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Original Article

DEVELOPMENT AND OPTIMIZATION OF COATED TABLET CONTAINING AMLODIPINE AND VALSARTAN FOR HYPERTENSION TREATMENT

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ABSTRACT

Objective: To develop and optimize the formulation of coated tablets containing these Active Pharmaceutical Ingredients (APIs) with *in vitro* equivalence to that of the original drug.

Methods: Design Expert and BCPharSoft OPT softwares were applied in the development and optimization of film-coated tablets of amlodipine 5 mg and valsartan 80 mg, in order to obtain a tablet formulation with *in vitro* equivalence to the original drug in three dissolution testing environments. Evaluating through appearance, identification, medium hardness, weight uniformity, *in vitro* equivalence, assay.

Results: An optimized formulation of film-coated tablets with *in vitro* equivalence to the referent drug was obtained. For the tablet core, it is composed of amlodipine besylate 6.94 mg (equivalent to 5 mg amlodipine) and valsartan 80 mg with excipients of 9.77% crospovidone XL, 2% aerosil, 2.75% magnesium stearate, 42.01% avicel PH 112, with a hardness of 70-90 N. The film-coating suspension comprises 4.75% Hydroxypropyl Methylcellulose 6cps (HPMC 6cps), 0.42% polyethylene glycol 6000 (PEG 6000), 0.84% talc, 1.77% titanium dioxide (TiO_2), 0.12% yellow iron oxide, in 92.1% ethanol 96%-water (2:1).

Conclusion: In the current study, a film-coated tablet formulation with *in vitro* equivalence of two APIs to the original drug in all three environments was successfully developed and optimized. The obtained results are an important premise for the development of related generic drugs in the pharmaceutical market of developing countries, which not only reduces the product price but also help less wealthy patients in developing countries to better control hypertension disease.

Keywords: Amlodipine, Valsartan, Film-coated tablets, *In vitro* equivalence, Hypertension

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INTRODUCTION

According to a report of the World Health Organization (WHO), there will be about 1.28 billion people aged 30-79 with hypertension around the world in 2021 [1, 2]. Combining multiple groups of drugs in the treatment of hypertension is a new trend for many pharmaceutical manufacturers. The combination of amlodipine and valsartan gives patients many advantages during treatment, such as enhancing treatment effectiveness [3], improving the stabilization of daily blood pressure levels that helps to significantly enhance the tolerability during the administration of separate medications, and minimizing side effects. Indeed, comparative analysis has suggested a reduction in peripheral edema occurrence compared to the utilization of elevated doses of amlodipine [4]. In the current pharmaceutical market, numerous products incorporating such active ingredients are available. However, they frequently fail to adequately address medical needs of vulnerable population, particularly in socioeconomically difficult regions where access to original drugs is normally limited. Consequently, there is a high demand of research for generic drugs containing these compositions.

Few studies have developed the formulation of these two active ingredients [6, 7]. In those studies, the wet granulation was used to prepare tablets. Nevertheless, it should be noted that amlodipine is susceptible to occasional degradation by humidity and heat. Therefore, this granulation method in large-scale industrial production presents potential risks. In terms of valsartan-an API with poor solubility (Biopharmaceutics Classification System Class II), in general, an additional method, such as solid dispersion technique, is commonly required to enhance its solubility [8, 9]. Nevertheless, this technique required a sophisticated fabrication method and not adequate to commercialize in developing countries. Furthermore, in such developing countries, no research on the preparation of tablets containing the above two active ingredients has been published. This study was conducted to formulate immediate-release tablets containing amlodipine and valsartan with an *in vitro* drug release rate equivalent to that of original drug, using a conventional method of dry granulation in combination with design of experiment. This is also the first study which combined design of experiments and dry granulation methods to prepare a complexe tablet of such APIs. The results obtained from the current study is a solid base for the industrial production of this kind of tablet that is helpful for better management of hypertension for related patients.

MATERIALS AND METHODS

Materials

Reference substances: Amlodipine besylate, batch number QT145 120122, content 100.3% calculated on anhydrous preparation; valsartan, batch number QT323 020122, content 99.4% based on anhydrous product provided by Ho Chi Minh City Drug Testing Institute. Allopathic drugs: Exforge® (Siegfried Barbera Company, SL-Spain) batch number BCXN8, expiry date 02-2025.

Solvents and chemicals: Acetonitrile (ACN) and methanol meet HPLC standard. Triethylamine (TEA), phosphoric acid and solvents used in analysis meet prescribed analytical standards. Ingredients amlodipine besylate, valsartan, avicel PH 112, crospovidone XL, aerosil, magnesium stearate, HPMC 6cps, TiO_2, yellow iron oxide, talc, macrogol-PEG 6000, distilled water and 96% alcohol met standards for pharmaceutical uses.

Equipments: Rimek 10-punch tablet compressing machine (India), Diode Array Detector (DAD) probe HPLC machine with ZORBAX Eclipse Plus C18 reversed-phase chromatography column (Agilent-USA), ERWEKA granulate flow tester, Pharmatest PTB hardness testing machine, Pharmatest PTF E Abrasion testing machine, Pharmatest PTWS 120D dissolution testing machine, Kern ABS 220-4 electrical scale (Germany).

Method

Dissolution investigation of Exforge®control tablets (amlodipine 5 mg and valsartan 80 mg)

The dissolution test of Exforge® control tablets was performed by a paddle-type dissolution tester (type 2), medium volume is 1000 ml,

pH 1.2, 4.5, 6.8, and the stirring speed is 50 rpm [10]. Samples are takend at 10, 15, 30, 45, 60 minutes with a volume of 10 ml, filtered through 0.45 µm RC membrane before performing chromatography. The samples were assayed by HPLC using PDA with the following chromatography conditions: ZORBAX Eclipse Plus C18 chromatography column (4.6 x 250 mm; 5 µm), detection wavelength 237 nm, flow rate 1 ml/minute, sample injection volume 20 µL, mobile phase: ACN-0.7% TEA solution (adjusted to pH 3.0 with 0.05% phosphoric acid) at a ratio of 40:60, isocratic elution.

Design and optimization of immediate-release tablets' formulation containing amlodipine 5 mg and valsartan 80 mg

Our previous studies indicated that the drug release rate was influenced by the content of crospovidone, HPMC 6cps, and tablet hardness in the tablet formulation. Consequently, three parameters, including crospovidone ratio, HPMC 6cps concentration, and tablet hardness, were used as independent variables in our design.

The design of the experiment was established using Design-Expert software with three independent variables x_1 for the crospovidone content, x_2 for tablet hardness, and x_3 for HPMC 6cps content. Each formulation was prepared with a quantity of 200 coated tablets.

Selection of the dependent variable: The dependent variable is the similarity coefficient (f_2 value) between amlodipine and valsartan in three distinct dissolution media at three pH levels of 1.2, 4.5, and 6.8, in comparison to the referent tablet. In which:

y_1, y_2, y_3: f_2 value for amlodipine of the formulation and control drug at pH 1.2; 4.5; 6.8.

y_4, y_5, y_6: f_2 value for valsartan of the formulation and control drug in pH 1.2; 4.5; 6.8.

f_2 value

$$f_2 = 50\log\left\{(1+\frac{1}{n}\sum_{i=1}^{n}(R_t - T_t)^2)^{-0,5} X100\right\} \quad \text{..... (1)}$$

n is the number of sampling points, R_t is the average of the percentage of control drug dissolved at time t since the start of the test; T_t is the average of the percentage of reagent dissolved at time t since the start of the test [11].

The main composition of the tablet core includes 6.94 mg of amlodipine besylate (corresponding to 5 mg of amlodipine), 80 mg of valsartan, 4 mg of aerosil, 5.5 mg magnesium stearate, crospovidone (x_1), avicel 102 sufficient for 200 mg of tablet core. The film-coating contained HPMC 6cps (x_2), 0.44 mg PEG 6000, 0.88 mg talc, 1.84 mg TiO_2, and 0.12 mg yellow iron oxide for the coating layer of 103.68 mg. The solvent used for coating suspension was 96% ethanol-water (2:1). The design of the experiments is presented in table 2.

Table 1: Independent variables and ranges

Independent variable	Symbol	Variation level		
		Upper level	Base level	Lower level
Crospovidone ratio (%)	x_1	15	10	5
Pellet hardness (N)	x_2	90-110	70-90	50-70
HPMC ratio 6cps (%)	x_3	5	4	3

Table 2: Design of experiments for coated tablets containing amlodipine and valsartan (5/80 mg)

Formula	Tablet core (mg/tablet)		Coating suspension (mg/tablet)
	Crospovidone XL (x_1)	Hardness (x_2)	HPMC 6cps (x_3)
F1	10	50-70	3.11
F2	10	50-70	4.15
F3	10	50-70	5.18
F4	10	70-90	3.11
F5	10	70-90	4.15
F6	10	70-90	5.18
F7	10	90-110	3.11
F8	10	90-110	4.15
F9	10	90-110	5.18
F10	20	50-70	3.11
F11	20	50-70	4.15
F12	20	50-70	5.18
F13	20	70-90	3.11
F14	20	70-90	4.15
F15	20	70-90	5.18
F16	20	90-110	3.11
F17	20	90-110	4.15
F18	20	90-110	5.18
F19	30	50-70	3.11
F20	30	50-70	4.15
F21	30	50-70	5.18
F22	30	70-90	3.11
F23	30	70-90	4.15
F24	30	70-90	5.18
F25	30	90-110	3.11
F26	30	90-110	4.15
F27	30	90-110	5.18

Tablet-core preparation's process

(1) Weigh the necessary amount of amlodipine, valsartan, avicel PH 112, crospovidone XL, 80% of aerosil, 60% of magnesium stearate and mix these components homogeneously; (2) Precompression of pellets with a weight of about 350 mg and hardness around 60 N; (3) Dry granulation through 0.8 mm sieve; (4) Screen pellets through 0.45 mm sieve; (5) Recalculate the necessary amount of aerosil,

sieve through 0.45 mm sieve, and mix with the above mixture; (7) Compression of tablet core with a weight of about 200 mg; hardness N (x_3); and a diameter of 7.5 mm.

Film-coating process

Prepare the film coating suspension: (1) 60 ml of 96% ethanol-distilled water (2:1) (solution A); (2) Dispersion of HPMC 6cps into solution A, mix thoroughly until total swelling; (3) dissolution of PEG 6000 into HPMC solution (solution B). (4) TiO_2 and yellow iron oxide was weighted and grinded. Slowly add 5 ml of solution A. Dilute the paste with the remaining amount of solution A (solution C). (5) Add the solution (C) into the solution (B). Disperse the talc into the final mixture and stir slowly for 60 min.

The coating process was conducted on CALEVA equipment (CALEVA-UK), including (1) Assemble the spray system, opening the compressed air system; (2) Put tablet core into coating pan, turn on the air blower at 15 m/s, adjust the pan vibration speed to 20 Hz, with a temperature of 60 °C. Blow the dust and dry the tablets for 10 minutes. Weigh dried tablet cores; (3) Spray the coating suspension for 10-15 minutes. Dry tablets for 10 minutes; (4) Weigh coated tablets. (5) Dry the tablets after coating for 10 minutes; (6) Keep coated tablets in a moisture-free environment for one day before dissolution tests.

RESULTS

The results of the solubility survey of Exforge®tablets

Dissolution tests were conducted for the original drugs-Exforge® at three different pH 1.2, 4.5, and 6.8. The results were presented in the table 3.

Optimization of the formulation of immediate-release coated tablets containing amlodipine 5 mg and valsartan 80 mg using dry granulation

f_2 value of amlodipine (y_1, y_2, y_3) and valsartan (y_4, y_5, y_6) of each formula in the design of experiments and the control drug at pH 1.2, 4.5, and 6.8 was determined and presented in table 4.

Table 3: Dissolution test results of Exforge® tablets in three pH environments (n = 6)

Time (min)	Release of active compounds (%)					
	Amlodipine			Valsartan		
	pH 1.2	pH 4.5	pH 6.8	pH 1.2	pH 4.5	pH 6.8
10	65.22±0.03	3.20±0.02	15.66±0.03	20.36±0.04	55.24±0.06	85.84±0.03
15	68.56±0.02	5.57±0.03	27.69±0.05	28.03±0.05	68.96±0.01	89.88±0.05
30	70.75±0.04	11.32±0.07	49.19±0.03	39.35±0.03	77.19±0.08	90.01±0.03
45	73.85±0.05	22.16±0.05	57.34±0.02	46.97±0.02	82.54±0.03	90.51±0,02
60	80.05±0.04	23.51±0.05	68.30±0.03	52.57±0.02	84.36±0.06	90.58±0.05

Data is given as mean±SD, n=6

Table 4: f_2 value of amlodipine and valsartan in each formula in the design of experiments compared to the control drug

No	x_1	x_2	x_3	y_1	y_2	y_3	y_4	y_5	y_6
1	5	1	3	30.61	25.71	28.22	35.97	35.04	35.57
2	5	1	4	28.94	24.92	27.28	34.25	34.03	34.11
3	5	1	5	27.69	23.84	26.74	33.29	32.24	32.31
4	5	2	3	26.12	22.45	24.53	31.36	31.18	31.26
5	5	2	4	26.47	20.43	23.45	30.49	29.33	30.07
6	5	2	5	23.85	19.24	20.16	29.04	28.41	28.64
7	5	3	3	14.73	12.97	13.02	19.44	17.36	18.74
8	5	3	4	13.21	11.86	12.01	17.98	15.22	17.03
9	5	3	5	12.89	10.09	10.75	17.46	14.54	16.31
10	10	1	3	35.12	32.46	34.25	36.17	34.52	35.55
11	10	1	4	41.99	40.16	41.45	43.54	41.26	42.68
12	10	1	5	45.35	41.94	43.07	46.82	45.11	46.05
13	10	2	3	45.76	42.14	43.61	47.23	45.67	46.56
14	10	2	4	46.55	44.42	45.57	51.03	48.95	49.26
15	10	2	5	49.41	46.82	48.17	52.23	50.07	50.62
16	10	3	3	59.78	56.94	59.11	65.02	59.27	62.72
17	10	3	4	64.13	59.12	62.15	76.23	64.50	70.01
18	10	3	5	64.02	58.89	61.96	76.11	64.19	69.45
19	15	1	3	12.46	9.48	10.15	17.24	14.47	16.43
20	15	1	4	13.99	11.42	11.77	18.35	16.03	17.95
21	15	1	5	15.42	12.78	13.06	20.01	18.21	19.37
22	15	2	3	15.07	14.02	14.79	16.67	15.23	16.11
23	15	2	4	17.22	16.58	17.1	20.54	19.47	20.21
24	15	2	5	21.09	19.79	20.94	24.89	23.44	24.86
25	15	3	3	29.27	28.65	29.06	33.89	32.64	33.35
26	15	3	4	35.08	33.47	34.95	37.88	36.19	37.66
27	15	3	5	41.35	40.37	41.18	44.61	43.68	44.41

Table 5: Optimized parameters and predicted results for the coated tablet using BCPharSoft OPT software

Parameters	y_1	y_2	y_3	y_4	y_5	y_6
R^2 training	0.90	0.90	0.93	0.90	0.93	0.98
R^2 testing	0.90	0.93	0.90	0.95	0.90	0.90
R^2	0.92	0.94	0.93	0.92	0.94	0.96

R^2 training and R^2 testing values in the range of 80-100% showed that the used model was significant and there was a significant correlation between the independent variables and the dependent variable. The graphs representing correlation of independent variables on dependent variable were presented in fig. 1-3.

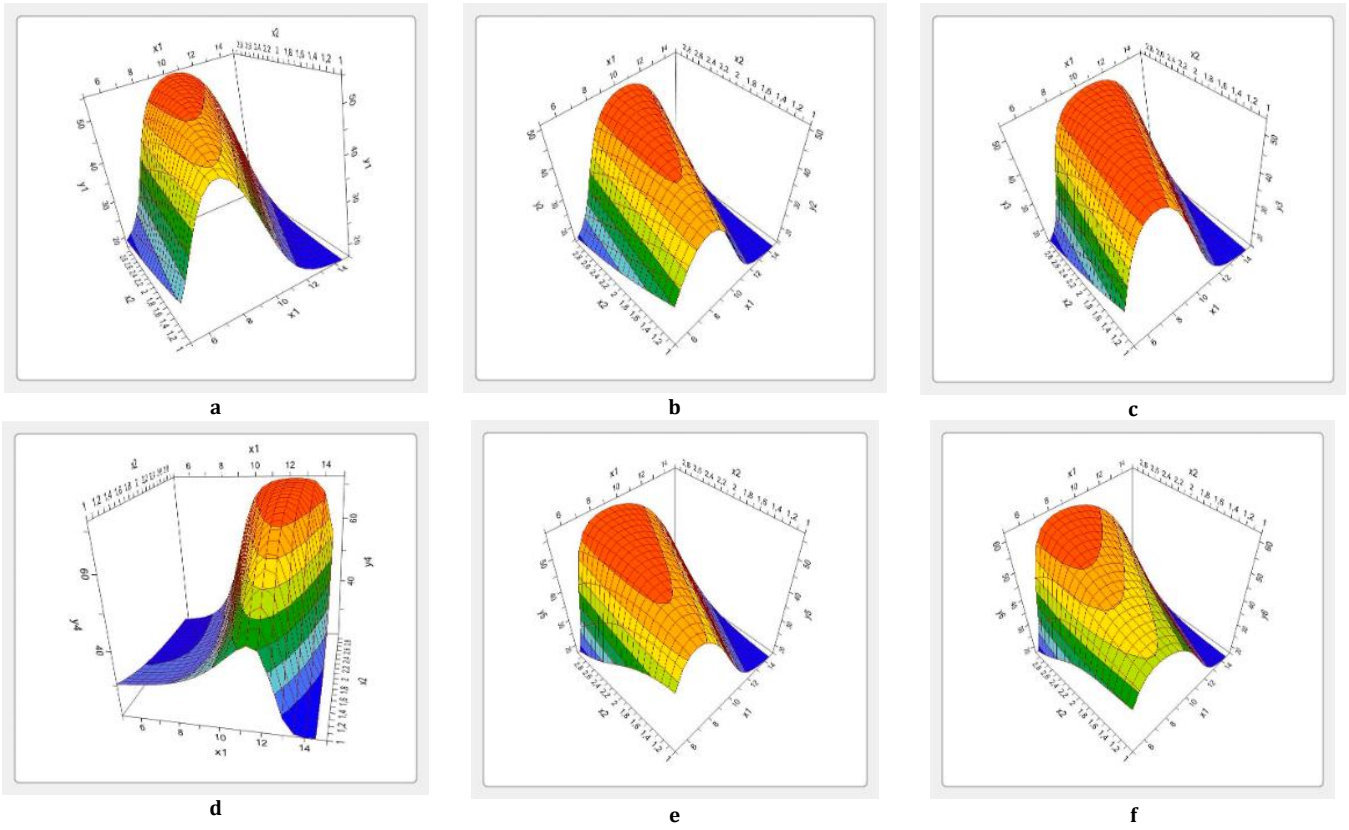

Fig. 1: Effects of independent variables x_1 and x_2 on the dependent variable (a) y_1, (b) y_2, (c) y_3, (d) y_4, (e) y_5, (f) y_6

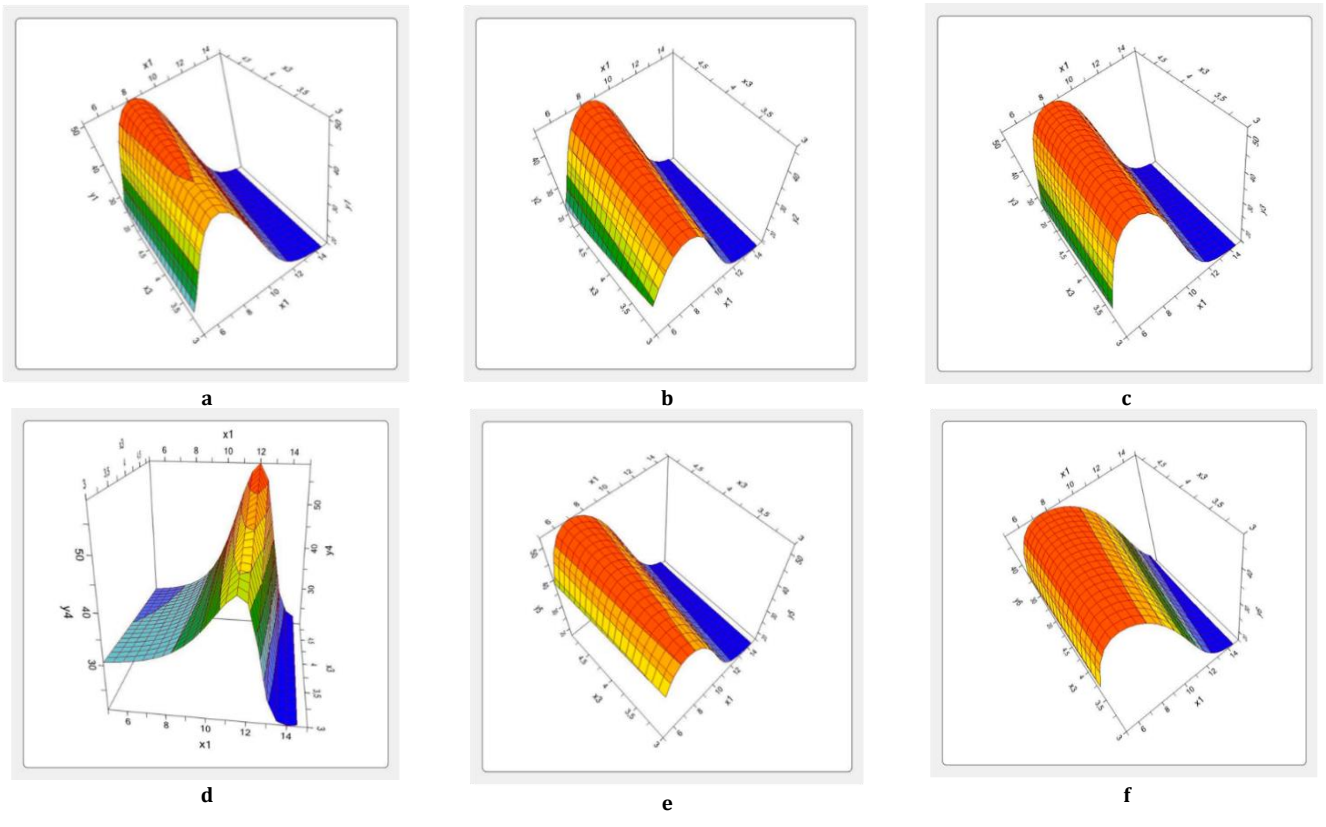

Fig. 2: Effects of independent variables x_1 and x_3 on the dependent variable (a) y_1, (b) y_2, (c) y_3, (d) y_4, (e) y_5, (f) y_6

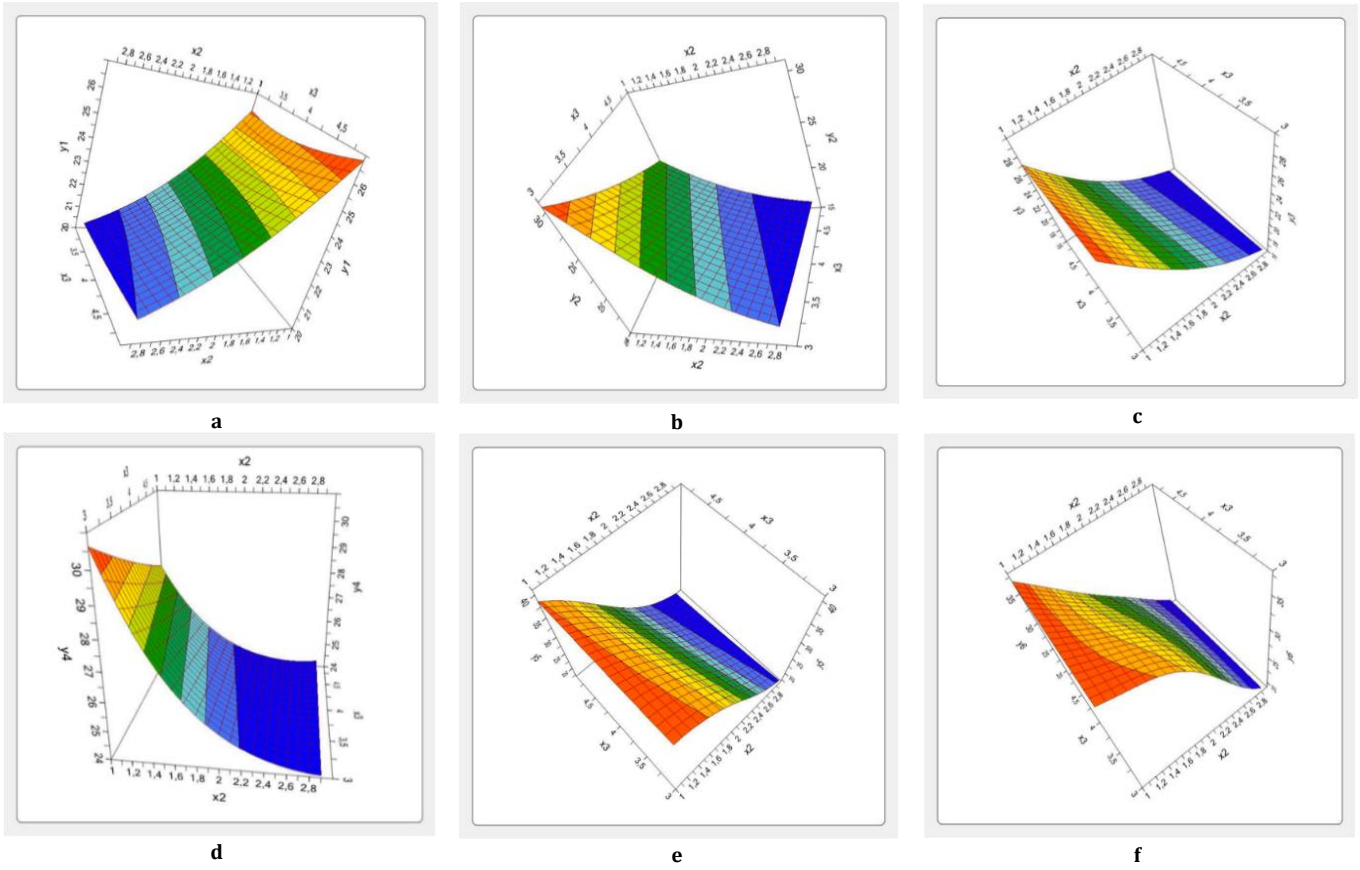

Fig. 3: Effect of independent variables x_2 and x_3 on dependent variable (a) y_1, (b) y_2, (c) y_3, (d) y_4, (e) y_5, (f) y_6

In fig. 1, the results showed that to obtain all y_1; y_2; y_3; y_4; y_5; y_6 value superior to 50%, the crospovidone content should be in the range of 8-12% and the tablet hardness should be 80-110 N.

The fig. 2, showed that to obtain the required value of the dependent variables, the crospovidone content should be in the range of 6-8.5% and the HPMC 6cps content should be 4.5-5%.

The results presented in the fig. 3 indicated that there is no independent variable value x_2; x_3 in the survey range that made the dependent variables reach over 50%.

Taking all of these results into consideration, to obtain all dependent values over 50%, the crospovidone content, the HPMC 6cps content and the tablet core's hardness should be in the range of 8-12%, 4.5-5% and 80-110 N, respectively.

Table 6: Optimal parameters for the coated tablet

Optimal parameters		Predicted value			
x_1	9.772%	y_1	54.565	y_4	53.719
x_2	70-90 N	y_2	50.006	y_5	54.364
x_3	4.748%	y_3	50.307	y_6	50.015

In order to validate the optimal results predicted by BCPharSoft OPT software, three batches of 1,000 tablets with crospovidone XL content of 9.772%, tablet hardness in the range of 70-90 N and HPMC 6cps content of 4.748%.

Table 7: Validation of optimal formulation through experimentation (n=6).

Independent variable	Experiment			Average value	Predicted value
	Batch 1	Batch 2	Batch 3		
y_1	53.65	53.13	52.72	53.17±0.47	54.565
y_2	50.08	50.06	50.15	50.09±0.05	50.006
y_3	53.12	52.39	52.91	52.81±0.38	53.307
y_4	52.35	52.98	52.23	52.52±0.40	53.719
y_5	54.03	52.94	53.64	53.54±0.55	54.364
y_6	50.14	50.21	50.22	50.19±0.04	50.015

The experimental results was compared to predicted one using one-factor ANOVA without repetition, the result was $F=0.343<F_{crit.}=4.964$, so there is no significant difference between experimental results and the predicted results by using BCPharSoft OPT software.

Table 8: Quality test of the optimized coated tablet containing amlodipine and valsartan (5/80 mg)

Quality attribute	Requirement	Results		
		Batch 1	Batch 2	Batch 3
Appearance (n = 10)	Yellow film-coated tablets, smooth and non-crumble surface	Correct	Correct	Correct
Identification (n = 10)	The chromatogram of the tested sample includes two peaks with retention times corresponding to the retention time of the standard sample.	Correct	Correct	Correct
Medium hardness (n = 20)	70-90 N	Pass (80.8±0.31 N)	Pass (85.3±0.15 N)	Pass (79.3±0.32 N)
Weight uniformity (n = 20)	Not more than two units' weight deviate from the 7.5% difference limit, and no unit's weight is superior to 15% of the average weight.	Pass (203.3±0.23 mg)	Pass (204.1±0.39 mg)	Pass (201.6±0.59 mg)
In vitro equivalence (n = 6)	f2 value (of amlodipine and valsartan in all three pH environments)>50%	Pass (f_2>50%)	Pass (f_2>50%)	Pass (f_2>50%)
Assay (n =6)	95-105%	Pass (100.2%)	Pass (101.9%)	Pass (102.5%)

DISCUSSION

Valsartan has poor water solubility and poor flowability nature. This property can affect the control of weight and hardness of tablets during tablet compression. Therefore, an improvement of flowability of the powder before the compression step is required. In addition, due to the sensitivity of amlodipine to moisture [12], wet granulation is not applicable for the related formulation. To improve the flowability of the powder, dry granulation method was chosen with avicel PH 112 as a diluent [12]. The weight of the tablet core was fabricated with a hardness of about 60 N. Using avicel PH 112 and application of appropriate hardness for the tablet core were proven to be helpful for the granulation. Crospovidone XL, a super disintegrant excipient, was also added into the optimized formulation and was showed to be crucial to ensure the release rate of the active ingredients. The obtained results revealed that the addition of this super disintegrant should be at the beginning of the fabrication process as it could lead to gradual swelling and capillary action, and help to prevent the excessive release of the active ingredient [13]. Similar benefits of using crospovidone XL as super disintegrant in immediate-release tablets containing amlodipine was also observed by Behin Sundara Raj *et al.* in 2012 [14].

The obtained results with the design of experiments showed a significant impact of all tested independent variables on the release rate of amlodipine and valsartan, thereby affecting the *in vitro* equivalence of the resulted film-coated tablets. Nevertheless, the impact level was showed to be different. Indeed, Crospividone XL demonstrated the greatest impact on the release level of the tablet's APIs. This important influence may be due to the fact that its positive impact on the flowability and compactibility of granules as well as its ability to form complexes with amino groups in valsartan, enhancing the solubility of valsartan [13, 15]. A similar result was also observed in the study of Ramirez *et al.*, in which a ratio of crospovidone XL at 10% produced the maximal release rate of API [15]. Secondly, the tablet's hardness also presented a significant impact on the release level of APIs but less important than that of crospovidone XL. Specifically, a softer tablet makes it easier to release the APIs. On the contrary, an increase in the hardness makes tablets more solid but harder, and takes more time to be disintegrated. In terms of HPMC 6 cps, the obtained results showed that there was the less significant impact on the release of APIs. Indeed, HPMC 6cps only creates a low-viscosity film when the tablets come into contact with the dissolution testing environment, that does not greatly affect the release ability of the tablets but only to protect against moisture that was similar to the results obtained by Chulhun Park *et al.*,[16].

From the above results, an equilibrium between these two parameters, as showed in the results, is indispensable to obtain a maximized dissolution rate of tablets, which was determined and validated using the design of experiment. This finding again highlighted the benefits of design of experiment softwares, such as BCPharSoft OPT, in the drug formulation, as it is considered a great forward step in the pharmaceutical industry, especially in developing countries. Such supporting tool can bring many advantages in formula research process, especially in shortening the time and number of tested formulas, and finally help saving time and wasted ingredients.

CONCLUSION

An optimal film-coated formulation was successfully developed for hypertension treatment, including 6.94 mg amlodipine besylate (3.47%) (equivalent to 5 mg of amlodipine), 80 mg valsartan (40%), 19.54 mg crospovidone XL (9.77%), 4 mg aerosil (2%), 5.5 mg magnesium stearate (2.75%), and 84.02 mg avicel PH 112 (42.01%) for the tablet core. Tablet core's hardness was in the range of 70-90 N. The film-coating layer comprises 4.92 mg HPMC 6cps (4.75%), 0.44 mg PEG 6000 (0.42%), 0.88 mg talc (0.84%), 1.84 mg TiO_2 (1.77%), 0.12 mg yellow iron oxide (0.12%), and 95.48 mg ethanol 96%-water (2:1) (92.1%). Optimized tablets met the *in vitro* equivalence in comparison to the reference drug, with f2 values for amlodipine recorded at 53.17 (pH 1.2), 50.09 (pH 4.5), and 52.81 (pH 6.8), and for valsartan at 52.52 (pH 1.2), 53.54 (pH 4.5), and 50.19 (pH 6.8). Results obtained from the current study reconfirmed the potential of using mathematical models in drug formulation to obtain desired properties and may be used as an example for the quality by design in the pharmaceutical industry. Further studies on clinical trials for bioequivalence test will be conducted in order to commercialize this optimized formulation.

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AUTHORS CONTRIBUTIONS

D. T. M. H: Methodology, Conceptualization, Writing-original draft, Project administration, Resources, Supervision, Other authors: Methodology, Conceptualization, Writing-original draft, Datacuration, Resources, M. N. T. l: Resources, Data curation, Phuoc-Vinh Nguyen: Writing-original draft, Data curation, Resources, Writing-Review and editing.

CONFLICT OF INTERESTS

The authors declare no competing interests.

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