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RESEARCH ON ENHANCING THE SOLUBILITY OF 8mg CANDESARTAN TABLETS

Vo The Anh Tai[*1,2], **Ngo Thi My Tien**[2]
Nguyen Thi Hoai Thuong[2] and **Tran Van Thanh**[1]

[1] *Faculty of Pharmacy,*
University of Medicine and Pharmacy at Ho Chi Minh City,
Ho Chi Minh City, Vietnam

[2] *Faculty of Pharmacy,*
Nguyen Tat Thanh University,
Ho Chi Minh City, Vietnam
e-mail: vtatai@ntt.edu.vn

Abstract

Candesartan cilexetil is a prodrug of angiotensin II receptor blocker (ARB). It is an effective antihypertensive but it has poor water solubility, resulting in low oral bioavailability. Research objective: enhancing the solubility of candesartan cilexetil to improve the bioavailability of the drug. Research method: to use a solid dispersion system to increase the solubility of candesartan cilexetil, thereby improving the bioavailability of the drug. Research results: The solid dispersion was successfully prepared by using polyethylene glycol 4000 (PEG 4000) as a hydrophilic carrier with a drug-to-polymer ratio of 1:3. The formulation (F8) consisted of candesartan cilexetil (8 mg), PEG 4000 (24 mg), sodium starch glycolate (8 mg), FlowLac 100 (116.8 mg), and a lubricant blend of magnesium stearate and talc (1.6 mg of each). Comparative in vitro dissolution testing showed that the F8 exhibited significantly increased active substance release compared to several generic products and it was comparable to ATACAND®. The research confirms that the solid dispersion method is a potential method for improving the biopharmaceutical performance of poorly water-soluble drugs.

Key words: solubility, candesartan cilexetil, candesartan 8 mg, tablet.
(*)Corresponding author: Vo The Anh Tai (email: vtatai@ntt.edu.vn)

1 Introduction

Candesartan cilexetil is a prodrug; during absorption through the gastrointestinal tract, it is completely metabolized and converted into its active form, candesartan. The medicine functions by inhibiting the non-peptide angiotensin II receptor, which is effective in treating mild, moderate, or severe hypertension, either alone or in combination therapy [1]. Candesartan cilexetil has been studied for its good tolerance in various patient groups, such as those with idiopathic hypertension in the elderly, severe hypertension, or hypertension accompanied by renal impairment, without increasing risk factors, and it offers protective effects for target organs [2]. Thus, candesartan cilexetil is the preferred drug for treating hypertension. However, the disadvantages of candesartan cilexetil include its lipophilicity and poor water solubility, which result in limited oral bioavailability (about 40%) [3]. This study aims to improve the solubility of candesartan cilexetil to enhance its oral bioavailability. One of the solutions developed by Chiou and Reigelman to improve the solubility of weakly water-soluble drugs is the solid dispersion [4]. In a solid dispersion system, the active ingredient exists in an amorphous form within polymer carriers, which increases the drug's dissolution rate compared to its crystalline form. Furthermore, this method improved the permeability of the active ingredient, thereby significantly increasing its bioavailability compared to conventional formulations. For these reasons, the authors conducted a study titled "Research on Enhancing the Solubility of 8 mg Candesartan Tablets" in which candesartan cilexetil was incorporated into a solid dispersion system with hydrophilic polyethylene glycol 4000 as the carrier. This approach aims to improve the solubility and enhance the bioavailability of the drug.

2 Materials and Methods

2.1 Materials and Instruments

Materials: candesartan cilexetil, croscarmellose sodium, sodium starch glycolate, lactose, Avicel PH102, polyethylene glycol 4000 (PEG 4000), magnesium stearate, and talc were sourced from China. FlowLac 100 was sourced from the USA. All materials passed quality standards. Chemicals used for analysis and testing met purity standards. Instruments: Riva Minipress 0001 single punch tablet press (Germany), Pharmatest Ptws 820D dissolution testing system (Germany), Shimazu UV-1900I dual-beam spectrophotometer (Japan), Ohaus MB45 moisture tester (USA), Erweka GTL flow tester (Germany), Pharmatest PTB311E hardness tester (Germany), Gouming CS-2 friability tester (China), Erweka ZT1220001 2-hour automatic disintegration tester (Germany).

2.2 Methods

2.2.1 Formulation method for the Solid Dispersion System containing Candesartan Cilexetil Candesartan cilexetil was transformed into an amorphous form within a solid dispersion system using PEG 4000 as the carrier by the melting method. Procedure: the hydrophilic carrier PEG 4000 was melted at approximately 80°C to form a clear liquid, into which candesartan cilexetil was added and completely dissolved to create the dispersion system. During natural cooling, a portion of filler excipients was added to reduce the waxy and solidified texture of the solid dispersion, which improved the flow properties of the formed granules and lowered content loss. The active ingredient to carrier ratios evaluated in the study were 1:8, 1:4, and 1:3. The filler excipients examined included lactose, Avicel PH102, and FlowLac 100.

2.2.2 Tablet formulation method The 8 mg candesartan cilexetil tablets were formulated using the direct compression method: the required amount of granules (solid dispersion system) and excipients were weighed according to the formulation and mixed thoroughly using the geometric dilution principle. Subsequently, the lubricants were added, and the mixture was compressed into tablets weighing 160 mg each using an 8 mm diameter punch with a breaking force ranging from 50 N to 80 N . **2.2.3 Quality standard evaluation methods**

2.2.3.1 Quality evaluation of semi-finished granules Moisture Content: the moisture content of the semi-finished granules was determined using the Ohaus MB45 (USA) moisture analyzer. Flowability: the flow rate of the semi-finished granules was assessed by an Erweka GTL flow tester (Germany) with a 10 mm diameter funnel. The flow rate was calculated using the formula: $v = \frac{m}{t}$

In which: v: flow rate (g/second)

m: mass of semi-finished granules (g)

t: flow time (second)

Apparent density: the apparent density of the granules and powder was calculated using the following formula:

$$d = \frac{m}{v}$$

In which:

d: apparent density (g/mL)

V: volume of the granules or powder after tapping (mL)

m: mass of the granules or powder (g)

2.2.3.2 Quality evaluation of tablets Physical characteristics: the tablets were white with smooth, glossy surfaces. Tablet breaking force: the breaking force of the tablets was measured using the Pharmatest PTB311E hardness tester (Germany). this test was conducted on ten randomly selected tablets, and the average value was recorded. Friability: friability was measured using the Gouming CS-2 friability tester (China). The procedure involved selecting

20 random tablets, wiping off any dust, and weighing them (m1). The tablets were then placed in the friability drum and rotated 100 times at a speed of 25 revolutions per minute. Following rotation, the tablets were removed, dusted off, and reweighed (m2). The friability was calculated using the following formula:

$$X(\%) = \frac{m_1 - m_2}{m_1} \times 100$$

In which: X: friability (%)

m_1: mass of tablets before friability test (g);

m_2: mass of tablets after friability test and de-dusted (g).

Weight uniformity: The weight uniformity of the tablets was evaluated according to Appendix 11.3 of the Vietnamese Pharmacopoeia V [5].

Twenty randomly selected units were individually weighed. The average mass was computed, and the permitted difference limit was determined in accordance with the regulations. *Disintegration test:* based on the guidelines of Appendix 11.6 - Vietnamese Pharmacopoeia V [5].

Tablet disintegration was assessed by using an Erweka ZT1220001 2-hour automatic disintegration tester (Germany). The test was conducted in 500 mL of a pH 6.5 buffer solution with 0.35 % tween 20 at 37 ± 2 °C. Quantification of Candesartan Cilexetil in Tablets: based on the Guidelines of United States Pharmacopoeia 46 [6].

Sample Preparation: weigh ten tablets to get an average weight, then grind them into a fine powder. Transfer an amount of powdered tablets equal to about 10 mg of candesartan cilexetil to a 250 mL volumetric flask. Add a pH 6.5 buffer solution with 0.35% tween 20 to about two-thirds of the volumetric flask. Sonicate the mixture for approximately 30 minutes to completely dissolve the active ingredient. Fill the volumetric flask to volume with the buffer solution and mix well. Pipette 5 mL of the solution into a 25 mL volumetric flask, add the buffer solution, mix thoroughly, and filter through a 0.45 μm millipore filter.

Standard Preparation: weigh out approximately 10 mg of candesartan cilexetil and transfer it to a 250 mL volumetric flask. Add a pH 6.5 buffer solution with 0.35 % tween 20 to about two-thirds of the volumetric flask. Sonicate the mixture for about 30 minutes to completely dissolve the active ingredient. Fill the volumetric flask to volume with the buffer solution and mix well. Pipette 5 mL of the solution into a 25 mL volumetric flask, add the buffer solution, mix thoroughly, and filter through a 0.45 μm millipore filter.

Blank Preparation: use a pH 6.5 buffer solution with 0.35 % tween 20.

Measurement: measure the absorbance of the solutions at the maximum wavelength of 258 nm using a 1 cm path length cuvette. The concentration of candesartan cilexetil in the sample solution is calculated by comparing its absorbance with that of the standard solution. Dissolution Test: based on

the Guidelines of Appendix 11.4 – Vietnamese Pharmacopoeia V [5]. The active ingredient's release from candesartan cilexetil tablets is evaluated by the PHARMATEST PTWS 820D dissolution testing system (Germany) with the following fixed parameters:

- Apparatus: paddle method
- Stirring speed: 50 rpm - Dissolution medium: 900 mL of pH 6.5 buffer solution with 0.35 % tween 20
- Medium temperature: 37 ± 0,5°C
- Sampling times: 5, 10, 15, 30, 45, 60 minutes. - Wavelength for analysis: 258 nm.

The formula to calculate the percentage of the active ingredient content in the dissolution test is as follows:

$$\%\ of\ drug\ release = \frac{A_T}{A_S} \times C_S \times P \times d_T \times \frac{m_{lt}}{m_{tt}} \times \frac{100}{8}$$

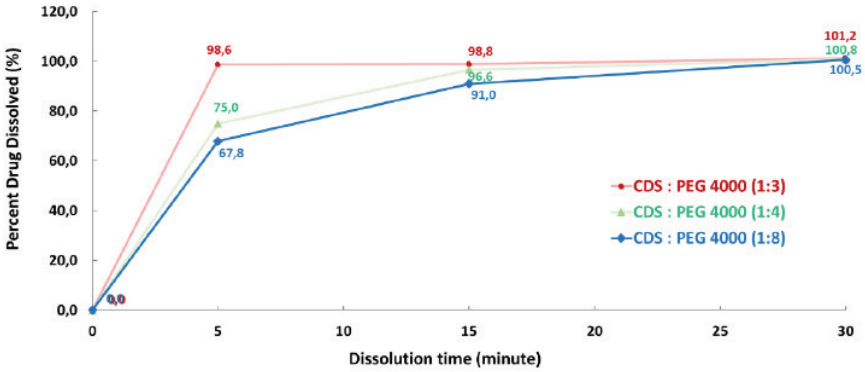
A_T: absorption of test sample
A_S: absorption of standard sample
C_S : concentration of standard sample (mg/ml)
d_T : dilution of standard sample
P: purity of the standard sample (%)
m_{lt}: theoretical mass of pellets (mg)
$m_{tt:}$ actual mass of pellets (mg)
8: drug content stated on the labeled (mg)

3 Results and Discussion

3.1 Investigation of the carrier ratio in the solid dispersion system

Candesartan cilexetil, a lipophilic drug, was incorporated into a solid dispersion system to transform it from a crystalline to an amorphous state, increasing its solubility and dissolution rate. PEG 4000 was chosen as the hydrophilic carrier due to its safety, compatibility, and melting point of around 80 ℃, which is suitable to improve the dissolution rate of poorly water-soluble drugs. The study investigated the ratios of candesartan cilexetil to PEG 4000 at 1:8, 1:4, and 1:3. The dissolution results of the active ingredient from the formulations were evaluated in a pH 6.5 buffer solution with 0.35 % tween 20, Figure 1. Based on the dissolution study results of the solid dispersion system, it was obvious that a 1:3 ratio of candesartan to PEG 4000 achieved the most effective release of the active ingredient, reaching approximately 98 % at the 5-minute mark, outperforming other ratios. As a result, the ratio of 1:3 has been chosen to formulate the solid dispersion system for candesartan cilexetil 8 mg tablet production.

Figure 1. Enhancement of active ingredient release in the solid dispersion system CDS : PEG 4000 at investigated ratios



3.2 Investigation of the influence of excipients

The solid dispersion system, which used PEG 4000 as the carrier, significantly improved the dissolution rate of candesartan cilexetil. However, post-formulation, the physical properties of the solid dispersion in its dry wax state, along with high adhesion, caused challenges in the granulation process, influencing tablet disintegration. Thus, several excipients were investigated to overcome the limits of the solid dispersion system, including Avicel PH102, lactose, FlowLac 100, and common super-disintegrants such as croscarmellose sodium (CCS) and sodium starch glycolate (SSG).

Table 1. Preliminary investigated formulation components (F1 - F5)

Composition / Formulation	CDS : PEG 4000 (1:3) (mg)	Avicel PH102 (mg)	Lactose (mg)	FlowLac 100 (mg)	CCS (mg)	MgS : Talc (1:1) (mg)
F1	32 (equivalent to 8 mg candesartan cilexetil)	118.8	-	-	6	1.6:1.6
F2		59.4	59.4	-	6	1.6:1.6
F3		-	118.8	-	6	1.6:1.6
F4		59.4	-	59.4	6	1.6:1.6
F5		-	-	118.8	6	1.6:1.6

After producing the solid dispersion system using candesartan cilexetil and PEG 4000 in a 1:3 ratio and cooling the mixture after melting, the relevant filler excipients for each formula were added in an amount twice that of the carrier.

Granules were prepared by sieving through a 1 mm mesh, and the remaining excipients were mixed following the principle of geometric dilution. A lubricant was added, and tablets were compressed using the direct compression method with a tablet weight of 160 mg and a punch diameter of ϕ= 8 mm.

The results showed:

- Tablets formulated according to F2 and F3 using lactose as the filler exhibited poor appearance (prone to discoloration, causing the tablets to yellow).

- Tablets formulated according to F1 with Avicel PH102 and F4 – F5 using FlowLac 100 showed substantial improvement (smooth, white, no discoloration).

The dissolution of the five tablet samples was shown in Table 2 and Figure 2. The dissolution test results showed that formulation F1, which used the ver-

Table 2. Dissolution parameters of candesartan cilexetil in tablet samples F1 - F5 compared to the reference drug

Tablet samples	Dissolution (%)				
	5 min	15 min	30 min	45 min	60 min
F1	6.0	9.3	20.7	21.4	25.2
F2	16.7	35.7	81.4	87.8	94.6
F3	28.2	77.3	81.6	89.3	91.5
F4	23.5	45.8	82.3	90.8	95.5
F5	31.4	80.9	88.6	95.6	95.9
ATACAND®	41.6	93.2	100.0	-	-

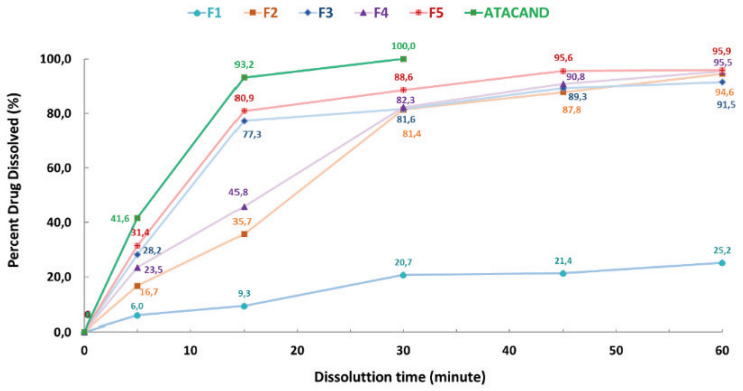


Figure 2. The dissolution of candesartan cilexetil in formulations F1 - F5 compared to the reference drug.

satile excipient Avicel PH102, widely used and suitable for direct compression, exhibited poor disintegration when combined with the solid dispersion system. This had a significant influence on the drug's solubility, releasing only about 25 % of the active ingredient after 60 minutes. In formulations F2 - F4, the drug dissolution rate remained slow at 5 minutes (less than 30 %) and at 15 minutes (less than 80 %). The drug release improved significantly in formulation F5 with the use of FlowLac 100 alone (88,6 % at 30 minutes and over 95 % at 60 minutes); however, this formulation still did not achieve dissolution equivalency with the reference drug. Therefore, the study proceeded to investigate another super-disintegrant, sodium starch glycolate (SSG), aiming to enhance both the dissolution rate and the extent of candesartan cilexetil dissolution in the solid dispersion system.

Table 3. Composition of formulations investigating disintegrants (F5 - F6)

Composition / Formulation	CDS : PEG 4000 (1:3) (mg)	FlowLac 100 (mg)	CCS (mg)	SSG (mg)	MgS : Talc (1:1) (mg)
F5	32 (equivalent to 8 mg candesartan cilexetil)	118.8	6	-	1.6:1.6
F6		118.8	-	6	1.6:1.6

Observation: When substituting the disintegrant CCS with SSG, formulation F6 achieved the targets for moisture content and flowability. Tablets were compressed with a weight of 160 mg using a punch diameter of 8 mm using the direct compression method, and dissolution testing was performed. The results were shown in Table 4 and Figure 3.

Table 4. Dissolution parameters of candesartan cilexetil in tablet samples F5 - F6.

Tablet samples	Dissolution (%)				
	5 min	**15 min**	**30 min**	**45 min**	**60 min**
F5	31.4	80.9	88.6	95.6	95.9
F6	41.5	88.6	99.7	-	-

The solubility test findings for formulations F5 - F6 showed that applying the disintegrant SSG greatly improved the dissolution of the active component. Specifically, at the 30-minute mark, the drug completely dissolved (99.7%). According to reference sources, the concentration of SSG in formulations typically ranges from 2 % to 8 % [7]. Therefore, the study will further investigate the amount of SSG excipient to determine the suitable concentration for achieving

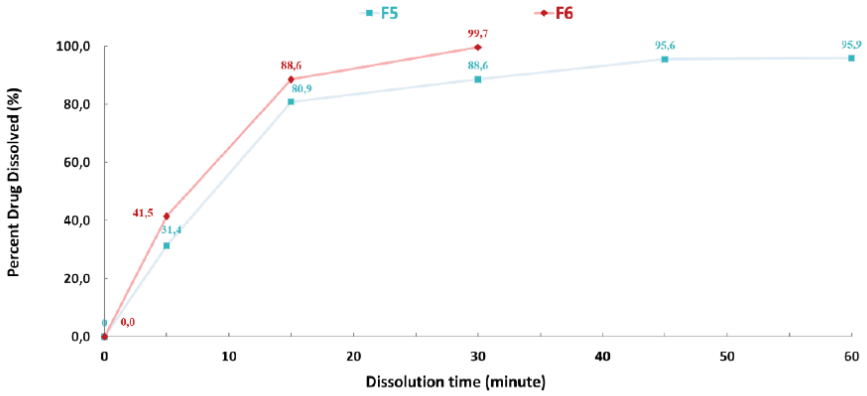


Figure 3. The dissolution of candesartan cilexetil in formulations F5 – F6

the best dissolution rate in the tablets.

Table 5. Composition of formulations investigating disintegrants (F6 - F9)

Composition / Formulation	CDS : PEG 4000 (1:3) (mg)	FlowLac 100 (mg)	SSG (mg)	MgS : Talc (1:1) (mg)
F7	32 (equivalent to 8 mg candesartan cilexetil)	120.8	4	1.6:1.6
F6		118.8	6	1.6:1.6
F8		116.8	8	1.6:1.6
F9		114.8	10	1.6:1.6

Table 6. Dissolution parameters of candesartan cilexetil in tablet samples F6 - F9 compared to the reference drug.

The dissolution results indicated that formulation F8 (using 8 mg of FlowLac 100) exhibited the best release of the active ingredient and was equivalent to the reference drug. The formulation with a 5 % disintegrant concentration per tablet significantly enhanced disintegration at the 5-minute mark, with approximately 46 % drug release, achieving completed dissolution at 30 minutes. Based on these findings, the study proposed the following formulation for manufacturing candesartan cilexetil 8 mg tablets, with the specified components per tablet:

Table 6. Dissolution parameters of candesartan cilexetil in tablet samples F6 - F9 compared to the reference drug.

Tablet samples	Dissolution (%)		
	5 min	15 min	30 min
F6	41.5	88.6	99.7
F7	44.1	89.7	99.9
F8	46.7	96.3	100.7
F9	44.7	91.5	100.4
ATACAND®	41.6	93.2	100.0

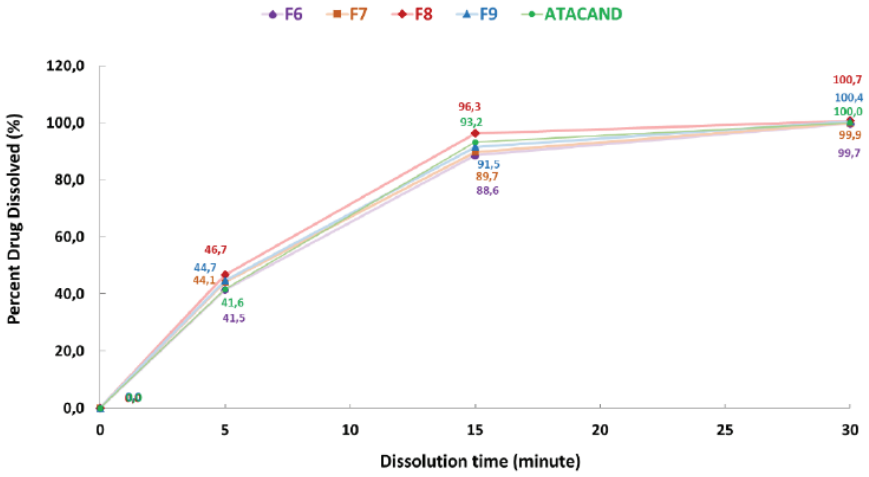


Table 7. The formulation composition for manufacturing candesartan cilexetil 8 mg tablets

Composition	Weight (mg)
Candesartan cilexetil	8
Polyethylene glycol 4000	24
Sodium starch glycolate	8
FlowLac 100	116.8
Magnesium stearate : Talc (1:1)	1.6:1.6
Total	160

3.3 Evaluation of quality parameters of solid dispersion containing candesartan cilexetil 8 mg tablets

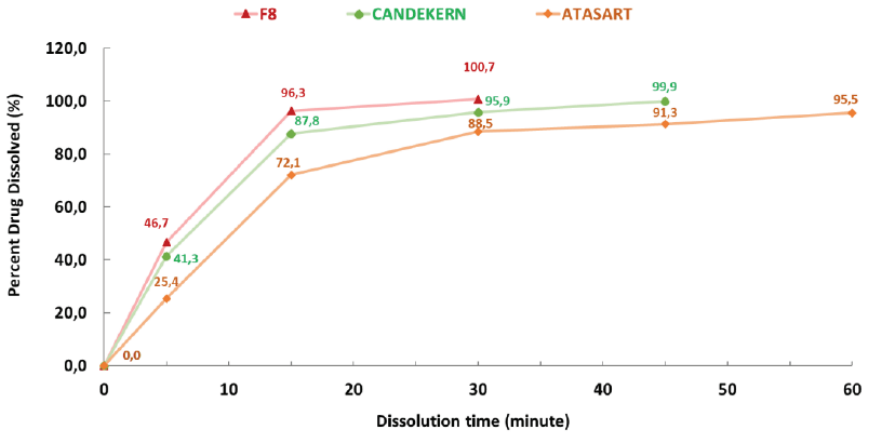
One hundred candesartan cilexetil 8 mg tablets were prepared according to the most efficient formulation identified in Section 3.2. The evaluation of several quality parameters of the resulting tablets yielded the following results: the tablets met visual inspection criteria, disintegration time was not more than 15 minutes, uniformity of weight complied with Vietnamese Pharmacopoeia standards, average hardness was approximately 64 N, friability was less than 1 %, and the content of candesartan cilexetil in the tablets averaged 100 %. Based on these findings, the study proposed several fundamental standards for the finished product of candesartan cilexetil 8 mg tablets containing solid dispersion, as presented in Table 8.

3.4 Evaluation of the formulation's effectiveness compared to marketed products

Candesartan cilexetil medications have been available on the market under various brand names. To assess the effectiveness of the research formulation targeted at improving candesartan cilexetil dissolution, an evaluation of the dissolution profiles of certain products, such as CandeKern (from Spain) and Atasart (from Pakistan), each containing 8 mg of candesartan cilexetil, was conducted. The purpose of this comparison was to establish the extent to which the study formulation improved medication solubility when compared to commercial products. The results of the dissolution tests of candesartan cilexetil tablets in formulations F8 compared to the surveyed medications were

Criteria	Requirement
Tablet properties	Smooth, glossy white tablet
Tablet breaking force	50 N – 80 N
Disintergration time	Not exceeding 15 minutes
Friability	Less than 3 %
Uniformly of tablet weights	± 5 %
Content per tablet	95.0 % - 105.0 %
Dissolution rate	After 45 minutes, the drug releases over 80 %

presented in Table 9 and Figure 5.



According to the dissolution test results, the research formulation demonstrated better drug release efficacy compared to other products on the market, such as Atasart and CandeKern. At the 15-minute mark, the F8 formulation released up to 96.3 % of the active ingredient, and achieved complete release at the 30-minute mark. Meanwhile, at the 15-minute and 30-minute marks, Atasart and CandeKern drugs released lower amounts of active component. Thus, the tablets formulated using the best formula (F8) met the research goal of enhancing the drug's solubility.

4 Conclusion

From the above results, several conclusions can be drawn: The study successfully developed a solid dispersion system containing 8 mg of candesartan cilexetil with PEG 4000 as the carrier at a ratio of 1:3 and granulated with the filler excipient FlowLac 100. Candesartan cilexetil 8 mg tablets were formulated according to formula F8, with the active ingredient candesartan cilexetil (8 mg) and excipients including polyethylene glycol 4000 (24 mg), sodium starch glycolate (8 mg), FlowLac 100 (116.8 mg), magnesium stearate:talc (1.6:1.6 mg), met the standards for hardness, friability, weight uniformity, and content as per reference compendia (Vietnamese Pharmacopoeia V and United States Pharmacopeia 46). The formulation greatly improved the drug's dissolution compared to conventional tablets, and it was equivalent to the reference drug ATACAND®.

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