RESEARCH ON THE PREPARATION OF AMLODIPINE 5MG IMMEDIATE-RELEASE FILM-COATED TABLETS TO IMPROVE ACTIVE INGREDIENT'S STABILITY

Huynh Thi My Duyen*, Dao Long Chau, Vo Dao Thao Vy, Tran Cao Truc Linh, Pham Nguyen Quoc Thong
Can Tho University of Medicine and Pharmacy
Corresponding author: htmduyen@ctump.edu.vn

ABSTRACTS

Background*: Amlodipine is a representative active ingredient of calcium channel blockers. In addition to the general advantages of calcium channel blockers in treating hypertension, amlodipine also effectively controls blood pressure for 24 hours and has no or just a little effect on neurohormonal activation, so it does not cause high blood pressure at the last dose. However, amlodipine has a plasma half-life of between 30 and 40 hours, slowing the drug's action duration. Besides, amlodipine is very hygroscopic, causing instability during storage and leading to loss of drug efficacy.* ***Objectives:*** *To design and optimize the formula of amlodipine 5 mg immediate-release film-coated tablets and formulate a film coating for amlodipine 5 mg immediate-release film-coated tablets.* ***Methods:*** *The immediate-release tablet was formulated by direct compression method and designed by Design-Expert software with different types and numbers of super disintegrants. Evaluation of the solubility of each formula to determine the most optimal one; Formulation of the protective coating to help to stabilize the tablet.* ***Results:*** *Preparation of immediate-release film-coated tablets containing amlodipine 5 mg with a 30-minute release of 96.76% of the active ingredient; formulation on the protective coating including titanium dioxide, PEG 6000, talc, HPMC E6, colorant, alcohol 96%, and distilled water.* ***Conclusion:*** *The research showed that the content of the amlodipine coating tablet released at 30 min in a pH 1.2 medium was near the maximum level and did not change significantly during 6 months of storage.*

Keywords: *Amlodipine besylate, fast-acting tablets, protective coating.*

I. INTRODUCTION

Hypertension is a common chronic disease, a leading cause of cardiovascular diseases, and premature death, so it has been a severe problem in the world and Vietnam [3]. According to a report by the World Health Organization (WHO) in 2021, around the world, there were about 1.28 billion people with high blood pressure between the ages of 30 and 79. It is predicted that the number of people with hypertension will increase sharply in the future under the current socioeconomic and lifestyle conditions. Hypertension is increasing in younger people. Also, patients have to suffer from complications such as cerebrovascular accidents, myocardial infarction, heart failure, kidney failure, etc., which burdens their families and society[8].

In modern medicine, it is not only stopping the treatment of the disease but also limiting the patient's side effects. Clinical trials have demonstrated the role of calcium channel blockers in the treatment of hypertension and in protecting patients from cardiovascular events [7]. At the same time, with long-term treatment, calcium channel blockers do not cause lipid disorders, do not affect blood sugar, fight atherosclerosis, reduce left ventricular hypertrophy, and improve cholesterol metabolism, making calcium channel

blockers widely used in clinical medicine. Amlodipine is a representative active agent of calcium channel blockers. In addition to the general advantages of calcium channel blockers, amlodipine also effectively controls blood pressure for 24 hours and has no or just a little effect on neurohormonal activation, so it does not cause high blood pressure at the last dose. However, amlodipine has a plasma half-life of 30-40 hours, slowing the drug's action duration. Besides, amlodipine is very hygroscopic, causing storage instability and leading to drug efficacy loss. Therefore, it is necessary to study the protective coating to improve the above disadvantages. This study aimed to design and optimize the formula of amlodipine 5 mg immediate-release tablets and the film protective coating for amlodipine 5 mg immediate-release tablets.

II. MATERIALS AND METHODS

2.1. Materials

Amlodipine besylate (India); A-tab, ProSolv, Opadry QX, Ethocel, and HPMC E6 (USA); Aerosil, Eugrarite E, and Methanol (Germany); Sodium croscarmellose and Sodium starch glycolate (Taiwan); PEG 6000, Magnesium stearate, Potassium chloride, Acid hydrochloride, Titanium dioxide, and Talc (China); Alcohol 96% (Vietnam); AmLor®5 mg was manufactured in Australia by Pfizer (Pfizer Australia Pty., Ltd).

2.2. Research Methods

2.2.1. Design and optimization of the formula of amlodipine 5 mg immediate-release tablet

We prepared more than 200 tablets to investigate two types of super disintegrating agents including sodium croscarmellose and DST with rates varying from 1.5% to 5.4%.

The experimental model was designed by Design-Expert software with two independent variables including x1 (the croscarmellose sodium content) and x2 (the DST content).

Table 1. Formula from F1 to F12

Ingredients	Weight of 1 tablet (mg)											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Amlodipine besilate	6.994											
ProSolv	90											
Sodium croscarmellose	6.525	8.1	12.15	3.375	3.375	8.775	3.375	12.15	12.15	12.15	4.275	12.15
DST	3.375	12.15	7.875	12.15	3.375	7.875	8.1	3.375	12.15	12.15	7.65	3.375
Aerosil	1.5											
Magnesium stearate	2											
A-tab (a sufficient amount)	**225**											

We prepared tablets according to the above formulas; then we checked the dependent variables including y_1 (percentage of active ingredient release (%)) and y_2 (the flow rate (s/g).

Active ingredient release percentage (y1): we tested through the solubility test.

We tested 6 tablets in each formula. We used a dissolution meter with the parameters (agitator speed: 75 rpm; temperature: 37 ± 0.5ºC; 500 mL of a buffer solution with pH = 1.2). Quantification by the UV-Vis method was validated successfully following the ICH guideline.

After 30 minutes, we used a 10 mL syringe to take the solution of amlodipine besylate sample through the filter tip of the dissolution meter. Then we filtered through filter paper, then quantified by UV-Vis method at a wavelength of 363 nm.

Requirements: within 30 minutes, the tablet releases as much active ingredient as possible, and the active ingredient content must be at least 85%.

Flow rate (y2): We weighed about 50 g of granules. Next, we put them into the funnel of the Erweka flow meter. The diameter of the funnel hole is 15mm. We read the result of measuring the flow rate of the granules (s/g). Requirements: 9-11 (s/g).

The above results were input data for the optimization software BCPharSoft OPT to optimize the formula and predict the optimal one.

After that, we made 03 lots (each had 1000 tablets) to verify the optimal formula. The summary procedure is as follows:

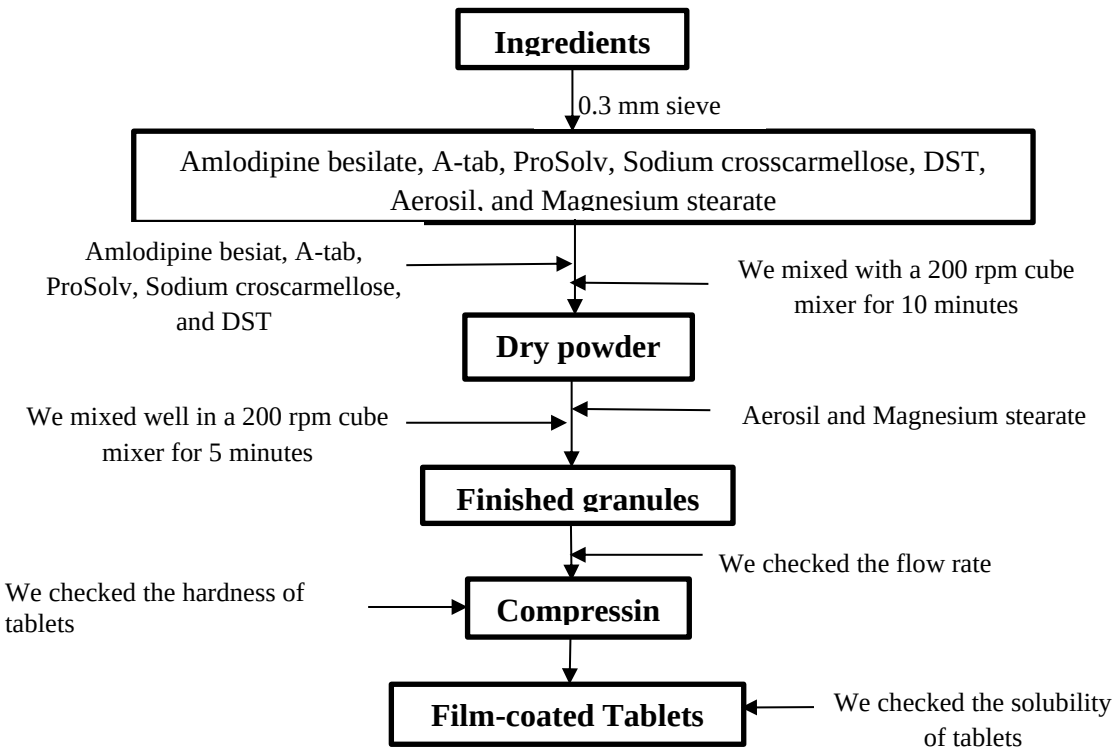

Figure 1: Summary of the preparation process for the optimal tablet formula containing amlodipine

2.2.2. Formulation of protective coating for amlodipine 5 mg immediate-release tablets

Table 2. Ingredients in the formula

Ingredients	**Ratio (%)**				
	CT1	**CT2**	**CT3**	**CT4**	**CT5**
Titanium dioxide	0.4	0.4	0.4	0.4	-
PEG 6000	1.0	1.0	1.0	1.0	-
Talc	2.5	1.5	2.5	1.5	-
HPMC E6	3.5	4.5	-	-	-
Eugrarite E	-	-	3.5	4.5	-
Opadry	-	-	-	-	8
Colorant	0.6	0.6	0.6	0.6	-
Distilled water	46.0	46.0	46.0	46.0	46.0
Alcohol 96%	46.0	46.0	46.0	46.0	46.0
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

Stages in the protective coating process

- Preparing ingredients: We separately ground the ingredients and weighed them.
- We slowly dissolved the polymer into the alcohol-water mixture on a magnetic stirrer, stirring gently for 15 minutes. We added the remaining ingredients to the polymer solution.
- We continued sifting the above mixture through a 0.4 mm sieve to obtain a coating solution. The coating solution was stirred during the coating process.
- We prepared equipment with specifications (number of pellets: 100; spraying air pressure: 15 PSI; vibration speed of tablet bed: 25 Hz; fan speed: 16 m/s; drying air temperature: 50ºC; coating solution injecting speed: 50%: coating solution spraying time: 7 minutes).
- After spraying, we dried the pellets for 5 minutes and then let them cool.

We compared the formulas after coating according to criteria such as physical characteristics, solubility (%), moisture (%), and mass gain (%) to choose the best formula. Next, we made 3 batches and surveyed the stability of the coating under normal storage conditions (temperature: 30 ± 2 ºC; relative humidity: 75 ± 5%) for 6 months.

III. RESULTS

3.1. Design and optimization of amlodipine 5 mg immediate-release tablet formula

3.3.1. **Survey on dissolubility of AmLor® 5 mg control tablets**

Table 3. Percentage of amlodipine besylate released from AmLor® 5mg tablets

Time (minute)	**Percentage of amlodipine besylate (%)**						
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**TB**
30	105.46	101.92	104.02	102.63	100.16	103.11	102.88

Comment: the percentage of the release of the amlodipine besylate of the control tablet AmLor® 5 mg at 30 minutes was ≥ 85%. This result was consistent with that of the immediate-release tablet. Therefore, this study aimed to prepare a 5 mg amlodipine immediate-release tablet with a release equivalent to an AmLor® 5 mg tablet.

3.3.2. Optimization of the formula of amlodipine 5 mg immediate-release tablets

Table 4. Experimental results

Formula	X_1	X_2	$\overline{Y1}$	$\overline{Y2}$
1	2.9	1.5	93.77	5.4
2	3.6	5.4	81.79	6.2
3	5.4	3.5	94.23	7.3
4	1.5	5.4	91.56	9.6
5	1.5	1.5	98.1	10.2
6	3.9	3.5	93.38	11.2
7	1.5	3.6	98.29	9.0
8	5.4	1.5	92.32	10
9	5.4	5.4	99.78	10.7
10	5.4	5.4	100.39	10.4
11	1.9	3.4	87.86	8.5
12	5.4	1.5	100.33	7.4

$\overline{Y1}$: percentage of active ingredient release (%); $\overline{Y2}$: flow rate of tablets (s/g)

Data processing

We have R^2X (a value taken from BCPharSoft OPT software after processing 12 results of the above formulas) and R^2Y (a value taken by comparing R^2X to some of the 12 results). The optimal parameters and predictive results for BCPharSoft OPT software were as follows:

$\overline{Y1}$: $R^2X = 0.97$ $R^2Y = 0.97$ $R^2 = 0.97$

$\overline{Y2}$: $R^2X = 0.96$ $R^2Y = 0.95$ $R^2 = 0.98$

The results of R^2X and R^2Y showed that the accuracy of the model's predictability was high, so this model was directly used to predict the optimal formula:

Optimal parameters: Predictive properties:

X_1: 1.826% $\overline{Y1} = 99.359$

X_2: 5.371% $\overline{Y2} = 10.017$

The optimal results predicted by BCPharSoft OPT software were verified experimentally. We prepared 1000 tablets with the ingredients according to Table 5.

Table 5. Optimum formulation ingredients

No.	Ingredients	Formula	
		Mass (mg)	Ratio (%)
1	Amlodipine besilate	6.994	3.108
2	Sodium crosscarmellose	4.109	1.826
3	DST	12.085	5.371
4	ProSolv	90	40
5	Aerosil	1.5	0.667
6	Magnesium stearate	2	0.889
7	A-tab (a sufficient amount)	225	100

Table 6. Experimental results and predictive results

Features	Experiment			Prediction
	Lot 1	Lot 2	Lot 3	
$\overline{Y1}$	97	96.41	96.87	99.359
$\overline{Y2}$	10.4	10.5	10.6	10.017

The experimental mean (t_{tn}) and the predictive value (t_{lt}) were compared to each other with the T-test. Results: $t_{tn} < t_{lt}$. That meant the experimental results obtained were consistent with the predictive results of BCPharSoft OPT software.

3.2. The formula of protective coating for amlodipine 5 mg immediate-release tablets

Table 7. Survey results of pellets after coating between formulas

Formulas / Standards	CT1	CT2	CT3	CT4	CT5
Physical characteristics	Passed	Passed	Passed	Passed	Not passed
Solubility (%)	99.08	99.16	85.73	84.30	98.94
Humidity (%)	3.22	3.27	2.98	4.10	4.21
Mass gain (%)	2.5	3.7	2.3	2.8	3.2

Comment: firstly, CT5 did not meet the requirements of physical characteristics. Secondly, the percentage of active ingredient release of CT3 and CT4 was relatively low compared to the remaining formulas. CT1 and CT2 met the output target of pellets after coating. However, the amount of HPMC used in CT1 was 3.5% less than that in CT2 at 4.5%, so CT1 was selected as the optimal formula for film coating solution.

We surveyed the stability of the coating under the condition (temperature: 30 ± 2ºC; relative humidity: 75 ± 5%) for 6 months. The results are presented in Table 8, Table 9, and Table 10.

Table 8. Physical characteristics of pellets under long-term conditions

Lot number	Time (months)				
	0	1	2	3	6
1	Passed	Passed	Passed	Passed	Passed
2	Passed	Passed	Passed	Passed	Passed
3	Passed	Passed	Passed	Passed	Passed

Comment: in terms of physical characteristics, all the tablets retained a smooth surface, and the color was almost unchanged compared to before testing.

Table 9. Results of solubility test of amlodipine tablets after 30 minutes

Lot number	Time (months)				
	0	1	2	3	6
1	97.08	98.18	99.58	100.01	100.59
2	97.66	97.34	98.70	99.21	100.83
3	97.70	98.47	99.13	99.26	99.98

Comment: the content of amlodipine besylate released at 30 minutes in a pH 1.2 medium did not change significantly during 6 months and still reached the baseline standard.

Table 10. Results of moisture test of amlodipine tablets after certain periods

Lot number	Time (months)				
	0	**1**	**2**	**3**	**6**
1	3.22	3.21	2.99	3.03	2.92
2	3.93	3.90	3.15	3.22	3.07
3	4.11	4.13	3.96	4.02	3.93

Comment: moisture test results of amlodipine tablets after a certain period were within the allowable range of the moisture level of tablets.

IV. DISCUSSION

Testing the AmLor® 5mg control tablet was the premise for the research on the amlodipine 5mg immediate-release tablet met requirements equivalent to the control tablet. This is the basis and the decisive condition for establishing the baseline standard for the solubility of amlodipine 5 mg immediate-release tablets.

There are many methods to prepare immediate-release tablets, but the direct compression method is most suitable for preparing tablets containing amlodipine. That is because it protects the active ingredient from moisture compared to the wet granulation method. Furthermore, it ensures pellets meet quality requirements and helps reduce stages with less equipment than the dry granulation method. Atram (2011) [1] and S. Mohamed Halith (2011)[5] also used the direct compression method to prepare amlodipine tablets.

The results of solubility and flow rate tests of 12 formulas were input data for BCPharsoft OPT software. The results showed that R^2X of the release of the active substance and the flow rate had good compatibility ($R^2X > 95\%$) and R^2Y of the release of the active substance and the flow rate had good predictability because all of the R^2Y values were all greater than 85%. The disintegration rate of sodium croscarmellose and DST predicted by BCPharsoft OPT software were 1.826% and 5.371%, respectively. In addition, the software also predicted that the percentage of amlodipine besylate released of the optimal formula was 99.359%, and the flow rate was 10.017 s/g as a basis for testing. Survey results of solubility and flow rate of 3 experimental batches in Table 3.4 show that $t_{tn} < t_{lt}$, which meant that the experimental results were consistent with the predictive results.

According to the results, combining two types of super disintegrants with different mechanisms helped increase the substance's solubility. That was similar to the results of S. Mohamed Halith (2011) [5], who used a combination of two super disintegrants at 8.33%, including sodium starch glycolate and pregelatinized starch, 99.24% of the active ingredients were released at 30 minutes.

There are many ways to protect active ingredients and improve the stability of tablets such as hard capsules, sugar coating, film coating, etc. Rajesh, M. [6] and Zaid AN [9] used the coating method to improve pellet stability. In this study, the film coating method was chosen because of its simple preparation technique with thin coating, less time-consuming, and less effect on releasing active ingredients.

Most studies have used polymeric excipients such as HPMC and eugrarite or a complete coating system like Opadry [2]. They are non-toxic, pharmacologically inert substances readily soluble or dispersible in water. In addition, using these agents helps easily remove the solvent even when the solution is highly viscous, shortening the coating

time. Moreover, they have high stability during storage. Last but not least, they are suitable for the preparation method, so these excipients were selected to make the composition of the protective coating solution in this study.

When examining coatings with different ratios, HPMC rates were 3.5% and 4.5% in CT1 and CT2, Eugrarite E rates were 3.5% and 4.5% in CT3 and CT4, respectively, and Opadry QX rate was 8%. The results showed a difference in the parameters of pellets after coating between formulas of protective coating. The results of the release of active ingredients in CT3 and CT4 were lower than 85%, which did not meet the requirements of the immediate-release tablets, so they were not selected. Regarding CT5, the criteria of physical characteristics were not passed because the Opary content was low, which was not enough to completely coat the tablet surface compared to the study by Dr. Zaid AN [9], who used an Opadry concentration of 15%. So if the concentration of Opadry was increased, CT5 could meet the requirements for physical characteristics, which would increase the cost of the tablets. CT1 and CT2 were suitable for the research objectives. However, the study proposed to use CT1 because it contained HPMC polymer with a rate of 3.5% lower than that of CT2 with a rate of 4.5%, which helped to save raw materials and preparation time with lower costs.

Stability test results of amlodipine immediate-release film-coated tablets in 0, 1, 2, 3, and 6 months showed that the percentage of active ingredient release and the moisture level of the pellets only fluctuated within the allowable range compared to the optimized ones, which proved that the coating could protect tablets from adverse environmental impacts during the research period. This is the basis to continue to upgrade the batch size and study the stability of tablets according to regulations, thereby determining the expiry date of the drugs.

V. CONCLUSION

The amlodipine 5 mg immediate-release film-coated tablets were prepared to increase the stability of active ingredients with no significant change in the solubility and moisture content of pellets during 6 months of storage at a temperature of 30 ± 2ºC and relative humidity of 75 ± 5%.

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(Received: 10/10/2022 – Accepted: 14/02/2023)