DEVELOPMENT OF A COMBINATION TABLET TO TACKLE THE DRUG RESISTANCE OF ORAL CANDIDIASIS

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ABSTRACT

Candida infections, particularly those caused by *Candida albicans*, pose significant health risks, especially due to increasing antifungal resistance. Fluconazole, a commonly used antifungal, is losing efficacy against resistant strains, necessitating new treatment strategies. This study aims to develop and evaluate tablets combining ibuprofen and fluconazole to address fluconazole-resistant *candidiasis*. Fluconazole and ibuprofen were formulated into tablets using wet granulation. Various excipients and superdisintegrants were tested to optimize tablet properties. The final formulation was assessed for flowability, compressibility, and quality control specifications. Antifungal susceptibility was tested *in vitro* against fluconazole-sensitive and fluconazole-resistant *C. albicans* strains. The optimal tablet formulation contained 150 mg fluconazole, 50 mg ibuprofen, Avicel PH-101, PVP K30, sodium croscarmellose, and magnesium stearate. Quality control tests showed compliance with pharmacopoeia standards, including hardness, friability, and disintegration time. Antifungal testing revealed that the combination tablets-maintained activity against fluconazole-sensitive strains and exhibited significant antifungal effects against fluconazole-resistant strains, demonstrating a synergistic interaction. This study successfully developed a combination tablet of fluconazole and ibuprofen that is effective against fluconazole-resistant *C. albicans*. The findings support the potential of this combination therapy for treating resistant *candidiasis*, warranting further clinical investigation.

Keywords: *Candida albicans, fluconazole, ibuprofen, tablets.*

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I. INTRODUCTION

Candida infection represents a prevalent opportunistic infection triggered by the proliferation of various *Candida* species, with *Candida albicans* emerging as the most frequently encountered pathogen. Statistical data from 2006 to 2016 highlights the dominance of *C. albicans* in infection rates [1]. The consequences of antifungal drug resistance are severe, as illustrated by a global study in 2017, which estimated the annual incidence of systemic *Candida* infections to be 700,000 cases with a mortality rate nearing 50% [2]. The trend of *C. albicans* strains developing resistance to antifungal drugs poses a significant threat to immunocompromised patients, increases treatment costs, and adds an economic burden on healthcare systems [3]. Consequently, by 2022, the World Health Organization (WHO) classified *C. albicans* as a fungal strain requiring prioritized research and development of new treatments [4]. This underscores the global urgency to address the issue of antifungal resistance.

The mechanism of action of current antifungal drugs includes inhibition of the enzyme 14-alpha-demethylase (azole group) to prevent the synthesis of ergosterol in fungal cell membranes, and selective binding

to ergosterol to increase fungal cell membrane permeability (polyene group). Additionally, the echinocandin group of antifungal drugs inhibits the enzyme β-(1,3)-D-glucan synthesis in fungal cell walls. Among these, the azole group, particularly fluconazole, is commonly used to treat *Candida* spp. infections due to its high effectiveness, urinary excretion, and convenient oral administration [5]. However, the incidence of fluconazole-resistant *Candida* spp. has been increasing. In 2012, the United States reported a low fluconazole resistance rate in *C. albicans* of about 0.5-2%. By 2020, the US Centers for Disease Control and Prevention (CDC) reported that approximately 7% of blood samples isolated fluconazole-resistant *Candida*, with *C. albicans* being among the isolated strains [6]. In Vietnam, a 2016 study on candidemia in the Asia-Pacific region recorded *C. albicans* as the causative agent in 39.9% of cases [7]. By 2021, descriptive cross-sectional studies indicated that 18.6% of patient samples isolated *C. albicans*, with only 19.4% of these strains remaining susceptible to fluconazole [8]. Despite these alarming trends, there are currently few drugs available to effectively treat fluconazole-resistant *Candida* spp.

Significant research efforts have focused on finding solutions to to tackle the drug resistance of *Candidiasis*. Notably, the combination of fluconazole with other agents, such as antibiotics, calcineurin inhibitors, calcium homeostasis regulators, and NSAIDs, has shown promise [9]. Specifically, studies have demonstrated that fluconazole and ibuprofen exhibit a synergistic effect in reducing the minimum inhibitory concentration (MIC) of fluconazole against *Candida* spp. [10-12]. Although fluconazole tablets are among the most commonly used dosage forms for treating *Candida* infections, no research has yet investigated tablets combining these two active ingredients. Therefore, the objective of this study is to develop a formulation and preparation process for tablets containing both ibuprofen and fluconazole, and to evaluate the antifungal activity of these preparations in anticipation of future clinical studies.

II. MATERIALS AND METHOD

2.1 Materials

Fluconazole, ibuprofen, Avicel PH-101, PVP K30, sodium croscarmellose, sodium starch glycolate, crospovidone, magnesium stearate, and ethanol were provided by Boston Pharma Vietnam, Ho Chi Minh City, Vietnam and met the pharmaceutical grade.

2.2 Developing Formulas and Processes

Evaluation of raw material properties

Potential incompatibility between APIs and excipients

To assess the potential incompatibility between the active ingredients and excipients, a powder mixture was prepared. The composition of the mixture included the following: 0.3 g fluconazole, 0.1 g ibuprofen, 0.4 g lactose monohydrate, avicel PH-101, 0.05 g PVP K30 (Polyvinylpyrrolidone), 0.03 g sodium croscarmellose, 0.03 g sodium starch glycolate, 0.03 g crospovidone, and 0.02 g magnesium stearate.

The components were thoroughly mixed to ensure homogeneity. The resulting mixture was divided and stored under two different environmental conditions to evaluate the stability and potential interactions between the ingredients. The storage conditions were as follows: 40 °C / 75% Relative humidity

(RH) and 30 °C / 75% Relative humidity (RH). The mixtures were monitored for sensory changes, such as color, texture, and odor, over a two-week period. This evaluation aimed to identify any physical or chemical incompatibilities that could affect the stability and efficacy of the final tablet formulation.

These observations provide critical insights into the suitability of the chosen excipients and the stability of the active ingredients under different storage conditions, thereby informing the optimization of the tablet formulation process.

Flow and compression behavior of APIs

To assess the flow and compressibility of the powder mixture, fluconazole and ibuprofen were combined in a 3:1 ratio. The mixture was blended thoroughly to ensure uniform distribution of the APIs. The evaluation of the powder's flowability and compressibility involved the following tests:

- Flowability assessment: The angle of repose (α) was measured to determine the powder's flow characteristics. A lower angle of repose indicates better flowability. The measurement was performed by allowing the powder to flow through a funnel and forming a cone on a flat surface. The angle formed between the surface and the slope of the cone was recorded as the angle of repose.

- Compressibility assessment:

• The Carr's index (CI) was calculated to evaluate the compressibility of the powder. A lower Carr's Index indicates better compressibility. This index is derived from the bulk density (ρ_{bulk}) and tapped density (ρ_{tap}) of the powder:

Carr's index (%) =(ρtap−ρbulk ρtap Carr's index (%) =($\frac{\rho_{tap}-\rho_{bulk}}{\rho_{tap}}$) ×100

• Hausner ratio (HR): The Hausner Ratio, another indicator of compressibility, was also calculated using the bulk and tapped densities. a lower Hausner Ratio suggests better flowability and compressibility.

$$\text{Hausner ratio} = \frac{\rho_{tap}}{\rho_{bulk}}$$

These assessments provide crucial data on the powder mixture's suitability for tablet formulation, ensuring that the mixture flows well and compresses adequately during the tableting process. This information is essential for optimizing the formulation to achieve consistent and high-quality tablets containing both ibuprofen and fluconazole.

Developing a preparation process

Screening of diluents

To investigate the optimal preparation process, both direct compression and wet granulation processes were employed. Various filler excipients were evaluated at different ratios to determine their impact on the granule formulation.

Screening of superdisintegrant excipients

To select the optimal disintegrant, super disintegrants such as sodium croscarmellose, sodium starch glycolate, and crospovidone were tested at a concentration of 3% in the formulation.

Evaluation of semi-finished products

The evaluation criteria for semi-finished products (granules) included: Angle of Repose (α) (< 30°), Carr's index (< 15%), and Hausner ratio (< 1.18)

The evaluation criteria for finished tablets included: General Appearance (Round, white tablets, 9 mm in diameter, with no defects), hardness (> 39.2 N), and disintegration time (< 15 minutes).

2.3 Quality control tests of tablet

Tablets containing fluconazole and ibuprofen were evaluated according to the

standards set by the Vietnamese Pharmacopoeia V and the United States Pharmacopeia (USP). The evaluation criteria included:

- General Appearance: Assessment of the tablet's visual characteristics.
- Thickness Test: Measurement of the tablet's thickness to ensure uniformity.
- Hardness Test: Determination of the tablet's mechanical strength.
- Friability Test: Evaluation of the tablet's ability to withstand abrasion.
- Weight Variation: Assessment of the consistency of tablet weight.
- Disintegration Test: Measurement of the time required for the tablet to disintegrate.

These evaluations ensure that the tablets meet the required quality standards for effective and safe use in treating fungal infections, providing a robust foundation for future clinical studies.

2.4 Antifungal susceptibility tests

The antifungal efficacy of the product was evaluated using the agar disk diffusion test. The following steps outline the procedure in detail:

Sample preparation:

Test samples included.

- F500: 500 µg/mL fluconazole phosphate buffer at pH 6.8.
- I167: 167 µg/mL ibuprofen phosphate buffer at pH 6.8.
- I:F (1:3): A mixed solution containing 500 µg/mL fluconazole and 167 µg/mL ibuprofen phosphate buffer at pH 6.8.
- Tablets: Solutions derived from the dissolution of tablets in phosphate buffer at pH 6.8.

Activation of Fungal Suspension:

1. Fungal strains were stored at -80 ℃ and activated by culturing on Sabouraud Dextrose Agar (SDA) plates, followed by incubation at 37 ℃ for 36-48 hours.

2. A small cluster of fungal colonies (1-2 clusters) was transferred from the agar plate to 5 mL of Sabouraud Dextrose Broth (SDB) medium and incubated overnight at 37 ℃ to reach the equilibrium phase.

3. The fungal suspension density was measured using a spectrophotometer at a wavelength of 530 nm, ensuring the optical densities of the tested samples ranged from 1 to 3.

Procedure:

1. Prepare petri dishes containing 15 mL of SDA medium and allow the agar surface to dry in a Level 2 biological safety cabinet.

2. Using a sterile cotton swab, evenly spread the prepared fungal suspension on the surface of the SDA agar plates.

2. Create wells with a diameter of 6 mm on the SDA agar plates.

3. Inject 50 µL of each test sample solution into the respective wells.

4. Place the agar plates in a refrigerator for 2 hours to facilitate the diffusion of the culture fluid into the agar medium.

5. Incubate the plates at 37 ℃ for 48 hours.

6. After the incubation period, measure the diameter of the antifungal inhibition zones using Fiji software.

III. RESULTS AND DISCUSSION

3.1Material characteristics

The mixture of active ingredients and excipients exhibited no physical, color, texture, and odor changes after two weeks under both test conditions (40 ℃/75% RH and 30 ℃/75% RH) compared to the initial condition. This indicates no sensory incompatibility between the active ingredient

mixture and the excipients, validating their selection for further investigation.

Fluconazole and ibuprofen are known to have poor flowability, as demonstrated in previous studies [13, 14]. In this study, a powder mixture containing fluconazole and ibuprofen at a 3:1 ratio was analyzed for flowability. The results indicated that the mixture had very poor flowability. The Carr index was determined to be 36.3% (within the range of 32-37%) and the Hausner ratio was 1.57 (within the range of 1.46-1.57), confirming the poor compressibility of the mixture. Consequently, further investigation into filler excipients and granulation methods was necessary to address these issues.

3.2Formula and preparation process

Screening of filler excipients and tablet manufacturing process

The investigation of diluents was conducted using both direct compression and wet granulation methods. The initial results showed that the powder mixture of active ingredients and filler excipients had very poor flowability and could not be pressed into tablets effectively. According to previous studies, both fluconazole and ibuprofen are stable at high temperature and humidity [15]. This suggests that tablets containing these two active ingredients can be prepared using the wet granulation process rather than direct compression.

During the wet granulation process, lactose monohydrate presented challenges due to its tendency to dissolve in 50% ethanol solvent. This issue was mitigated by reducing the amount of solvent used during granulation. Sensory evaluation revealed that granules produced with lactose monohydrate were more spherical and had a more uniform particle size compared to those produced with avicel PH-101. Consequently, granules made with lactose monohydrate exhibited a smaller angle of repose (α) and better flow properties than those made with avicel PH-101.

Overall, the selection of filler excipients and the optimization of the wet granulation process were crucial in overcoming the poor flowability and compressibility of the active ingredient mixture, leading to the successful formulation of tablets containing both fluconazole and ibuprofen.

Table 1. ***Survey of diluents using wet granulation process***

Ingredients	F1	F2	F3	F4	F5	F6
Fluconazole (mg)	150.00	150.00	150.00	150.00	150.00	150.00
Ibuprofen (mg)	50.00	50.00	50.00	50.00	50.00	50.00
Lactose monohydrate (mg)	100.00	200.00	400.00	-	-	-
Avicel PH-101 (mg)	-	-	-	100.00	200.00	400.00
PVP K30 (mg)	15.00	17.50	22.50	17.00	20.00	25.00
Magnesium stearate (mg)	0.79	1.05	1.57	0.79	1.05	1.56
Ethanol 50% (mL)*	0.15	0.175	0.225	0.17	0.25	0.417
Quality control						
Angle of repose α	23.5°	26.5°	27.6°	29.5°	31.5°	30.7°
Carr index (%)	10.4	12.0	11.5	5.4	14.2	6.1
Hausner Ratio	1.11	1.13	1.13	1.05	1.16	1.06
Hardness (N)	107.30	118.80	90.70	120.56	23.1	24.02
Disintegration (min)	>30	>30	>30	19.06	-	-

Note (*): The solvent will evaporate during the drying process.

Formulas F1, F2, F3, and F4 met all criteria for moisture content (< 5%), angle of repose α (< 30°), Carr index (≤ 15%), and Hausner ratio (≤ 1.18), indicating very good flowability. Although formulas F5 and F6 did not meet the angle of repose requirement, an angle of repose between 30° and 35° still provides good flowability according to the United States Pharmacopeia (USP) 42 [16]. Additionally, these formulas satisfied the Carr index and Hausner ratio requirements. Therefore, all six granule formulations were deemed suitable for tableting.

Post-tableting, tablets containing lactose monohydrate (F1, F2, and F3) exhibited a brighter surface compared to those containing avicel PH-101 (F4, F5, and F6). However, tablets from formulas F5 and F6 failed the hardness test, thus further evaluations for these formulations were discontinued. Formulas F1 and F4, despite having lower diluent content, produced tablets with satisfactory hardness and good tactile properties without necessitating an increase in diluents, thereby avoiding increased production costs.

Although granules made with lactose monohydrate showed better flowability than those made with avicel PH-101, none of the formulations met the disintegration test requirement of < 15 minutes. However, the disintegration time for formula F4 was shorter than that for formula F1, attributed to the fact that Avicel PH-101 is a multifunctional excipient with a expansion disintegration mechanism [17], offering superior disintegration properties compared to lactose monohydrate. Consequently, formula F4 was selected for further investigation with different superdisintegrant excipients.

Screening of superdisintegrant excipients

Formula F4, optimized with avicel PH-101 as the diluent, was selected for further investigation into the type and ratio of superdisintegrant excipients. Among the tested superdisintegrants, sodium croscarmellose demonstrated superior disintegration properties compared to sodium starch glycolate and crospovidone at the same content levels. Consequently, formula F7, which incorporated sodium croscarmellose as the superdisintegrant, achieved a disintegration time of 3.3 minutes and was chosen as the optimal formula.

Table 2. ***Survey of diluents using wet granulation process***

Ingredients	**F7**	**F8**	**F9**
Fluconazole (mg)	150	150	150
Ibuprofen (mg)	50	50	50
Avicel PH-101 (mg)	100	100	100
PVP K30 (mg)	17	17	17
Sodium croscarmellose (mg)	10	-	-
Sodium starch glycolate (mg)	-	10	-
Crospovidone (mg)	-	-	10
Magnesium stearate (mg)	3	3	3
Ethanol 50% (mL)*	q.s.	q.s.	q.s.
Quality control			
Angle of repose α	28.2°	27.2°	29.5°
Carr index (%)	13.0	10.7	12.2
Hausner Ratio	1.15	1.12	1.14
Tablet weight (mg)	330 ± 4.55	331 ± 4.19	330 ± 4.72

Ingredients	F7	F8	F9
Hardness (N)	79.91 ± 1.47	90.76 ± 1.37	89.1 ± 1.3
Hardness	5.75 ± 0.03	5.78 ± 0.02	5.74 ± 0.03
Friability	0.33	0.31	0.31
Disintegration (min)	3.3 ± 0.06	4.22 ± 0.07	4.02 ± 0.07

Note (*): The solvent will evaporate during the drying process.

The formulation and tablet manufacturing process survey confirmed that tablets containing fluconazole and ibuprofen could be successfully prepared using the wet granulation process. The optimal ingredient composition is detailed in Table 3.

Table 3. ***The composition of the finalized tablet formulation***

Ingredients	Weighing (mg)	Percentage (%)
Fluconazole	150	45
Ibuprofen	50	15
Avicel PH-101	100	30
PVP K30	17	5
Sodium croscarmellose	10	3
Magnesium stearate	3	1
Ethanol 50%*	q.s.	
Tablet weight	330	100

Characterization of tablets

Fig. 1. ***Tablets containing concurrent fluconazole and ibuprofen.***

The pharmaceutical tablets, formulated from the optimal recipe, comply with quality standards outlined in the Vietnamese Pharmacopoeia V and the United States Pharmacopeia (USP). The test results are summarized in Table 4.

Table 4. ***Quality control tests of tablets***

Specifications	Results	Limits
General appearance	Round, white tablets, 9 mm in diameter, with no defects.	
Thickness test	Average: 5.75 ± 0.03 mm RSD: 0.52%	Average ± 5% RSD ≤ 2%
Hardness test	Average: 79.91 ± 1,47 N RSD: 1.83%	Average > 39.2 N RSD ≤ 2%
Friability test	0.33%	< 1%
Weight variation	330 ± 4.55 mg	Average ± 5%
Disintegration test	Average: 3.3 ± 0,06 min RSD: 1.91%	Average < 15 min RSD ≤ 2%

Antimicrobial susceptibility tests

Antibacterial testing was conducted on two *Candida albicans* strains: a fluconazole-sensitive strain (ATCC) and a fluconazole-resistant strain (8XL). The results demonstrated that fluconazole at a concentration of 500 µg/mL (F500) retained antifungal activity against the sensitive ATCC strain but was ineffective against the resistant 8XL strain. Conversely, ibuprofen at a concentration of 167 µg/mL (I167) exhibited no antifungal activity against either strain.

For the fluconazole-sensitive ATCC strain, the combination of fluconazole and ibuprofen at a 1:3 ratio (I:F) produced an antifungal effect with a zone of inhibition similar to that of F500 alone, with no statistically significant difference (p-value > 0.05). These results were consistent with those observed for the tablet samples, indicating that combining fluconazole and ibuprofen at this ratio does not enhance antifungal activity compared to using fluconazole alone. Notably, tablets containing both fluconazole and ibuprofen maintained their antifungal activity.

Table 5. ***Results of in vitro antifungal susceptibility tests***

Sample	Antifungal diameter	
	C. albicans ATCC	*C. albicans* 8XL
F500	3.913 ± 0.17	0
I167	0	0
I:F (1:3)	4.103 ± 0.13	4.2 ± 0.17
Tablet	3.79 ± 0.27	4.09 ± 0.16

In contrast, for the fluconazole-resistant 8XL strain, the combination of fluconazole and ibuprofen at a 1:3 ratio exhibited significant antifungal activity, effectively combating *C. albicans* in a state of fluconazole resistance. Comparison with the tablet samples revealed no significant difference in the zone of inhibition (p-value > 0.05), confirming that tablets containing both active ingredients were effective against fluconazole-resistant strains.

The synergistic effect between ibuprofen and fluconazole observed in this study aligns with previous research. A study demonstrated the synergistic effect of ibuprofen with fluconazole on fluconazole-resistant *C. albicans* strains, with no effect on fluconazole-sensitive strains [18]. Additionally, J. Król et al. reported similar findings for fluconazole-resistant *C. albicans* strains 2905 and 3057 [10]. The mechanism underlying this synergistic effect remains unclear, but it is hypothesized that ibuprofen inhibits fluconazole efflux pumps in resistant fungal strains [19]. Sensitive strains express fewer efflux pumps, explaining the lack of synergy in these cases. These results are consistent with previous studies and suggest that ibuprofen may inhibit drug efflux pumps in fluconazole-resistant fungal strains.

IV. CONCLUSION

This study successfully developed a formula and process for preparing tablets containing 50 mg of ibuprofen and 150 mg of fluconazole. Antifungal activity evaluation revealed that the combination of fluconazole and ibuprofen in a 3:1 ratio was effective against the fluconazole-resistant *C. albicans* 8XL strain but did not enhance the antifungal effect on the fluconazole-sensitive *C. albicans* ATCC strain. The combination

retained antifungal activity in tablet form, indicating that ibuprofen and fluconazole combination tablets hold potential for future clinical studies targeting fluconazole-resistant *Candida* infections.

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