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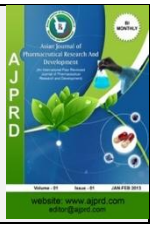

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Review Article

Review: The Discovery and Development of Amlodipine Drug

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A B S T R A C T

Background: Amlodipine is a calcium channel blocker drug (CCBs) used to treat hypertension.

Purpose: This review article aims to discuss the history of the discovery of amlodipine starting from the presence of hypertension that motivated researchers to find drugs that can reduce high blood pressure, namely the antihypertensive group. The most commonly used antihypertensive drug is amlodipine.

Research Methods: The method used is the study of relevant literature which is accessed through online sites such as Google Scholar, Research Gate, Science Direct, Springer Link, and NCBI.

Results: Amlodipine, which is currently approved to treat high blood pressure and angina, was first patented in 1982 but approved as a prescription drug in 1990 sold under the brand name Norvasc. In its development, several trials such as clinical, preclinical, and silico trials have shown significant results.

Conclusion: This drug is safe and effective for treating hypertension and angina.

Keywords: Amlodipine, Drug Discovery, Hypertension

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INTRODUCTION

The drug discovery process includes many complex and scientific processes that focus on the identification, optimization of chemistry and pharmaceuticals, and the development of new compounds to treat human disease states[1]. Preclinical trials and clinical trials are important stages in drug discovery and development, which must meet various aspects such as sources of raw materials, drug targets, research and costs. The drug discovery program was started because there was a disease or clinical condition with inappropriate medical products and clinical needs that could not be met[2].

Hypertension is a health problem that is often faced by developing countries or economically developing countries[3]. To overcome this, research on hypertension has been carried out. The results showed that there is a class of drugs that can lower blood pressure, namely the antihypertensive group. Antihypertensives are a class of drugs used to treat hypertension[4]. Some of the discoveries of antihypertensive drugs commonly used by the general public include amlodipine.

Amlodipine is the most widely used drug for the treatment of hypertension showing that the use of amlodipine reduces vascular events requiring hospitalization and the need for invasive surgical procedures[5]. Therefore, I am interested in discussing the history of the discovery of amlodipine.

It is necessary to know what are the steps in identifying and developing amlodipine drugs include drug action testing, followed by determination that explains the compound process based on its chemical structure (in silico), followed by preclinical tests (in vitro and in vivo) and clinical trials to see the reaction medicine in the human body. If the testing stage has been passed, then the registration stage is the final stage to obtain a distribution permit from the

authorized party in order to strengthen the drug safety statement[2].

METHODS AND DATA COLLECTION

The author made study methods relevant to the purpose of the review. Information from international journals are accessed through online sites such as Google Scholar, Research Gate, Science Direct, Springer Link, and NCBI. The keywords used to search the journal were amlodipine, drug discovery, and hypertension.

RESULTS AND DISCUSSION

Literature Review

Amlodipine was first patented in 1982 but approved as a prescription drug in 1990[6]. Amlodipine is in the form of salt, the available salt forms are besilat, mesilate, and maleate. Amlodipine is an approved drug used to treat high blood pressure and coronary artery disease. Amlodipine is also sold under the brand name Norvasc[7]. Amlodipine was evaluated against diuretics in the treatment of hypertension and was found to be useful in controlling arterial pressure[8]. In the Circadian Antiischemia Program in Europe (CAPE) trial, amlodipine was shown to reduce ischemia in patients with coronary artery disease[9]. Amlodipine has been shown to increase peripheral and coronary blood flow[10,11].Amlodipine works by inhibiting the influx (entry) of calcium ions through the membrane into vascular smooth muscle and cardiac muscle so that it affects the contraction of vascular smooth muscle and cardiac muscle. Amlodipine selectively inhibits calcium ion influx, which mostly has an effect on vascular smooth muscle cells compared to cardiac muscle cells[12]. Amlodipine with the chemical formula $C_{20}H_{25}ClN_2O_5$ has a structural formula that can be seen in Figure 1 below.

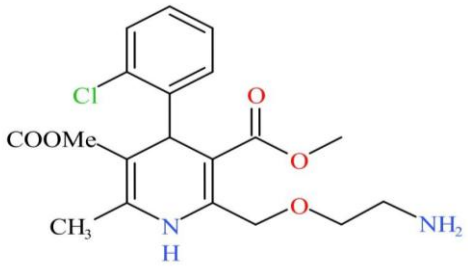

Figure 1: Amlodipine structure[13]

Amlodipine is slightly soluble in water, freely soluble in methanol, slightly soluble in anhydrous ethanol, and slightly soluble in 2-propanol[14].

AMLODIPIN SYNTHESIS

Synthesis is a chemical reaction to obtain a chemical product that involves one or more reactions. Amlodipine synthesis pathway go through several processes, Figure 2 below represents the amlodipine synthetic pathway.

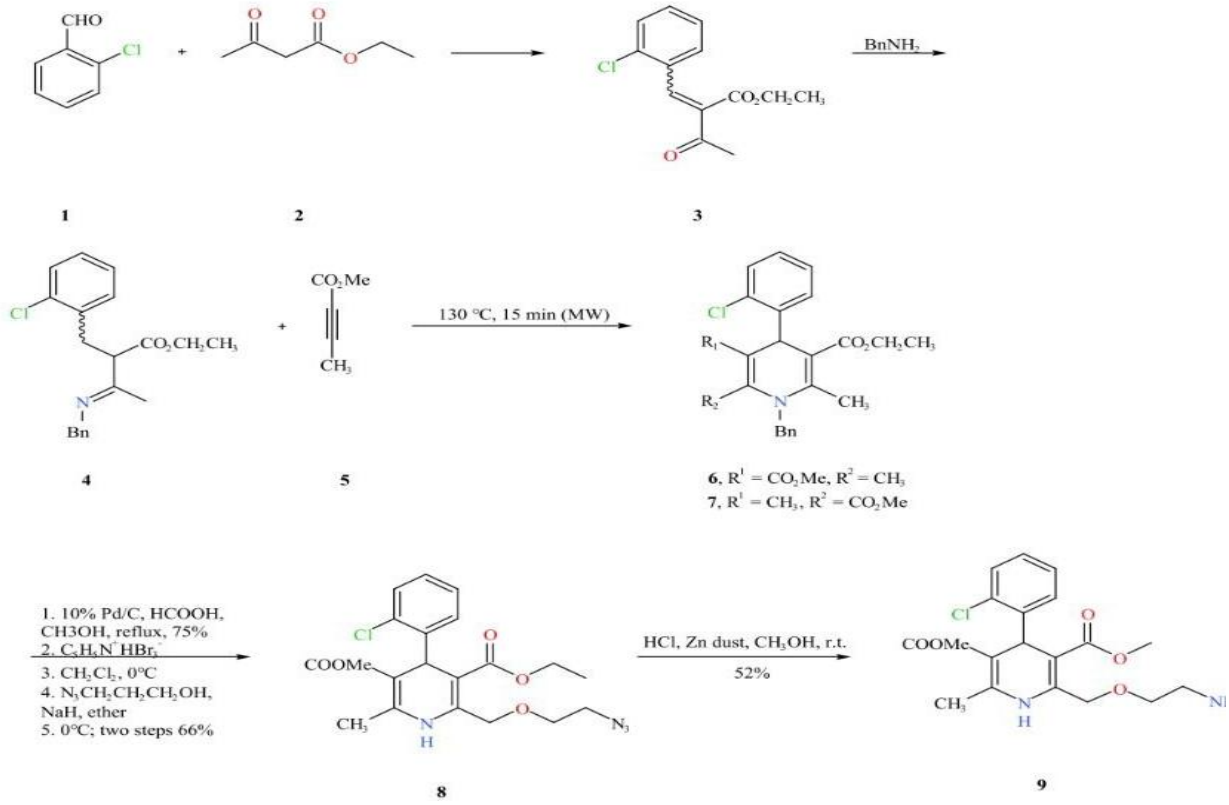

Figure 2: Synthesis of Amlodipine

1,4-Dihydropyridines are often synthesized via an approach explored by Hantzsch in 1882[15]. This name reaction involves a simple procedure and direct isolation of the product. Amlodipine was synthesized as shown in Figure 2. Initially, the reaction of 2-chlorobenzaldehyde **1** with ethyl acetoacetate **2** under conventional heating gave the expected Knoevenagel product **3** as an E,Z mixture with 70% yield. Then, compound **3** was reacted with benzylamine in the presence of anhydrous MgSO under microwave irradiation (MWI) at 70 5 to complete imine

compound **4** which was not isolated but then methyl butanoate was added to the reaction mixture in the same container and exposed again to MWI to obtain products Aza–Diels–Alder **6** and **7** as a mixture in a combined yield of 45%. Reversed-phase HPLC analysis of the reaction mixture confirmed the compound **6** was regioselectively formed over **7** with a ratio of 7 : 3. The structure of the main product **6** was described by its spectroscopic data with authentic samples prepared by classical Hantzsch reaction followed by N-benzylation. Subsequently, the side chain at C-2 in amlodipine **9** was successfully introduced via a procedure patented by the Pfizer company[15]. Product **6** was obtained by the Aza-Diels-Alder reaction on treatment with formic acid followed by re-uxing of the reaction mixture in the presence of Pd/C resulting in the removal of a benzyl group which was then brominated with pyridinium tribromide to give the corresponding bromo compound. It was found that only the C-2 position was selectively brominated over the C-6 position[16]. The reaction of the bromo compound with 2-azidoethanol in the presence of the sodium hydride of the compound provided **8** in two steps yields good overall results. Finally, reduction of the azido group using zinc dust to the amine was achieved to give the desired amlodipine **9** with satisfactory results[17].

PRECLINICAL DEVELOPMENT

Pharmacology

Pharmacological processes that occur in healthy volunteers after being given amlodipine. Amlodipine is administered orally and is slowly absorbed from the human gastrointestinal tract, evenly distributed in tissues and binding to plasma proteins, the volume of distribution (Vd) of amlodipine is relatively large, averaging 21 L/kg after intravenous administration[18]. Amlodipine is extensively metabolized in the liver, but there is no significant pre-systemic or first pass metabolism and is slowly cleared with a terminal elimination half-life of 40-60 hours19[and] is excreted in the urine[20].

A single intravenous dose of 10 mg produces an absolute bioavailability of 64% and a calculated half-life elimination of 34 hours[21]. Amlodipine is effective for 24 hours after a single oral dose and Amlodipine has also been shown to have natriuretic and diuretic properties, which may affect its ability to reduce blood pressure without provoking fluid retention[22]. Amlodipine is highly effective for the treatment of hypertension and stable angina as evidenced by fewer hospitalizations for unstable angina and revascularization in randomized controlled trials. Amlodipine also showed a strong reduction in CV endpoints (mainly stroke) but did not alter the prognosis in heart failure[12].

In Silico Test

This test is a method that utilizes computational technology and databases to develop further research, such as: The results of research using Swiss modeling tools, Sopma software, iGemdock and Hex software show that amlodipine besylate has the best binding energy[23].

In Vitro Test

This test is a preclinical test on isolated cell cultures or isolated organs, some of the research results are as follows:

Plasma protein proteolysis by incubating plasma for 2 hours in pepsin solution: Amlodipine was measured using a dual-wavelength TLC scanner, This method provides a direct estimate of the total plasma amlodipine[24]. Pig aortic segments (n = 8) were pre-incubated in oxygenated pancreatic elastase for 24h before culture under standard conditions for 6 days and 100 g/l amlodipine showed control segments were cultured with or without amlodipine[25].

In Vivo Test

This test is a preclinical test conducted on whole animals. Some of the research results are as follows:

Amlodipine at a dose of 10 mg/day/kg given to rats has no significant effect on a tocopherol level in plasma or heart tissue in rats[26]. Amlodipine at a dose of 0.12-0.21 mg/kg given to cats is effective and has been shown to be an antihypertensive agent[27]. In mice treated with amlodipine 15 mg kg^{-1} day^{-1} orally for one week showed that mice with amlodipine prevented the decrease in vascular response induced by LPS[28].

Toxicity Test

This test is a test to detect the toxic effect of a substance on a biological system, some of the research results are below:

Amlodipine and curcumin were injected intraperitoneally; no side effects were observed after concurrent administration[29]. The effect of amlodipine of 0.1-3.0 mg/kg on suppressed rats, amlodipine was administered to two groups of rats consuming alcohol: one group that regularly consumed sweetened alcoholic beverages and the other consumed unsweetened alcoholic beverages. The only effect of amlodipine seen on alcohol intake was associated with the highest dose and only with rats consuming sugary drinks. The effect of this high dose can easily be attributed to the behavioral toxicity evoked by the dose[30].

Hepatotoxicity Test

Hepatotoxicity is a condition in which liver cells are damaged by toxic chemicals, such as the results of the amlodipine study below: An 87-year-old woman was treated with amlodipine (Norvasc®) for several years for hypertension. One month before he was admitted to the hospital, he developed pruritus and 2 weeks later painless jaundice. Abdominal CT showed a normal, homogeneously structured liver without focal injury and abdominal sonography excluded cholelithiasis. Laboratory tests exclude viral or autoimmune hepatitis and show (upper limit of normal). Liver biopsy showed severe intra-hepatocellular and canalicular cholestasis with moderate inflammatory infiltrate without necrosis, consistent with drug-induced liver damage. After discontinuation of amlodipine, transaminases and cholestatic parameters decreased sharply; within 2 weeks the multimorbid patient died from pulmonary embolism[31].

Teratogenicity test

This test aims to obtain information on fetal abnormalities that occur due to administration of amlodipine during the formation of fetal organs (organogenesis period), such as:

The results show that amlodipine at high concentrations can cause a decrease in parthenogenetic activation and inhibit early embryonic development in mice[32].

CLINICAL TESTING

Phase I

Phase I is the phase in which the drug is tested on healthy volunteers to see if the traits observed in experimental animals are also seen in humans. The amlodipine drug has gone through phase I involving 12 healthy volunteers. Healthy volunteers were given a single dose of 10 mg intravenous amlodipine, trials showed that there were no side effects[33].

Phase II

Phase II is the phase in which the drug is tested on about hundreds of patients, observing its efficacy in the disease being treated. Amlodipine phase II involved 425 hypertensive patients with a daily dose adjusted as needed up to a maximum of 10 mg. After 8 weeks of treatment, the cure rates and therapeutic efficacy with side effects are generally mild, and the overall prevalence is relatively low[34].

Phase III

Phase III involves large groups of patients consisting of about thousands of people and comparing their effects and safety with known comparison drugs. In this phase amlodipine and perindopril test involved 19,257 patients with doses of drugs as needed. Experimental results show that it can reduce mortality and stroke[12].

Phase IV

After the drug is marketed, post-marketing surveillance studies are still being conducted which are observed in patients with various conditions, ages, and races. This research was conducted over a long period of time to see the therapeutic value of a drug. In this phase, laboratory data was monitored involving 88 patients given amlodipine and perindopril, of which 83 patients recovered, 4 patients did not recover, and 1 patient had a fatal hypertensive crisis[35].

Biological Tests

Biological tests or BioAssays are a step in drug discovery. The tests performed usually focus on a drug target such as a cell, protein, gene, or biopharmaceutical. The results showed that the peak concentration and the area under the plasma concentration curve were log transformed and analyzed to obtain a 90% confidence interval. Peak time was analyzed according to a non-parametric test. The mean terminal half-life of amlodipine is approximately 40 hours, which indicates that plasma concentrations should be followed over a 6-day period in bioavailability studies. The bioequivalence test was performed on 18 healthy volunteers (9 males and 9 females). Subjects were given a single dose of 10 mg[36].

Stability Test

This test aims to determine the ability of an amlodipine product to survive within the specified limits during storage and use, some research results are as follows:

Amlodipine, which is formulated in capsule form, was stable at 40 ± 2°C and 75 ± 5% RH during three months[37]. Amlodipine formulated in Dissolving Tablets (FDT) was stable at 40°C and 75% RH for six months[38]. Amlodipine, which was formulated in the form of blister pack tablets, was stable at a temperature of 40 ± 2 °C and a RH of 75 ± 5% for five months in the stability chamber[39].

Formulation

Amlodipine formulation from several research results:

Amlodipine formulation which is made in tablet form in 5 mg and 10 mg once a day dosages is well tolerated and there are no serious side effects in hypertension[40]. Amlodipine formulations in capsule form can provide rapid dissolution but require some time to initiate release[37]. Orally Dissolving Film (ODF) formulation uses sodium alginate as a polymer film and sodium starch glycolate as a disintegrant. The study was carried out at pH 6.2 and it was observed that the sodium alginate film on the tablets started to disintegrate within 30 seconds and almost 75-80% of the drug was released after 6 minutes in all formulation[41]. The suspension formulation has been successfully used by (Rivero) in the treatment of a 5 year old girl with hypertension[42]. Nanoemulsion formulation to obtain enhanced bioavailability and drug delivery of amlodipine[43]. Topical formulation in the form of a gel containing dexamethasone (0.3%) and amlodipine (0.5%) for drug penetration in the flap tissue through the excised rat skin. It was observed that the compound gel containing both drugs could penetrate into the skin tissue which could significantly increase the viability of the ischemic skin flap[44]. Amlodipine has antioxidant properties and plays an important role in apoptosis[45]. Because of this activity, targeted delivery of amlodipine in liposome preparations, either alone or in combination with other drugs, has been used by a wide variety of people with significant success[46]

CONCLUSION

Amlodipine is approved to treat high blood pressure and angina, it was first patented in 1982 by Hantzsch but it was approved as a prescription drug in 1990. After being marketed amlodipine was still subject to several trials such as clinical trials, preclinical trials, and in silico trials with promising results. This drug is non-toxic, so it is effective and safe to fight hypertension and angina.

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