FORMULATION AND STABILITY OF ORALLY FAST DISINTEGRATING TABLETS OF AMLODIPINE BESYLATE

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ABSTRACT

Background*: The demand for fast disintegrating tablets has been growing during the last decade especially for geriatric and pediatric patients because of swallowing difficulties. Amlodipine besylate is commonly used for the treatment of chest pain, commonly known as angina, due to ischemia of the heart muscle, and a result of obstruction or spasm of the coronary arteries. The study would involve the use of various disintegrants along with other excipients for the formulation of orally fast disintegrating tablets to achieve rapid disintegration and release. The stability studies of the prepared dosage form would be carried out according to the guideline of the ASEAN guideline for drug products stability study.* ***Objectives:*** *To formulate orally fast disintegrating tablets containing amlodipine 5mg at pilot scale and develop in-house specification.* ***Materials and methods:*** *Orally fast disintegrating tablets containing amlodipine 5mg were prepared by direct compression method. Formulations were designed by Design Expert 12.0 using Optimal model and were optimized by BCPharSoft software. Studied ingredients are disintegrants and fillers for directly compressed tablets. After being prepared, tablets were developed in-house specifications including these criteria: organoleptic parameters, identification, assay, uniformity of mass, disintegration time, dissolution, then the batch size was scaled up to 10,000 tablets. The tablets stability study was proceeded and shelf life of the product under accelerated condition was calculated within 6 months according to Van't Hoff principle.* ***Results:*** *After being scaled up, orally fast disintegrating tablets containing amlodipine 5mg met in-house specifications. Tablets have a good stability and shelf life of 766.3 days (at 30 ^{o}C).* ***Conclusions:*** *Orally fast disintegrating tablets containing amlodipine 5mg were successfully studied at 10,000 tablets batch size and showed a great promise for production scale.*

Keywords: *Orally fast disintegrating tablets, Amlodipine besylate, Pilot scale; Stability study.*

I. INTRODUCTION

Hypertension requires a long-term or even a lifelong treatment. This disease needs to be treated properly and sufficiently every day; therefore, treatment adherence is very important to reduce potentially dangerous complications. Amlodipine besylate is a long-acting calcium channel blocker used to treat chronic stable angina, vasospastic angina, and hypertension. Amlodipine is a sparingly soluble orally administered drug, and the rate of absorption is often controlled by the rate of dissolution [3]. The rate of dissolution will increase by incorporating the drug in a fast-dissolving dosage form. Usual dosage forms (tablet, capsule) are difficult for elderly patients to swallow, and are inconvenient for busy patients who cannot use them immediately or forget to bring water. Orally fast disintegration dosage form can improve treatment adherence without water [5].

With the aim of diversifying dosage forms and targeting many types of patients, the study "***Formulation of orally fast disintegrating tablet of amlodipine 5 mg at pilot scale***" was proceeded with these following purposes: (1) Designing and optimizing formulation of orally fast disintegrating tablets of amlodipine 5 mg with different excipients; (2) Setting up in-house specifications for orally fast disintegrating tablet of amlodipine 5 mg. (3) Upgrading into 10,000 tablets batch size; (4) Determining shelf-life of orally fast disintegrating tablets of amlodipine 5 mg by using the accelerated stability testing.

II. MATERIALS AND METHODS

2.1. Materials

Amlodipine besylate (Cadila Health Care Limited-Indian), super disintegrants: sodium starch glycolate, croscarmellose sodium, crospovidone, polacrillin potassium sponsored by Asia Shine Ltd., Other excipients and chemicals are pharmaceutical and analytical grade, respectively.

2.2. Methods

2.2.1. Designing and optimizing of formulation of orally fast disintegrating tablets containing amlodipine 5 mg with different excipients

Basic formulation of orally fast disintegrating tablets containing amlodipine:

Amlodipine besylate		6.93 mg (equivalent to 5 mg of amlodipine)
Avicel PH 102		x mg
Super disintegrant		y mg
Aspartame		5 mg
Menthol		1 mg
Magnesium stearate		1.5 mg
Aerosil		3 mg
Mannitol	q.s	150 mg

Orally fast disintegrating tablets were prepared by direct compression method, batch size was 150 g (1,000 tablets).

Four types of disintegrants were studied: croscarmellose sodium, sodium starch glycolate, crospovidone and polacrillin potassium. The amount of super disintegrants was researched at 3% of content. Typical criteria of orally fast disintegrating tablets such as disintegration time and wetting time were determined. Other criteria were also checked. Then some super disintegrants meeting these criteria were chosen for design and optimization.

Disintegration time: 2 mL of purified water was taken in a 10-mL measuring cylinder. Temperature was maintained at 37 ± 2°C. A tablet was put into it and time required for complete disintegration of the tablet was noted. The time reported to obtain complete disintegration of six tablets were recorded and average was reported [8].

Wetting time: Five filter papers was placed in a Petri dish having an internal diameter of 6.5 cm to that 10 ml of purified water containing a methylene blue solution (0.5% w/v) was added to Petri dish. A tablet was carefully placed on the surface of the paper in the Petri dish. The time required for dye to reach the upper surface of the tablet and to completely wet was noted as the wetting time. The wetting time of six tablets were recorded and average was reported [2].

Formulation of orally fast disintegrating tablets containing amlodipine 5 mg includes:

Independent variables:

x_1 : Type of super disintegrant

x_2 : Amount of super disintegrant (3 – 4.5 – 6) (mg) corresponding to 2-3-4%

x_3 : Amount of filler for directly compressed tablets (100-110-120) (mg)

Dependent variable (product properties)

- Disintegration time (y_1): ≤ 30 seconds
- Wetting time (y_2): ≤ 60 seconds

The optimal formulation was verified on 3 batches. Test results were compared with the predicted results from the software.

2.2.2. Setting in-house specification for the product of orally fast disintegrating tablets containing amlodipine 5 mg

In-house specification of fast orally disintegration tablets was set according to Vietnamese Pharmacopoeia V (usual criteria of a tablet) and Guideline of Orally Disintegration Tablets – FDA (disintegration time) including organoleptic parameters, identification, assay, uniformity of mass, disintegration time, dissolution test [4], [6].

2.2.3. Upgrading into 10.000-tablets batch size

The formulation at pilot scale was similar to the optimal one; the proportion of ingredients was kept fixed, only the batch size increased from 1,000 tablets (150 g) to 10,000 tablets (1,500 g). The process of preparing orally fast disintegrating tablets containing amlodipine underwent two main stages: Mixing dry powder and tableting. When mixing powder, the uniformity of content was evaluated at different times and different positions of cube mixer. In addition, pre-compression parameters such as Carr's compressibility index, flowability were also calculated. While tableting with rotary tablet machine at a speed of 12 rpm, compression force and speed of compressor were maintained to ensure the uniformity of tablets. Simultaneously, the coefficient of variation (CV) of uniformity of mass and the hardness were also kept below 2% while dissolution test was proceeded. Test preparation was conducted on 3 batches, with the evaluated procedure and the quality of product was controlled by in-house specifications.

2.2.4. Estimating of shelf-life of orally fast disintegrating tablets containing amlodipine 5 mg with accelerated stability testing

Stability of 3 testing batches was studied under accelerated condition (40^{o}C ± 2^{o}C, RH 75% ± 5%) in climate chamber (Jeiotech-Korea) according to the ASEAN guideline for drug products stability study for 0, 1, 3, 6 months. Organoleptic parameters, assay, the dissolution was measured in triplicate and the mean was calculated. Shelf-life was determined according to Van't Hoff principle [1].

III. RESULTS

3.1. Design and optimization of formulation of orally fast disintegrating tablets containing amlodipine 5 mg with different excipients

Formulations of orally fast disintegrating tablets containing amlodipine were researched by changing 4 types of disintegrants: croscarmellose sodium (F1), sodium starch glycolate (F2), crospovidone (F3) and polacrillin potassium (F4). Test results of semi-finished products showed that all formulations were suitable for tableting.

Test results of disintegration time and wetting time were performed in **Table 1.**

Table 1. Disintegration time (s) and wetting time (s) of tablets in researching disintegrants

	Disintegration time (s)	**Wetting time (s)**
F1	21.66	54.52
F2	8.28	41.21
F3	46.83	254.81
F4	8.13	49.44

These results above indicated that F2 and F4 were two formulations with the shortest disintegration time and wetting time.

D-Optimal experimental model was designed by Design Expert, with three *independent variables:*

x_1: Type of super disintegrant (sodium starch glycolate or polacrillin potassium)

x_2: Amount of super disintegrant (3-4.5-6 mg)

x_3: Amount of fillers for directly compressed tablets (100-110-120 mg)

Dependent variable:

y_1: Disintegration time (s)

y_2: Wetting time (s)

After experimentation and optimization with software, this following optimal formulation of orally fast disintegrating tablets containing amlodipine 5 mg was obtained.

Amlodipine besylate	**6.93 mg (equivalent to 5 mg of amlodipine)**
Avicel PH 102	105 mg
Super disintegrant	5.4 mg
Aspartame	5 mg
Menthol	1 mg
Magnesium stearate	1.5 mg
Aerosil	3 mg
Mannitol	q.s 150 mg

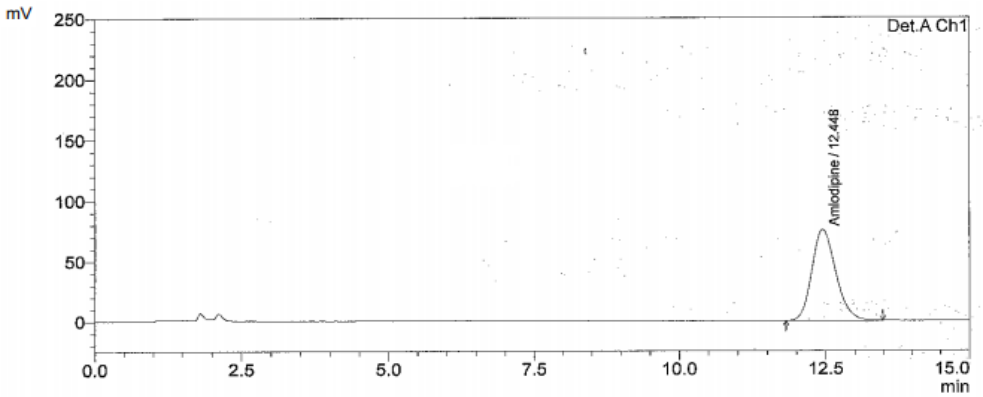
Test results of three experimental batches implied that the difference between the mean of experimental value and theoretical value was not statistically significant ($P = 0.757 < 9.277$, $\alpha = 0.05$).

3.2. Setting in-house specification for product of orally fast disintegrating tablets containing amlodipine 5 mg

After being prepared from the optimal formulation, orally fast disintegrating tablets containing amlodipine 5 mg were testing against the criteria described in Tablet Monograph of Vietnamese Pharmacopoeia V. It laid a foundation for setting in-house specification of orally fast disintegrating tablets containing amlodipine 5 mg.

Table 2. Testing results of post-compression tablets

Criteria	Method	Requirement	Result
Organoleptic parameters	Visual observation	Round, white tablets, with minty smell	Passed
Uniformity of mass	20 tablets were tested with analytical balance	±7.5% compared with average mass	Passed
Disintegration time	6 tablets were added to 2 ml distilled water, respectively	Average result was no more than 30 seconds.	Passed (6.85s)
Dissolution	HPLC	Not less than 75% after 30 minutes	Passed (90.60%)
Assay	HPLC	90.0-110.0% of amlodipine	Passed (99.8%)



PeakTable

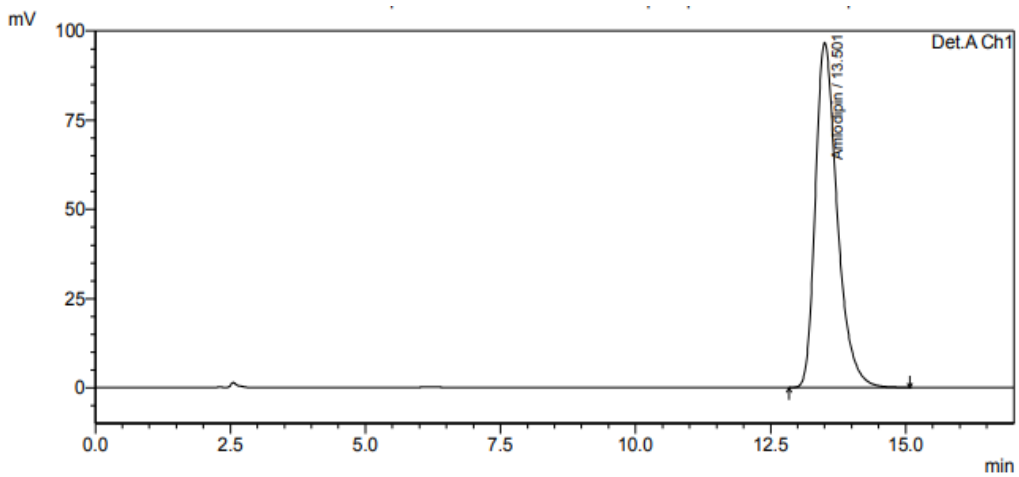
Detector A Ch1 237nm

Peak#	Name	Ret. Time	Area	Height	Theoretical Plate#	Tailing Factor
1	Amlodipine	12.45	2453129	84674	4396	1.2
Total			2453129	84674		

Figure 1. The HPLC chromatogram of amlodipine besylate in dissolution test

Through testing results, in-house specification of orally fast disintegrating tablets containing amlodipine 5 mg was set as follows:

- Organoleptic parameters: Round, biconvex, smooth, white tablet, with minty smell.
- Identification: The retention time of the amlodipine peak of test solution is similar to the standard solution.
- Uniformity of mass: ± 7.5%, compared with average mass of tablet.
- Disintegration time: no more than 20 seconds.
- Dissolution: Not less than 75% of amlodipine $C_{20}H_{25}ClN_2O_5$ compared with the labelled content after 30 minutes.
- Assay: 90.0% - 110.0% of $C_{20}H_{25}ClN_2O_5$ compared with the labelled content.



PeakTable

Detector A Ch1 237nm

Peak#	Name	Ret. Time	Area	Area %	Resolution	Theoretical Plate#	Tailing Factor
1	Amlodipin	13.501	2718842	100.000	0.000	5594.206	1.383
Total			2718842	100.000			

Figure 2. The HPLC chromatogram of amlodipine besylate in content uniformity test.

3.3. Upgrading into 10,000-tablets batch size

Formulation of orally fast disintegrating tablets containing amlodipine at pilot scale:

Amlodipine besylate	**6.93 kg (equivalent to 5 kg of amlodipine)**
Avicel PH 102	105 kg
Super disintegrant	5.4 kg
Aspartame	5 kg
Menthol	1 kg
Magnesi stearate	1.5 kg
Aerosil	3 kg
Mannitol	q.s 150 kg

The optimal powder mixing time was 7 minutes. After being prepared with the scale of 10,000 tablets, the products were tested and showed no significant difference, in comparison with the scale of 1,000 tablets ($p = 0.263 > 0.05$).

3.4. Calculation of shelf-life of orally fast disintegrating tablets containing amlodipine 5 mg with accelerated degradation method

Stability study under accelerated condition according to ASEAN guidelines indicated that tablets also met the requirement of organoleptic parameters, dissolution, disintegration time and content after 6 months of experimentation. The shelf life of the orally fast disintegration tablet was calculated based on the amlodipine content, recorded in **Table 3**.

Table 3. Shelf-life calculation of the orally fast disintegration tablet

Month	**F1**		**F2**		**F3**	
	[C%]	**k**	**[C%]**	**k**	**[C%]**	**k**
0	100.2		100.3		100.1	
30	99.8	0.00013	99.5	0.00027	99.2	0.00030
60	98.2	0.00034	98.9	0.00023	98.3	0.00030
90	97.6	0.00029	98.1	0.00025	97.4	0.00030
180	96.1	0.00023	96.8	0.00020	96.7	0.00019
Average		0.00025		0.00024		0.00027
t_{90} (40 ^oC)		423.9		445.7		383.2
t_{90} (30 ^oC)		847.8		891.5		766.3

$k=-ln([C\ \%]/[C_o\ \%]/t$

The estimated shelf-life of tablets according to Van't Hoff principle was 766.3 days.

IV. DISCUSSION

The combination of aspartame and mannitol helps balance the sweetness, creates a pleasant sensation and conceals the bitterness of the API. The appearance of menthol creates minty taste in order to help patients to use drug easily. During the research phase of disintegrants, four common types of super disintegrants were selected including croscarmelose, sodium starch glycolate, crospovidone and polacrillin potassium. Optimization results performed that polacrillin potassium was the best choice with the shortest disintegration and wetting time. Polacrillin potassium is a super disintegrant with advantages such as high-water absorption and swelling capacity, immediately disintegrates when contacting with water or gastric juice to form fine particles without plaques. Simultaneously, while disintegrating, polacrillin potassium becomes a milky soft substance without tingling tongue like some other super disintegrants. Moreover. polacrillin potassium

can improve dissolution by increasing the surface contacting with gastric juice. This disintegrant is suitable for both direct compression and wet granulation method. Therefore, polacrillin potassium is widely used in orally fast disintegrating tablets. sublingual lozenges… [7]. This research has used the optimization method with BCPharsoft software to find a formulation with an optimal amount of disintegrants and filler. Using software can reduce costs and time for optimization.

There is no general monograph for orally fast disintegrating tablets in Pharmacopoeias. Therefore, amlodipine monograph in Vietnamese Pharmacopoeia V and some in-house specifications of orally fast disintegrating tablets were considered as a reference to set in-house specifications for this amlodipine product. The specifications include two parts specifications and methods. Compared with the specifications of normal tablet, there are some differences such as disintegration time is no more than 20 seconds, dissolution is 75% within 30 minutes.

The optimal formulation for laboratory scale was built. However, this formulation is labelled Research Use Only (RUO). To approach market, it is necessary to scale up batch size. Scaling up process keeps the composition and proportion of substances in the optimal formulation, but the operation parameter of production needs to be studied and determined. Mixing time of raw materials was researched and the result showed that the shortest mixing time to achieve content dispersion of amlodipine below 2% was 7 minutes. In addition, pre-compression parameters such as flowability, compressibility index, bulk density were evaluated. Post-compression parameters such as disintegration time, wetting time and other criteria of in-house specifications were also assessed. Results indicated that product of three batches met the in-house specifications and were not significantly different.

Stability study was proceeded under accelerated condition according to ASEAN Guideline. Results showed that after 6 months of storage at $40^oC \pm 2°C$ and $75\% \pm 5\%$ RH, three batches was met organoleptic parameters, content of amlodipine, dissolution and disintegration time. Hence, in can be inferred that shelf-life of tablets is 766.3 days at normal condition ($30^oC \pm 2^oC$ and $75\% \pm 5\%$ RH).

V. CONCLUSIONS

The orally fast disintegrating tablets containing amlodipine 5 mg was successfully researched and formulated at pilot scale. The prepared orally fast disintegrating tablets met in-house specifications. The stability was determined by accelerated stability method. The shelf life of the tablets is 766 days (at 30^oC), according to Van't Hoff principle.

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