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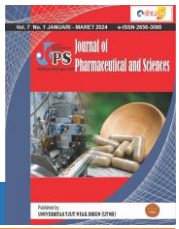

Dissolution Enhancement of Tadalafil Tablets by the complex method of betacyclodextrin inclusion and variation of disintegrating excipients

Peningkatan Disolusi Tablet Tadalafil Dengan Metode Kompleks Inklusi Betasiklodekstrin dan Variasi Eksipien Penghancur.

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Abstract

Tadalafil (TDL) is a drug clinically proven to treat erectile dysfunction, benign prostatic hyperplasia, and pulmonary hypertension. TDL is classified as a BCS Class II drug, which means it has high permeability but low solubility. Solubility enhancement is achieved through the inclusion complex method and verified by dissolution testing. This study aims to determine the dissolution profile of tadalafil inclusion complex tablets using the β-cyclodextrin (βCD) inclusion complex method with disintegrant variations. The results show that the tablet hardness is: R1 = 6.6 ± 0.5 kgf, R2 = 6.48 ± 1.4 kgf, and R3 = 6.6 ± 1.3 kgf. The disintegration time evaluation shows: R1 = 4.66 ± 1.08 minutes, R2 = 5.08 ± 0.91 minutes, and R3 = 5.1 ± 1.1 minutes. Each formulation's tensile strength test results are: R1 = 1.3 MPa, R2 = 1.3 MPa, and R3 = 1.1 MPa. The average drug content in the inclusion complex tablets is: R1 = 104.11 ± 1%, R2 = 106.23 ± 0.1%, and R3 = 105.09 ± 1.9%. The dissolution profile of the inclusion complex tablets at the 30-minute mark is: R1 = 85.2 ± 4.2%, R2 = 79.7 ± 3.6%, and R3 = 77.4 ± 5.3%. Variations in disintegrants significantly affect the dissolution profile during the early minutes, which impacts the overall dissolution profile. The TDL-βCD inclusion complex method successfully achieved the Q value by the monograph specifications.

***Keywords*: Tadalafil, Inclusion Complex, Beta Cyclodextrin, Comparable Dissolution Test, Tensile Strength.**

Abstrak

Tadalafil (TDL) merupakan obat yang terbukti secara klinis mengobati disfungsi ereksi, hiperplasia prostat jinak, dan hipertensi paru. TDL diklasifikasikan sebagai obat BCS Kelas II, yaitu obat dengan permeabilitas tinggi namun kelarutan rendah. Peningkatan kelarutan dilakukan melalui metode kompleks inklusi dan diverifikasi dengan uji disolusi. Penelitian ini bertujuan menentukan profil disolusi tablet kompleks inklusi TDL menggunakan metode kompleks inklusi beta-siklodekstrin (βCD) dengan variasi disintegrant. Hasil menunjukkan bahwa kekerasan tablet sebesar: R1 = 6,6 ± 0,5 kgf, R2 = 6,48 ± 1,4 kgf, dan R3 = 6,6 ± 1,3 kgf. Evaluasi waktu hancur menunjukkan: R1 = 4,66 ± 1,08 menit, R2 = 5,08 ± 0,91 menit, dan R3 = 5,1 ± 1,1 menit. Hasil uji kekuatan tarik untuk masing-masing formulasi adalah: R1 = 1,3 MPa, R2 = 1,3 MPa, dan R3 = 1,1 MPa. Rata-rata kadar tablet kompleks inklusi adalah: R1 = 104,11 ± 1%, R2 = 106,23 ± 0,1%, dan R3 = 105,09 ± 1,9%. Profil disolusi tablet kompleks inklusi pada menit ke-30 adalah: R1 = 85,2 ± 4,2%, R2 = 79,7 ± 3,6%, dan R3 = 77,4 ± 5,3%. Variasi pada disintegran secara signifikan memengaruhi profil disolusi pada menit-menit awal, yang berdampak terhadap keseluruhan profil disolusi. Metode kompleks inklusi TDL-βCD berhasil mencapai nilai Q yang sesuai dengan spesifikasi monografi.

***Kata Kunci*: Tadalafil, Kompleks Inklusi, Beta siklodekstrin, Uji Disolusi Terbanding, Tensile strength.**

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Introduction

Drug solubility is a complex issue commonly encountered in drug development. Approximately 40% of marketed drugs and 75% of active compounds currently in development are poorly soluble. [1]. The drug dissolution process affects absorption into the systemic circulation. Solubility and permeability influence the low absorption of drug compounds in digestive fluids. Drugs with low absorption often result in reduced efficacy. [2]. One drug with numerous therapeutic effects but low solubility is tadalafil. Tadalafil falls under Class II of the Biopharmaceutical Classification System (BCS), meaning it has poor solubility but good permeability [3]. Tadalafil is reported to be practically insoluble in water, slightly soluble in propylene glycol and ethyl alcohol, and soluble in polyethylene glycol-400 (PEG-400) in its crystalline molecular form [4,5].

Enhancing solubility to support drug dissolution can be achieved through various methods, one of which is the inclusion complex method [3]. Inclusion complexes involve encapsulating a guest compound within a host compound, in this case, cyclodextrin. Cyclodextrins are cyclic oligosaccharides capable of binding lipophilic guest compounds [6]. There are three types of cyclodextrins—alpha (α), beta (β), and gamma (γ)—which differ in the number and size of their cavities. Beta-cyclodextrin (βCD) is commonly used in the pharmaceutical industry due to its excellent binding properties. βCD has been reported to enhance the solubility and dissolution profile of flibanserin, a drug used to increase sensitivity in the female reproductive area, with a linear relationship observed between its dissolution profile and the concentration of βCD added [7].

To assess the solubility of TDL under physiological conditions, a dissolution test of the TDL inclusion complex tablets must be conducted. Dissolution testing is a parameter used to predict a drug's in vitro bioavailability correlation. It is an essential aspect of drug development and formulation, quality control, ensuring in vitro bioequivalence between batches, and is included in drug product marketing regulations. To ensure product quality, the Indonesian BPOM stipulates that dissolution testing includes a similarity factor (f2) analysis to compare the test product with a reference product [8]. This study aims to determine the dissolution profile of TDL inclusion complex tablet formulations using the inclusion complex method (βCD) with variations in the use of disintegrant.

Experimental Section

Materials and Apparatus

Tadalafil (Reference standard), beta-cyclodextrin (pharmaceutical grade,) Cialis® tablet 10 mg, sodium lauryl sulfate (SLS) (pharmaceutical grade), sroscarmellose (pharmaceutical grade), Sodium starch glycolate (SSG), ethanol (p.a), acetonitrile (p.a), magnesium stearate (pharmaceutical grade), ethanol 96% (technical grade), 70% ethanol (technical grade), distilled water (pharmaceutical) and lactose (pharmaceutical grade).

High Performance Liquid Chromatography (HPLC) (series L203056 Shimadzu®), Analytical balance (Ohaus®), Glassware (Pyrex®), Dissolution tester (Electrolab®), Oven (Binder®), Hardness tester (Olabo®), Disintegration tester (Electrolab®), Friability tester Olabo®, Magnetic stirrer (Thermo Scientific®), ATR FTIR (Bruker®), Sonicator (Elma®), Powder X-Ray Diffractometer (Panalytical Xpert Pro PW3373/00), IBM SPSS software for Windows, Originlab® 2023 software.

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Preparation of an Inclusion Complex

Various sources varied the mixing time, ranging from 30 minutes to 45 minutes to 1–5 hours, resulting in 14 different dissolution outcomes in a pH 6.8 dissolution medium. [4], [9], [11]. Thirty grams of a TDL:βCD mixture in a 1:5 (w/w) ratio was stirred in an aqueous ethanol solvent with a 1:2 ratio for 5 hours for formula R1 and 3 hours for formulas R2 and R3.

Tablet manufacturing

TDL tablets with a 10 mg dose were prepared using the wet granulation method, with tablet excipients as listed in Table 1. The active ingredient, filler (lactose), and disintegrant (croscarmellose/SSG at maximum concentration) were first dry-mixed. A binder solution (10% PVP) was sprayed onto the dry mixture, which was then wet-mixed until homogeneous. The wet mixture was then sieved, dried in an oven at 45°C, and sieved again after drying. The lubricant (magnesium stearate) was added and mixed for 5 minutes. The tablets were then compressed using a tablet press. The use of the maximum concentration according to HPE for disintegrants can increase the disintegration time of tablets [12].

Table 1. Tadalafil inclusion complex tablet formula with the wet granulation method

Active substances and excipients	(R1)	(R2)	(R3)
TDL:CD	24%	24%	24%
Filler	61%	61%	64%
Binde	5%	5%	5%
(Disintegrant) Crosscarmelose	8%	8%	-
(Disintegrant) SSG	-	-	5%
Lubricant	2%	2%	2%

Evaluation of tablets

Tablet evaluation was conducted using hardness testing, tensile strength testing, and disintegration time assessment [13].

Determination of tablet content

A 250 mg tablet was weighed, ground, and dissolved in a 1:1 acetonitrile and trifluoroacetic acid solution. The mixture was sonicated for 15 minutes, transferred to an HPLC sample vial, and analyzed at the specified wavelength [13].

Dissolution test

The dissolution test was conducted at pH 6,8 using apparatus 2 (paddle) at a speed of 50 rpm and a temperature of 37°C ± 2°C. A 2 ml sample was taken at 5, 10, 15, 20, 30, 45, and 60-minute intervals for samples R1, R2, R3, and Cialis® as the innovator reference[13].

Analysis method

Data analysis was performed using IBM SPSS Statistics 25 for Windows, including Shapiro-Wilk normality testing ($p > 0.05$), homogeneity analysis ($p > 0.05$), and one-way anova to determine significance ($p < 0.05$). Further analysis was conducted using Tukey's test if a significant difference was found.

Results and Discussion

Evaluation of tablets

The tablet evaluation in Table 2 includes hardness testing, disintegration time testing, and tensile strength testing according to USP standards. The hardness test determines the tablet's hardness and serves as supporting data for calculating the tablet's tensile strength. The disintegration test is performed to determine the tablet's dissolution time and to ensure it meets the standards for dissolution profile testing. The tensile

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strength test assesses the tablet's compactibility and ability to withstand pressure during stacking in packaging, distribution, and storage. Tensile strength values are influenced by hardness, diameter, thickness, and wall height. In tensile strength testing, the results are not solely affected by the excipients but are also influenced by the selected tablet design.

The hardness test results meet the USP standard, ranging between 4-8 kgf, by placing the tablet on a hardness tester. This test aims to determine the hardness of the tablet to meet the requirements for solid dosage forms. Factors affecting this include the compression speed of the tablet press, granule flow properties, and the formulation. Compression speed influences the punch's momentum, affecting the strength generated during tablet compression. In addition to compression speed, granule flow influences hardness, affecting the trapped air within the granule components filling the die cavity. Trapped air can impact the tablet's weight and the punch's momentum toward the die. The primary factor affecting tablet hardness is the formulation. The use of binders is essential in determining tablet hardness. Binders accumulate fine particles into larger particles (granules) by enhancing cohesive compaction [14,15].

The disintegration time test results for the three formula samples meet the USP requirements of less than 15 minutes, with the tablet disintegration time aligning with its dissolution profile. The disintegration test was conducted by placing the tablet in a disintegration tester and testing it for 15 minutes at a temperature of 37°C ± 1. Disintegrants and binders influence tablet disintegration time in the formulation. Disintegrants cause the tablet matrix to break apart upon contact with liquid. This formula uses superdisintegrants, specifically sodium starch glycolate (SSG) and croscarmellose. Binders, on the other hand, enhance the bonding strength within the matrix. Therefore, the tablet formulation must contain a balanced concentration of binders and disintegrants to achieve an optimal balance between binding strength and disintegration ability [14,15].

The tensile strength test results for the three formula samples meet the USP requirement above 1 MPa. The test was coducted by measuring and calculating hardness, tablet diameter, thickness, and wall height. The tensile strength test aims to ensure the tablet's structural integrity so it can withstand compression during packaging, distribution, and storage. Tensile strength is influenced by hardness, tablet diameter, thickness, and wall height. These results indicate that tablet shape affects the tablet's tensile strength [13,16,17]

The factors affecting the results of hardness, disintegration time, and tensile strength tests were met in the production of tadalafil inclusion complex tablets. These stablet evaluation results are also representative of the dissolution test. Tablets that are too hard slow down dissolution time, with a slower dissolution time indicating a gradual dissolution profile in the initial minutes [7],18,19].

Table 2. Evaluation of tablet

Evaluation tablets	R1 (Percentage mean + SD)	R2 (Percentage mean + SD)	R3 (Percentage mean + SD)	Requirements
Hardness tester	6.6+0,5	6,48+1,4	6,6+1,3	4-8
Disintegration tester	4,66+1,08	5,08 +0,91	5,1+1,1	< 15 minutes
Tensile strength	1,3	1,3	1,1	> 1 MPa

Determination Tablets

Determining tablet content aims to control the dosage of the tadalafil inclusion complex tablets (TDL 10 mg). Content determination was performed using a validated HPLC instrument. Tablets with a weight equivalent to 250 mg were dissolved in 50 ml of acetonitrile: Solution A (0.1% Trifluoroacetic Acid) in a 1:1 ratio [13]Table 3 shows the tablet content test results for formulas R1, R2, and R3. The inclusion complex content of the tablets in all three formulas meets the USP and FI IV standards, which require 90-110%. The tablet concentration results show that the 10 mg TDL dosage meets these requirements. The achieved tablet content was determined by the quality of the granulation process, which maintained tadalafil content homogeneity from the formation of the inclusion complex powder to the granule flow properties during tablet compression.

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Table 3. Tablet contents

Formulas	Tablet of content (Percentage mean + SD)
R1	104,11+11
R2	106,23+ 0,1
R3	105,09+1,9

Dissolution Test Results

Dissolution testing for the sample and Cialis innovator in Table 4 was conducted at pH 6.8. A 2 mL sample was withdrawn at 5, 10, 15, 20, 30, 45, and 65 minutes, with a paddle rotation speed of 50 rpm at a temperature of 37°C ± 1. The dissolution medium with pH 6.8 was selected to represent the intestinal pH as recommended by the USP. Shapiro-Wilk analysis at a 95% confidence level ($\alpha = 0.05$) for the dissolution results at 5, 10, 15, 20, 30, 45, and 65 minutes showed that the Innovator, R1, R2, and R3 had p-values > 0.05, indicating that the data were normally distributed. The homogeneity test results indicated that all samples were homogeneous across the different time points ($p > 0.05$), except at the 5th minute, where a significant difference was observed ($p < 0.05$; $p = 0.007$). Within the first 5 minutes, the R3 formulation exhibited a significantly higher dissolution profile than the sample and innovator. One-way ANOVA analysis yielded a p-value of 0.03 ($p < 0.05$), indicating a significant difference between the innovator, R1, R2, and R3 samples during the first 5 minutes. This suggests a difference in the disintegration mechanism characteristics between croscarmellose and SSG. This early time point is critical for assessing the tablet's disintegration ability. Tablet dissolution results are assessed based on the Q value, as specified by the Indonesian FDA (BPOM RI), which represents the minimum amount of active ingredient that must be released, by the active substance's monograph [20]. According to the USP monograph for tadalafil tablets, 80% of the active ingredient should be released by the 30-minute. In this test, only sample R1 achieved the Q value, with >80% release at 30 minutes, whereas the innovator, R2, and R3 samples released <80%. A one-way ANOVA analysis with a p-value of 0.01 ($p<0.05$) indicated a significant difference in Q values among the R1, R2, R3 samples, and the innovator [13]. The inability of the innovator (Cialis®) to meet the Q value is not considered a research error, as before the dissolution testing, method validation was conducted. The results demonstrated that Cialis® batch 2300039 had a retention time of 8.5 minutes with an RSD value of 0.11 (<2%), a theoretical plate number (N) of 8,202, a tailing factor of 1.05 (<2), specificity of 4.08, and resolution of 4.08 (Rs > 2). The intraday precision test showed RSD values of 1.67 for 125 ppm, 0.67 for 100 ppm, and 1.52 (RSD < 2). The interday precision test resulted in RSD values of 1.81 for 125 ppm, 0.86 for 100 ppm, and 1.29 for 75 ppm (RSD < 2). Accuracy testing also indicated acceptable percent recovery values: 98.5% at 80% concentration, 101.6% at 100%, and 101.2% at 120 ppm, all within the acceptable range of 95–105%. [21]. This test was conducted using an HPLC system, Shimadzu® series L203056. Results may vary when using different instruments.

Table 4. Dissolution profile

Time	Innovator (%)	R1 (%)	R2 (%)	R3 (%)
0	0	0	0	0
5	7,5+1,2	14,8 + 4,0	4,7 + 2,2	20,8 + 5,0
10	48,2+2,2	40,4 + 3,0	42,4 + 1,7	21,5 + 4,2
15	63,5+1,80	66,5 + 3,7	56,7 + 4,5	38,5 + 4,3
20	71,5+1,3	77,8 + 3,3	74,2 + 3,6	51,6 + 2,5
30	75,3+2,2	85,2 + 4,2	79,7 + 3,6	77,4 + 5,3
45	77,5+1,7	87,7 + 3,1	81,7 + 0,5	82,9 + 2,0
60	78,2+1	87,2 + 3,9	82,2 + 1,6	85,4 + 2,3

The dissolution profile of the inclusion complex tablets shows a significant difference in the initial minutes between the innovator, R1, and R2 samples, compared to sample R3, as seen in Table 4. Another difference appears at the 30-minute mark when only sample R1 reached the Q value. This pattern is influenced by the disintegrants, fillers, and binders used in the tablets. Formula R3, containing the disintegrant SSG

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(sodium starch glycolate), demonstrated faster dissolution than samples R1 and R2 and the innovator, which used croscarmellose as the disintegrant. This increased speed in formula R3 is also attributed to a 3% higher amount of lactose filler than R1 and R2. Lactose, as a soluble filler, aids disintegration by increasing matrix porosity [15].

Another factor influencing tablet disintegration is the concentration of disintegrant. The selected concentrations of 8% croscarmellose and 5% SSG (sodium starch glycolate) were based on the maximum concentrations recommended in the Handbook of Pharmaceutical Excipients (HPE) [22]. Choosing the concentration of disintegrant is not solely based on the quantity but also compatibility with binders, fillers, and the active ingredient [15]. The rationale for selecting 8% croscarmellose and 5% SSG was to accommodate the hydrophobic nature of the active ingredient, allowing the tablet to break easily and rapidly separate the matrix and inclusion complex components.

Although tablets containing SSG disintegrate more quickly, this does not guarantee the solubility of TDL in the dissolution medium. The results show that only sample R1, which was mixed for 5 hours, reached the Q value, while samples R2 and R3, mixed for 3 hours, did not. A longer mixing time increases the amount of TDL forming an inclusion complex with β-cyclodextrin (βCD), as the complex formation process involves the breaking of water molecules within βCD, the incorporation of TDL, and the restructuring of βCD. The inclusion complex formation mechanism begins when TDL and βCD come into proximity, followed by hydrolysis of βCD, which releases water molecules from its cavity. The structured water surrounding the TDL breaks apart, allowing the drug to enter the internal cavity of βCD, displacing the water molecules into the surrounding solution. Thus, transferring the water molecules into the solution, which automatically changes the drug's property from hydrophobic to hydrophilic [23] [24]. This process requires a longer time to proceed optimally so that the seven glucopyranose units of βCD can fully encapsulate the TDL molecule within its internal cavity s26]. The more TDL complexes with βCD inclusion, the easier it is for TDL to dissolve in the dissolution medium.

Table 5. UDT F2 and F1

Dissolution media pH 6,8			
UDT Value	R1	R2	R3
F2	59,9	65,4	38,7
F1	6,1	3,5	12,1

The results of the comparative dissolution test are expressed in terms of F2 (similarity) and F1 (difference) values, as shown in Table 5. An F2 value above 50 indicates that the sample is similar to the innovator, while an F1 value approaching 15 reflects increasing dissimilarity. The F2 values for the dissolution test (UDT) were R1 = 58.3, R2 = 65.4, and R3 = 38.7. The F2 calculations indicate that samples R1 and R2 differ significantly from R3, as confirmed by a one-way ANOVA analysis with a p-value of 0.005 ($p<0.05$). This significant difference is due to the dissolution profile of sample R3, as shown in Table 4, which differs from that of the innovator. This is most likely caused by the difference in disintegrants used in the formulation.

Based on the comparative dissolution test, formula R2 is most similar to the innovator Cialis®, while formula R3 is the most different. The significant difference in formula R3 is an interpretation of the tablet's breakage mechanism due to using a disintegrant excipient. The innovator, formula R1, and formula R2 use croscarmellose as an excipient, while formula R3 uses SSG. Although formula R2 is the most similar to the innovator product, this does not necessarily make it the best formulation. Based on the dissolution profile, formula R1 is considered the best, as it is the only formulation that meets the required standard, namely the Q value at 30 minutes, compared to the innovator and other formulations. The f2 value only indicates the similarity of a formulation to the innovator, whereas the Q value determines dissolution performance.

The combination of SSG, lactose, and PVP (polyvinylpyrrolidone) leads to high water absorption, causing the tablet to swell and fragment into smaller particles more rapidly than R1 and R2, which used croscarmellose. Croscarmellose produces larger fragments than SSG, thus tablets with SSG disintegrate more quickly [27]–[29]. This means that even though the tablet disintegrates easily during the dissolution process, it does not necessarily guarantee that the drug will achieve the standardized dissolution value, because drug solubility is influenced not only by the tablet disintegration process but also by the hydrophilic properties of the drug. Tadalafil (TDL) has already formed an inclusion complex with β-cyclodextrin (βCD).

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Conclusions

The disintegrant primarily affects the dissolution profile during the initial stage (first 5 minutes); thereafter, the tablet fails to maintain the required dissolution rate. The mixing time of the TDL-βCD inclusion complex significantly affects the dissolution profile of tadalafil tablets, achieving the Q value at 30 minutes.

Conflict of Interest

The authors affirm that this study does not involve conflicts of interest. The research process was conducted impartially, without external interference, and no personal, financial, or professional factors influenced the results.

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Supplementary Materials

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