	<b>Constraints</b>		
	Minimum		
	Maximum		
	Minimum		

### Uniformity of tablet weight

Twenty tablets from each batch were selected at random and weighed individually using a digital analytical balance (XB 220A; Precisa, Dietikon, Switzerland). The average weight of the tablets was then determined. Percentage deviation of each individual tablet from the average weight was calculated.

### Disintegration test

The disintegration tests were performed according to the British Pharmacopoeia [13]. Six tablets were separately placed into the basket rack assembly of a disintegration test apparatus (ZT 501, Erweka, Germany). The tablets were immersed into 800 ml distilled water maintained at 37±2 °C. The time was recorded when each tablet completely disintegrated with no residue remaining. The results were recorded as the mean±standard deviation.

### Hardness test

The hardness test was carried out using a hardness tester (TBH 210, Erweka, Germany). Ten tablets from each batch were selected at random. Each tablet was placed between the jaws of the hardness tester and force was applied until the tablet broken. The average hardness±standard deviation was calculated.

### Friability test

Friability test was performed according to the British Pharmacopoeia [12] using a friability tester (Model: TA3B, Erweka, Germany). The drum was rotated at 25 rpm for 4 min. The tablets were dedusted and weighed before and after using the tester. The percentage friability was calculated using the following equation.

$$\% \text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where  $W_1$  and  $W_2$  are the initial and final weights of all tablets, respectively.

### Dissolution study

The dissolution study of the optimized *A. crassna* tablet was carried out using a dissolution apparatus (Erweka DT 700, Germany). Dissolution was conducted in 900 ml of simulated gastric fluid without enzyme (SGF) at a temperature of 37±0.5 °C and a paddle speed of 100 rpm. At the predetermined time intervals 0, 5, 10, 15, 20 and 30 min, 5 ml of release medium were withdrawn and replaced each time with 5 ml of fresh medium. Mangiferin concentrations in the samples were determined by a validated HPLC method.

### Analytical method of mangiferin

Mangiferin was analyzed by an Azura HPLC system (Knauer, Germany). The separation was performed on a Synchronis C18 column (250 x 4.6 mm; 5 µm) (Thermo Scientific, USA). Mobile phase was mixtures of acetonitrile and 0.2 % acetic acid in water with a gradient program. The ratios of acetonitrile were 8 %, 12 %, 25 % and 50 % at 0 min, 12 min, 30 min and 35 min, respectively. The flow rate was set at 1 ml/min. Detection was performed at a wavelength of 330 nm at 30 °C. The sample injection volume was 20 µl. The HPLC analytical method was validated according to the International conference on harmonization (ICH) guidelines on system suitability, specificity, linearity, precision and accuracy.

## RESULTS AND DISCUSSION

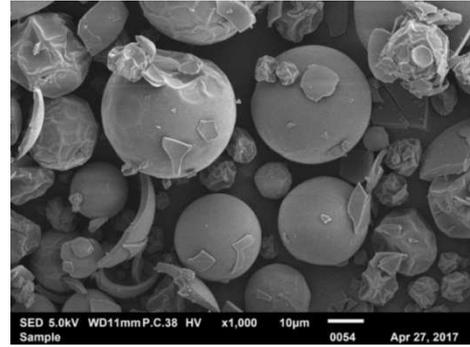
### Physicochemical properties of *A. crassna* spray-dried extract

Morphology of *A. crassna* spray-dried extract is shown in fig. 2. SEM image revealed that *A. crassna* spray-dried extract particles had nearly spherical shape with the average diameter of less than 30 µm.

As the general guide, the maximum angles of repose of powder close to 25 ° correspond to excellent flow properties. *A. crassna* spray-dried extract powder with an angle of repose greater than 45 ° was found to possess a very poor flowability in spite of their spherical shape. This phenomenon can be explained by the cohesiveness of the small particles of *A. crassna* spray-dried extract powder due to the electrostatic charge interactions [14].

**Optimization data analysis and validation of optimization model**

The values of independent variables and their responses of 14 formulations generated by Design Expert software are shown in table 2. The ranges of weight variation (Y<sub>1</sub>), disintegration time (Y<sub>2</sub>), hardness (Y<sub>3</sub>) and friability (Y<sub>4</sub>) were found to be 0.74–3.39 %, 4.00–18.45 min, 24–116 N and 0.04–16.25 %, respectively.



**Fig. 2:** SEM image of *A. crassna* spray-dried extract powder

**Table 2: The independent variables of 14 formulations (F1–F14) and their responses**

Formulation	Independent variables			Dependent variables			
	X <sub>1</sub> (%)	X <sub>2</sub> (%)	X <sub>3</sub> (%)	Y <sub>1</sub> (%)	Y <sub>2</sub> (min)	Y <sub>3</sub> (N)	Y <sub>4</sub> (%)
F1	10	40	4	1.85±0.11	9.09±3.04	45.87±9.79	1.48±0.37
F2	30	40	8	1.75±0.10	8.54±2.64	49.53±8.21	1.34±0.84
F3	30	60	8	1.10±0.43	5.84±0.21	86.37±9.35	0.75±0.21
F4	50	40	8	2.87±0.18	7.80±1.90	54.27±11.65	1.32±1.16
F5	50	60	8	1.37±0.46	7.31±1.23	95.53±9.12	0.55±0.52
F6	30	60	0	1.68±0.14	15.71±1.45	84.63±7.80	0.55±0.18
F7	10	40	8	2.85±0.66	8.63±2.02	44.80±7.95	1.27±0.83
F8	10	40	0	1.47±0.21	10.60±3.11	44.50±9.72	1.19±0.72
F9	30	40	4	2.54±0.48	10.46±2.27	48.60±8.98	1.56±1.31
F10	10	60	0	1.58±0.24	11.98±5.79	74.37±15.79	0.75±0.74
F11	30	40	0	2.99±0.26	9.64±1.04	47.50±5.09	1.17±0.64
F12	10	60	4	1.51±0.60	6.98±2.24	80.07±7.40	0.46±0.18
F13	50	60	4	1.55±0.34	8.01±0.67	93.97±13.51	0.61±0.25
F14	50	60	0	1.58±0.18	15.82±3.03	96.03±8.24	0.71±0.11

X<sub>1</sub> (% DCPA in filler); X<sub>2</sub> (% filler); X<sub>3</sub> (% CCNa); Y<sub>1</sub> (weight variation, %); Y<sub>2</sub> (disintegration time, min); Y<sub>3</sub> (hardness,N); Y<sub>4</sub> (friability,%). Values are expressed as mean±SD (n=3)

The data in table 2 were used as inputs for BCPharSoft OPT to study on the cause-effect relations and optimize the *A. crassna* tablet formulation.

Training parameters were set at:

-Test groups: Y<sub>1</sub> [9, 13], Y<sub>2</sub> [6, 12], Y<sub>3</sub> [5, 7], Y<sub>4</sub> [2, 13]

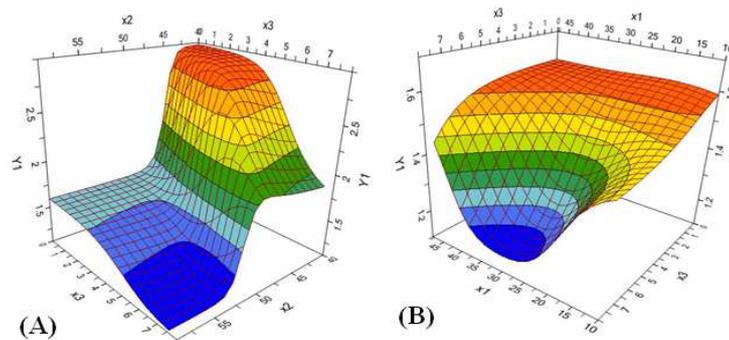
-Transfer function: Back Propagation Learning

The three-dimensional (3D) response surface plots were used to study the interaction effects of two independent variables on the dependent variables at one time, when the third variable was kept at a constant level.

**Table 3: Model statistics from BC phar soft OPT outputs**

Dependent variables	R <sup>2</sup> training	R <sup>2</sup> test
Y <sub>1</sub> : weight variation (%)	1.00	0.99
Y <sub>2</sub> : disintegration time (min)	0.99	0.99
Y <sub>3</sub> : hardness (N)	0.99	0.99
Y <sub>4</sub> : friability (%)	1.00	0.99

All R<sup>2</sup> values which were found to be more than 0.9 indicated a very good reliability of the models (table 3). Therefore, these models could be used for multivariate optimization.

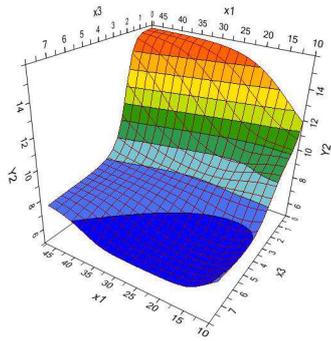


**Fig. 3:** Response surface plots showing the effect of (A) % filler (X<sub>2</sub>) and % CCNa (X<sub>3</sub>) on weight variation (Y<sub>1</sub>); (B) % DCPA in filler (X<sub>1</sub>) and % CCNa (X<sub>3</sub>) on weight variation (Y<sub>1</sub>) (n=3)

**Effect of variables on weight variation**

The weight variations of 14 formulations (between 0.74 % and 3.39 %, w/w) were found to be within the acceptable limits (not more than 5 %, w/w) (table 2). Weight variation ( $Y_1$ ) demonstrated the negative relationship with % filler ( $X_2$ ). It is evident from fig. 3 that weight variation ( $Y_1$ ) decreased with increasing % filler ( $X_2$ ). Percentage of filler played an important role in determining the weight variation. When % filler increased, the electrostatic charges of the powder mixture reduced and the cohesiveness decreased, hence the flowability of the powder mixture was improved. This relation was in accordance with the rule reported previously by Bushra R [15].

Weight variation ( $Y_1$ ) was found to be high at the low and high level of % DCPA in filler ( $X_1$ ). However, at the medium level of % DCPA in filler ( $X_1$ ) the weight variation decreased significantly (fig. 3B). It can be explained by the high density of DCPA. The separation of the powder mixture may occur at low and high level of % DCPA in filler ( $X_1$ ).



**Fig. 4: Response surface plots showing the effect of % DCPA in filler ( $X_1$ ) and % CCNa ( $X_3$ ) on disintegration time ( $Y_2$ ) (n=3)**

**Effect of variables on disintegration time**

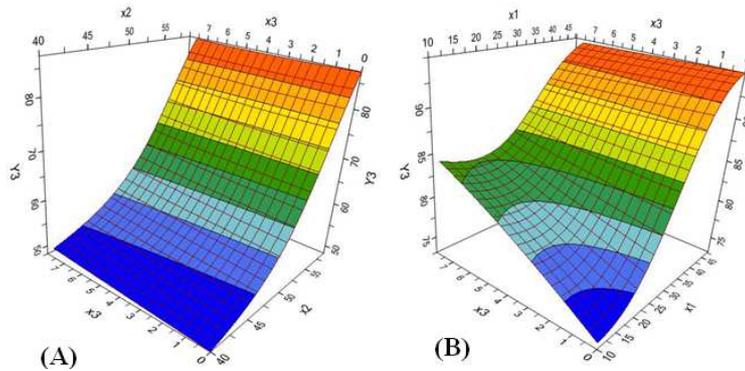
Disintegration data showed that all tablets of 14 formulations could be disintegrated completely within 20 min. It can be seen from fig. 4 that when % CCNa ( $X_3$ ) increased, disintegration time ( $Y_2$ ) significantly reduced. This relation could be explained due to the fact that CCNa is a supper disintegrant. CCNa could increase the hydrostatic pressure acting either via swelling or by water wicking, or by combination of these mechanisms [16]. Therefore, the disintegration of *A. crassna* tablets could be improved when CCNa was added.

Moreover, at a certain level of % CCNa ( $X_3$ ), when % DCPA in filler ( $X_1$ ) increased, disintegration time ( $Y_2$ ) increased. DCPA is a non-hygroscopic filler and absorbed less than 1 % water [17], therefore, when % DCPA in filler ( $X_1$ ) increased, the water penetration into the tablet may be slowed down and hence, the disintegration process was prolonged. This was in line with the rule reported previously by Tibalinda P [18].

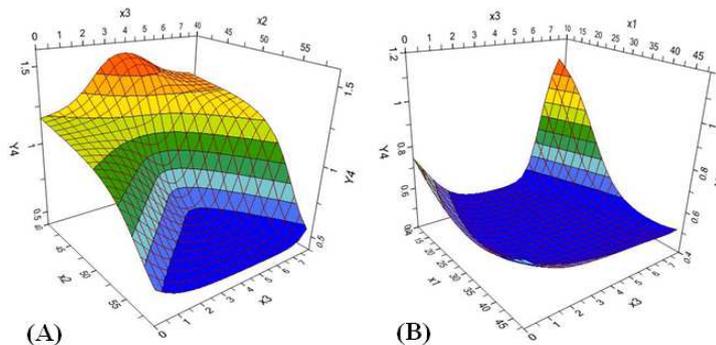
**Effect of variables on hardness**

Hardness data in table 2 shows that all formulations with 40 % filler (F1, F2, F4, F7, F8, F9 and F11) possessed low hardness compared to the other formulations with 60 % filler ( $X_2$ ).

Fig. 5A shows that when % filler ( $X_2$ ) increased, the hardness ( $Y_3$ ) significantly increased. The mixtures of DCPA and SMCC as fillers were found to be able to improve the hardness of *A. crassna* tablet. Moreover, fig. 5B shows that at a certain level of % filler ( $X_2$ ), the hardness ( $Y_3$ ) significantly increased when % DCPA in filler ( $X_1$ ) increased. DCPA is a brittle inorganic excipient therefore it could support the compaction process [19, 20]. SMCC which composed of 98 % microcrystalline cellulose had advantages in compressibility of microcrystalline cellulose. As a result, SMCC could improve the hardness of the *A. crassna* tablet [21]. Similar results were previously reported by Solaiman A [22, 23].



**Fig. 5: Response surface plots showing the effect of (A) % filler ( $X_2$ ) and % CCNa ( $X_3$ ) on hardness ( $Y_3$ ); (B) % DCPA in filler ( $X_1$ ) and % CCNa ( $X_3$ ) on hardness ( $Y_3$ ) (n=3)**



**Fig. 6: Response surface plots showing the effect of (A) % filler ( $X_2$ ) and % CCNa ( $X_3$ ) on friability ( $Y_4$ ); (B) % DCPA in filler ( $X_1$ ) and % CCNa ( $X_3$ ) on friability ( $Y_4$ ) (n=3)**

### Effect of variables on friability

It is shown from table 2 that formulations F1, F2, F4, F7, F8, F9 and F11 (with 40 % filler) have the friability more than 1 % which did not meet requirement of the British Pharmacopoeia.

Fig. 6A shows that when % filler ( $X_2$ ) increased, the friability ( $Y_4$ ) significantly decreased. The friability of *A. crassna* tablets was closely related to the hardness [24]. The mixtures of DCPA and SMCC as fillers were found to improve the hardness of *A. crassna* tablets. As a result, these mixtures of filler could decrease the friability of the tablets.

In the case of low level of % DCPA in filler ( $X_1$ ), the friability ( $Y_4$ ) increased if % CCNa ( $X_3$ ) increased (fig. 6B). CCNa possesses the

porous structure, therefore, the friability increased when % CCNa ( $X_3$ ). A similar finding was previously reported by Oza NA [25].

### Optimization of *A. crassna* tablet formulation

The optimized *A. crassna* tablet formulation was achieved with 35 % DCPA in filler, 60 % filler and 7 % CCNa. Three replicated batches of the optimized *A. crassna* tablet formulation were prepared to confirm the validity of the optimization procedure. Weight variation, disintegration time, hardness and friability of the optimized *A. crassna* tablet formulation were found to be at  $1.38 \pm 0.42$  %,  $6.29 \pm 0.54$  min,  $85.63 \pm 2.92$  N and  $0.41 \pm 0.08$  %, respectively. Table 4 demonstrates that the observed values were in good agreement with the predicted values ( $p > 0.05$ ).

**Table 4: Comparison of the predicted and observed responses of the optimized *A. crassna* tablet formulation**

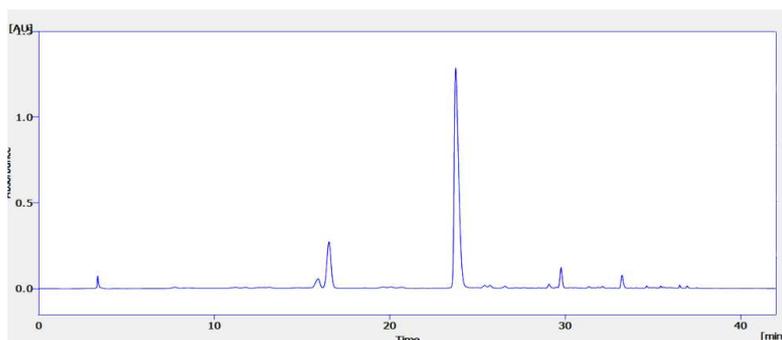
Responses	$Y_1$ (%)	$Y_2$ (min)	$Y_3$ (N)	$Y_4$ (%)
Predicted	1.15	6.34	89.10	0.491
Observed	$1.38 \pm 0.42$	$6.29 \pm 0.54$	$85.63 \pm 2.92$	$0.41 \pm 0.08$
P-value	0.400	0.853	0.054	0.208

Values are expressed as mean $\pm$ SD (n=3)

### Analytical method of mangiferin

A well-resolved HPLC chromatogram of mangiferin in *A. crassna* tablet sample is shown in fig. 7. The total run time was approximately 40 min and the retention time of mangiferin was at

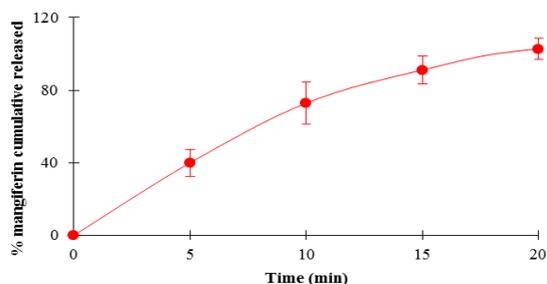
23.6 min. In a concentration range of 60–420  $\mu$ g/ml, a good correlation coefficient was observed between peak areas and concentrations of mangiferin standard solutions ( $r^2 = 0.9996$ ). The recovery values ranged from 99.62 % to 101.90 %. These results indicated that the method was reliable and reproducible.



**Fig. 7: HPLC chromatogram of mangiferin ( $R_t = 23.6$  min) in the optimized *A. crassna* tablet**

### Dissolution study

The active compound released properties are characterized by disintegration time and dissolution property. Dissolution profiles of the optimized *A. crassna* tablets in SGF (without enzyme) are shown in fig. 8. More than 97% of mangiferin could be rapidly released from the optimized *A. crassna* tablets within 20 min SGF. This observation can be explained by the fact that the optimized *A. crassna* tablets were disintegrated completely after 6.29 min. As a result, mangiferin could be released completely within 30 min.



**Fig. 8: Dissolution profiles of the optimized *A. crassna* tablets (n=6)**

### CONCLUSION

Effects of three independent variables (% DCPA in filler, % filler and % CCNa) on four dependent variables (weight variation, disintegration time, hardness and friability of *A. crassna* tablet) were investigated. All independent variables were found to possess significant effects on all dependent variables and the rules were raised up. The optimized *A. crassna* tablet formulation suggested by the BCPHARSOFT OPT intelligent software contained 35% DCPA in filler, 60 % filler and 7 % CCNa. Three replicates of the optimized formulation were prepared and the observed responses were found to be in good agreement with the predicted values which confirmed the optimized *A. crassna* tablet formulation.

### AUTHOR CONTRIBUTION

There are five authors who contribute to this manuscript. The percentages of contribution of Bui Thi Thu Huong, Boonyaphat Monsatta, Nguyen Duc Hanh, Phan Hoang Doan Phuong and Do Quang Duong are 25%, 25%, 30%, 10%, and 10%, respectively.

### CONFLICT OF INTERESTS

All authors declare that this article content has no conflict of interest

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