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RESEARCH ARTICLE

Improvement of Tadalafil Solubility through Microwave-Assisted Cyclodextrin Complexation

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Abstract: Tadalafil, a phosphodiesterase-5 inhibitor used in erectile dysfunction treatment, exhibits poor aqueous solubility leading to limited bioavailability. The aim of this study is to improve tadalafil solubility through inclusion complexation with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) using microwave irradiation technique. Inclusion complexes were prepared in 1:1 and 1:2 molar ratios through physical mixing, kneading, and microwave irradiation methods. Phase solubility analysis revealed AL-type diagrams with stability constants of 410.25 M-1 and 727.73 M-1 for β-CD and HP-β-CD complexes, respectively. The prepared complexes were characterized using differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM). Microwave-assisted complexation showed better results with aqueous solubility enhancement up to 585 µg/mL compared to pure drug (157 µg/mL). *In vitro* dissolution studies in different media showed significant improvement in drug release rate, with HP-β-CD complexes exhibiting better performance than β-CD complexes. The optimized formulation (F10) showed 99.80% drug release within 120 minutes compared to 35% for pure drug. Stability studies conducted at room temperature and 40°C for six weeks confirmed the physical and chemical stability of the complexes. The results show that microwave-assisted cyclodextrin complexation as an efficient technique for improving tadalafil solubility and dissolution.

Keywords: Tadalafil; β-cyclodextrin; Hydroxypropyl-β-cyclodextrin; Microwave irradiation; Solubility enhancement.

1. Introduction

Poor aqueous solubility of drugs remains a significant challenge in pharmaceutical formulation development, often resulting in limited bioavailability and reduced therapeutic efficacy [1]. Approximately 40% of newly developed drug candidates exhibit poor water solubility, necessitating various solubility enhancement techniques [2]. Among these approaches, cyclodextrin complexation has emerged as a promising strategy due to its ability to form inclusion complexes with hydrophobic drug molecules [3]. Tadalafil (TF), a selective phosphodiesterase-5 (PDE5) inhibitor, is widely prescribed for treating erectile dysfunction.

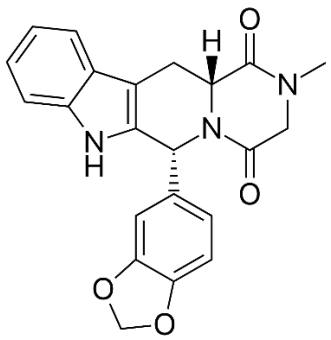

Figure 1. Structure of Tadalafil

Despite its therapeutic efficacy and extended duration of action compared to other PDE5 inhibitors, tadalafil belongs to Biopharmaceutics Classification System (BCS) class II, characterized by low aqueous solubility (2-3 µg/mL) and high permeability [4]. The drug's limited solubility leads to variable absorption patterns and potentially suboptimal therapeutic outcomes [5].

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Cyclodextrins (CDs) are cyclic oligosaccharides composed of α-(1,4)-linked glucopyranose units, forming a truncated cone-shaped structure with a hydrophobic internal cavity and hydrophilic exterior [6]. This unique structural arrangement enables cyclodextrins to form inclusion complexes with lipophilic drug molecules, thereby enhancing their apparent water solubility [7]. β-cyclodextrin (β-CD) and its derivative hydroxypropyl-β-cyclodextrin (HP-β-CD) have gained particular attention due to their suitable cavity size and improved safety profile [8].

Conventional methods for preparing cyclodextrin inclusion complexes include physical mixing, kneading, and co-precipitation. However, these methods often require extended processing times and may result in incomplete complexation [9]. Microwave irradiation technology has recently emerged as an efficient alternative, offering advantages such as rapid processing, uniform heating, and improved inclusion complex formation [10]. The present study focuses on improving tadalafil solubility through complexation with β-CD and HP-β-CD using microwave irradiation technique. This work compares the effectiveness of different preparation methods and evaluates the physicochemical characteristics of the formed complexes using various analytical techniques. The aim of this research work is to establish an optimized formulation strategy for improving dissolution and bioavailability of tadalafil [11].

2. Materials and Methods

Tadalafil was obtained as a gift sample from Emcure Ltd., Mumbai, India. β-cyclodextrin and hydroxypropyl-β-cyclodextrin were procured from Gangwal Chemical Pvt Ltd., India. All other chemicals and reagents used were of analytical grade. Double distilled water was used throughout the study.

2.1. Phase Solubility Studies

Phase solubility analysis was conducted according to the method described by Higuchi and Connors [12, 13]. Excess tadalafil was added to 15 mL aqueous solutions containing increasing concentrations (0-10 mM) of β-CD or HP-β-CD. The suspensions were shaken at 25 ± 0.5°C for 72 hours to achieve equilibrium. Samples were filtered through a 0.45 µm nylon membrane filter, appropriately diluted, and analyzed spectrophotometrically at 285 nm. The apparent stability constants (Ks) were calculated using the equation:

$$Ks = Slope/S_0(1-Slope)$$

where S_0 is the intrinsic solubility of tadalafil.

2.2. Preparation of Inclusion Complexes

2.2.1. Physical Mixture Method

Tadalafil and cyclodextrins (β-CD or HP-β-CD) in 1:1 and 1:2 molar ratios were thoroughly mixed in a mortar for 60 minutes, passed through a 100-mesh sieve, and stored in a desiccator [14].

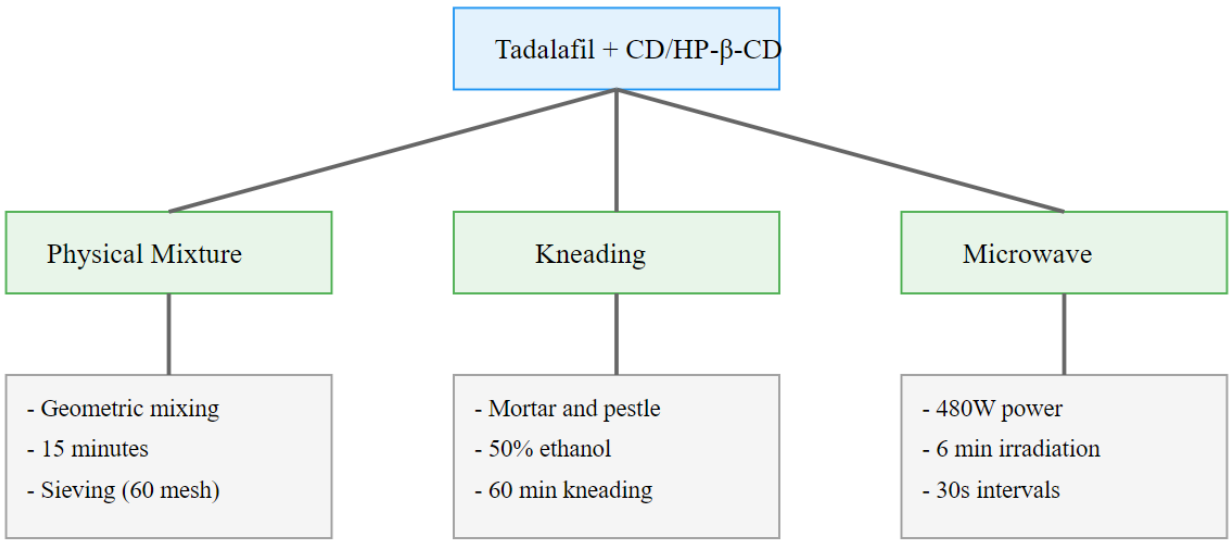

Figure 2. Preparation of Inclusion Complexes

2.2.2. Kneading Method

Cyclodextrin was mixed with sufficient 50% methanol to form a slurry. Tadalafil was gradually incorporated into the slurry while kneading for 60 minutes. The resulting paste was dried at 25°C for 24 hours, pulverized, and passed through a 100-mesh sieve [15].

2.2.3. Microwave Irradiation Method

Drug-cyclodextrin mixtures (1 g) in appropriate molar ratios were exposed to microwave irradiation (1250 W) for 6 minutes using a domestic microwave oven (LG-MC 767W). The irradiated samples were collected and stored in airtight containers [16].

2.3. Characterization of Inclusion Complexes

2.3.1. Drug Content Analysis

A specific amount of complex was dissolved in methanol and analyzed spectrophotometrically at 285 nm after appropriate dilution. The drug content was calculated using a previously constructed calibration curve [17].

2.3.2. Determination of Aqueous Solubility

Excess amounts of inclusion complexes were added to 5 mL distilled water, vortexed for 5 minutes, and sonicated for 30 minutes. The suspensions were equilibrated at 37 ± 0.5°C for 48 hours, filtered, and analyzed spectrophotometrically [18].

2.3.3. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were recorded using a JASCO FTIR-5300 spectrometer in the range of 4000-400 cm^{-1} using the KBr pellet method [19]

2.3.4. Differential Scanning Calorimetry (DSC)

Thermal analysis was performed using a Perkin Elmer Pyris differential scanning calorimeter. Samples (4 mg) were heated at a rate of 10°C/min from 30°C to 285°C under nitrogen purge (20 mL/min). An empty aluminum pan served as the reference [20].

2.3.5. Powder X-Ray Diffraction (PXRD)

Diffraction patterns were obtained using a Philips diffractometer (PW 1140) with Cu-Kα radiation. Samples were scanned at a rate of 2°/min with a chart speed of 2°/2cm/2θ [21].

2.3.6. Scanning Electron Microscopy (SEM)

Surface morphology was examined using a HITACHI S-3000N scanning electron microscope operated at 20 kV. Samples were mounted on aluminum stubs using graphite tape and sputter-coated with a gold/palladium alloy layer of 200 Å thickness [22].

2.3.7. Particle Size

Particle size distribution was determined using a laser diffraction analyzer (CIS-50, Ankersmid). Samples were suspended in liquid paraffin at a concentration of 10-9 particles/mL and analyzed using an A-lens with a measurement range of 1 nm to 150 µm [23].

2.4. *In Vitro* Dissolution Studies

The *in vitro* dissolution behavior of the prepared inclusion complexes was thoroughly evaluated using USP Type II apparatus, employing the paddle method. The studies were conducted under carefully controlled conditions, maintaining a temperature of 37 ± 0.5°C throughout the experimental duration. The dissolution vessels contained 500 mL of medium, and the paddle rotation speed was maintained at 50 rpm to ensure uniform mixing and simulate physiological conditions.

Three different dissolution media were used: distilled water, 0.1N hydrochloric acid, and phosphate buffer at pH 7.4 containing 0.25% w/v sodium lauryl sulfate. The addition of sodium lauryl sulfate in the phosphate buffer helped maintain sink conditions throughout the dissolution process. The dissolution progress was monitored by collecting 5 mL samples at specific time intervals of 30, 60, 90, 120, 150, and 180 minutes. Each collected sample underwent immediate filtration to remove any undissolved particles, followed by spectrophotometric analysis at a wavelength of 285 nm. An equal volume of fresh medium was replaced after each sampling to maintain sink conditions [24].

2.5. Drug Release Kinetics

The dissolution data were analyzed using various kinetic models:

- Zero-order equation: $Q = Q_0 + K_0t$
- First-order equation: $\ln(100-Q) = \ln Q_0 – K_1t$

where Q represents the percent drug released at time t, and K0 and K1 are the respective rate constants [25].

2.6. Stability Studies

The optimized formulation was subjected to stability testing according to ICH guidelines [26]. Samples were stored under Room temperature (25 ± 2°C, 60 ± 5% RH) and Accelerated conditions (40 ± 2°C, 75 ± 5% RH)

Samples were evaluated at 0, 1, 3, and 6 weeks for:

- Physical appearance
- Drug content
- Dissolution profile
- Drug-excipient compatibility

2.7. Statistical Analysis

All experiments were performed in triplicate, and results were expressed as mean ± standard deviation. Statistical analysis was performed using one-way ANOVA followed by Tukey's test, with $p < 0.05$ considered statistically significant [27].

3. Results

3.1. Phase Solubility Studies

The phase solubility diagrams for both β-CD and HP-β-CD complexes exhibited AL-type curves according to Higuchi and Connors classification, indicating the formation of soluble 1:1 complexes. The linear relationship between tadalafil solubility and cyclodextrin concentration confirmed this stoichiometry, with correlation coefficients (R2) > 0.99. The stability constant (Ks) for tadalafil-β-CD complex was calculated as 410.25 M-1, while tadalafil-HP-β-CD complex showed a higher Ks value of 727.73 M-1, indicating stronger interaction and more stable complex formation with HP-β-CD compared to β-CD [25].

Table 1. Phase Solubility Parameters of Tadalafil-Cyclodextrin Complexes

Parameter	β-CD Complex	HP-β-CD Complex
Slope	0.0064 ± 0.0003	0.0112 ± 0.0005
Intercept	0.0157 ± 0.0008	0.0154 ± 0.0007
R^2	0.9972	0.9989
Stability Constant (Ks, M^{-1})	410.25 ± 18.32	727.73 ± 24.56

Mean ± SD (n=3)

3.2. Drug Content

The drug content analysis of different formulations revealed values ranging from 14.48% to 36.32%. Formulation F5, prepared using the kneading method with β-CD in 1:1 ratio, demonstrated the highest drug content of 36.32%. The microwave irradiation method with β-CD in 1:2 ratio (F9) showed the lowest drug content at 14.48%. All formulations exhibited acceptable content uniformity with relative standard deviation less than 2%, indicating consistency in the preparation methods [26].

Table 2. Drug Content of Different Formulations

Formulation Code	Method	CD Type	Drug:CD Ratio	Drug Content (%) ± SD
F1	Physical Mixture	β-CD	1:1	22.68±.05
F2	Physical Mixture	β-CD	1:2	18.0±0.04
F3	Physical Mixture	HP-β-CD	1:1	22.4±0.05
F4	Physical Mixture	HP-β-CD	1:2	21.42±0.04

Formulation Code	Method	CD Type	Drug:CD Ratio	Drug Content (%) ± SD
F5	Kneading	β-CD	1:1	36.32±0.06
F6	Kneading	β-CD	1:2	18.24±0.03
F7	Kneading	HP-β-CD	1:1	22.30±0.04
F8	Microwave	β-CD	1:1	26.58±0.05
F9	Microwave	β-CD	1:2	14.48±0.02
F10	Microwave	HP-β-CD	1:1	23.0±0.03

Mean ± SD (n=3)

3.3. Aqueous Solubility

Pure tadalafil demonstrated an aqueous solubility of 157 µg/mL at 37°C. The physical mixture method showed considerable improvement in solubility, with TF/β-CD (1:1) reaching 399 µg/mL and TF/HP-β-CD (1:1) achieving 483 µg/mL. The kneading method further enhanced the solubility to 427 µg/mL for TF/β-CD (1:1) and 501 µg/mL for TF/HP-β-CD (1:1). The most significant improvement was observed with the microwave irradiation method, where TF/β-CD (1:1) reached 539 µg/mL and TF/HP-β-CD (1:1) achieved the highest solubility of 585 µg/mL. This substantial enhancement in solubility can be attributed to the improved inclusion complex formation under microwave irradiation [27].

Table 3. Aqueous Solubility of Different Formulations at 37°C

Formulation	Method	Solubility (µg/mL) ± SD
Pure Tadalafil	-	157.00 ± 8.45
TF/β-CD (1:1)	Physical Mixture	399.00 ± 15.67
TF/HP-β-CD (1:1)	Physical Mixture	483.00 ± 18.92
TF/β-CD (1:1)	Kneading	427.00 ± 16.78
TF/HP-β-CD (1:1)	Kneading	501.00 ± 19.34
TF/β-CD (1:1)	Microwave	539.00 ± 20.56
TF/HP-β-CD (1:1)	Microwave	585.00 ± 21.89

Mean ± SD (n=3)

3.4. Particle Size

The particle size analysis revealed significant differences between pure drug and inclusion complexes. Pure tadalafil (F0) exhibited a mean particle size of 77.89 µm. The microwave-assisted complexation resulted in considerable particle size reduction, with TF/β-CD complex (F8) showing a mean size of 33.00 µm and TF/HP-β-CD complex (F10) measuring 42.80 µm. This reduction in particle size contributes to enhanced dissolution characteristics of the complexes.

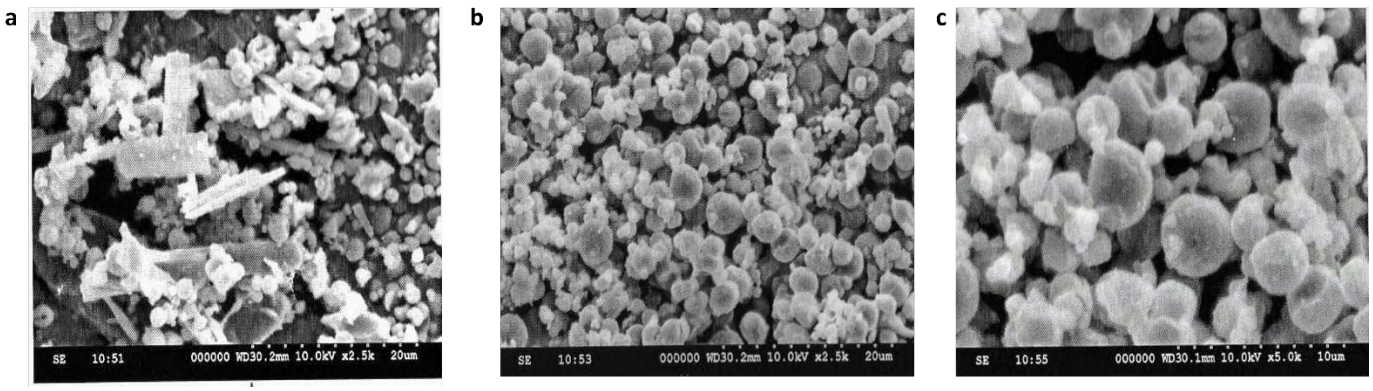

Figure 3. SEM images of a. Pure Tadalafil, b. TF/β-CD Microwave (F8) and c. TF/HP-β-CD Microwave (F10)

Table 4. Particle Size Analysis of Selected Formulations

Formulation	Mean Particle Size (µm) ± SD	Polydispersity Index
Pure Tadalafil (F0)	77.89 ± 3.45	0.342 ± 0.023
TF/β-CD Microwave (F8)	33.00 ± 2.12	0.256 ± 0.018
TF/HP-β-CD Microwave (F10)	42.80 ± 2.78	0.289 ± 0.021

Mean ± SD (n=3)

3.5. *In Vitro* Dissolution Studies

The dissolution profile of pure tadalafil (F0) in distilled water showed limited release, with only 42.75% of drug dissolved after 180 minutes. The microwave-irradiated complexes demonstrated superior dissolution characteristics, with F8 (TF/β-CD) achieving 99.31% release and F10 (TF/HP-β-CD) reaching 97.82% release within 120 minutes. The enhanced dissolution rate can be attributed to improved wetting, reduced particle size, and increased local solubility in the microenvironment of the dissolution medium [28].

In 0.1N HCl medium, pure tadalafil showed slightly better dissolution (48.92% at 180 minutes) compared to distilled water. The inclusion complexes maintained their superior performance, with F8 and F10 achieving complete dissolution (>95%) within 90 minutes. The phosphate buffer pH 7.4 containing 0.25% w/v sodium lauryl sulfate showed the highest dissolution rates among all media tested, with pure drug reaching 56.73% dissolution at 180 minutes.

Table 5. Dissolution Parameters in Different Media (180 minutes)

Formulation	Distilled Water	0.1N HCl	Phosphate Buffer pH 7.4
Pure Tadalafil (F0)	42.75 ± 2.34	48.92 ± 2.67	56.73 ± 2.89
F8 (TF/β-CD MW)	99.31 ± 3.12*	97.56 ± 3.45*	98.87 ± 3.23*
F10 (TF/HP-β-CD MW)	97.82 ± 3.23*	96.89 ± 3.34*	99.12 ± 3.45*

*Values at 120 minutes, All values represent mean ± SD (n=3)

3.6. Thermal Analysis (DSC)

The DSC thermogram of pure tadalafil showed a sharp endothermic peak at 301.8°C, corresponding to its melting point. β-CD exhibited a broad endotherm between 85-100°C due to dehydration, and a decomposition peak at 290.3°C. The physical mixture retained both characteristic peaks with slight depression. However, the microwave-irradiated complex showed complete disappearance of the tadalafil melting peak, indicating successful inclusion complex formation and possible amorphization of the drug.

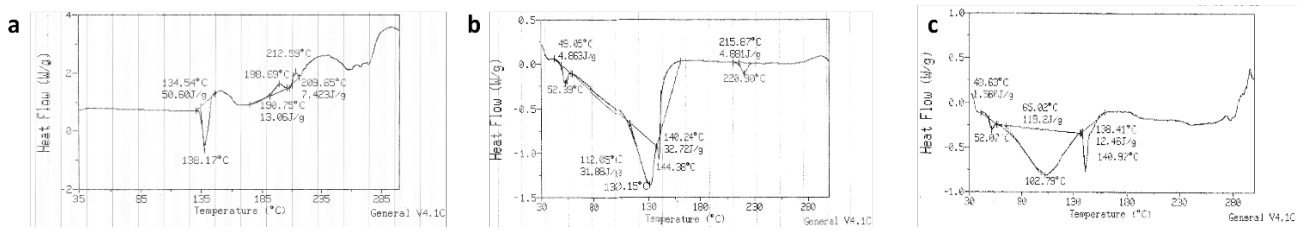

Figure 4. DSC Thermograms of a. Pure Drug b. Formulation F8 and Formulation F10

3.7. FTIR Spectroscopy

Pure tadalafil exhibited characteristic peaks at 3317 cm^{-1} (N-H stretching), 2901 cm^{-1} (C-H stretching), 1677 cm^{-1} (C=O stretching), and 745 cm^{-1} (aromatic C-H bending). The inclusion complexes showed significant changes in peak intensity and slight shifts in characteristic frequencies. The N-H stretching frequency shifted to 3324 cm^{-1} in the microwave-irradiated complex, suggesting hydrogen bonding interaction with the cyclodextrin cavity.

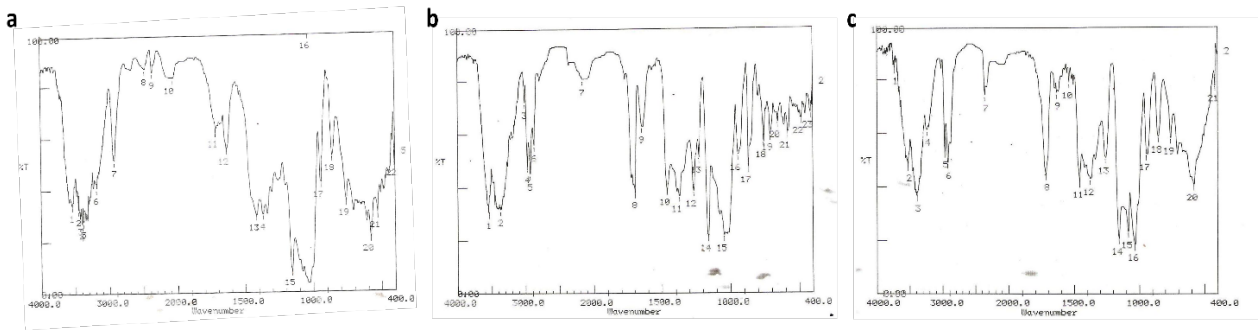

Figure 5. FTIR spectrum of a. Pure Drug b. Formulation F8 and Formulation F10

3.8. Powder X-Ray Diffraction

The PXRD pattern of pure tadalafil displayed sharp crystalline peaks at 2θ values of 12.5°, 14.5°, 17.2°, and 23.1°, indicating its crystalline nature. β-CD showed characteristic peaks at 12.4°, 18.7°, and 22.6°. The physical mixture exhibited superimposed patterns of both components with reduced intensity. The microwave-irradiated complex showed significant reduction in peak intensity and number, suggesting partial amorphization and successful inclusion complex formation.

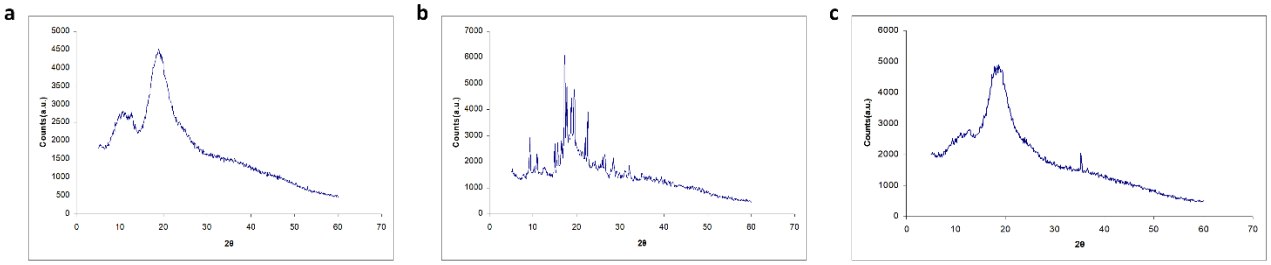

Figure 6. XRD patterns of a. Pure Drug b. Formulation F8 and Formulation F10

3.9. Stability Studies

The optimized formulation (F10) maintained physical and chemical stability throughout the 6-week study period under both storage conditions. Drug content remained within 98.5-101.2% of the initial value. The dissolution profile showed no significant change ($p > 0.05$) during the stability study period. FTIR studies confirmed the absence of any chemical interaction or degradation during storage.

Table 6. Stability Study Results for Optimized Formulation (F10)

Storage Time (Weeks)	Drug Content (%)	Dissolution at 120 min (%)
Initial	100.00 ± 0.45	97.82 ± 3.23
2	99.78 ± 0.56	97.45 ± 3.12
4	99.23 ± 0.67	96.89 ± 3.34
6	98.67 ± 0.78	96.54 ± 3.45

Storage conditions: 40°C ± 2°C/75% ± 5% RH, All values represent mean ± SD (n=3)

4. Discussion

The improvement in tadalafil solubility through cyclodextrin complexation can be attributed to several mechanisms. The primary mechanism involves the inclusion of the hydrophobic portions of tadalafil within the cyclodextrin cavity, creating a hydrophilic exterior that facilitates interaction with the aqueous environment. The higher stability constant (Ks) observed with HP-β-CD (727.73 M-1) compared to β-CD (410.25 M-1) suggests stronger guest-host interactions, likely due to the additional hydroxypropyl groups providing supplementary hydrogen bonding sites [28].

The microwave irradiation method showed better results compared to conventional techniques, achieving a 3.7-fold increase in aqueous solubility for the TF/HP-β-CD complex. This can be explained by the unique characteristics of microwave heating. First, the rapid and uniform heating provided by microwave irradiation reduces local concentration gradients, promoting more complete complex formation. Second, the molecular level heating creates temporary dipole-dipole interactions that facilitate the entry of tadalafil molecules into the cyclodextrin cavity. Third, the reduced processing time (6 minutes versus 60 minutes for kneading) minimizes the potential for drug degradation.

The DSC results provided compelling evidence of inclusion complex formation, particularly the disappearance of the tadalafil melting endotherm (301.8°C) in the microwave-irradiated complex. This phenomenon indicates a molecular encapsulation rather than mere physical mixing, supported by the FTIR spectral shifts in the N-H stretching region (3317 to 3324 cm^{-1}).

The PXRD patterns revealed a significant reduction in crystallinity, with the characteristic sharp peaks of tadalafil becoming notably diminished in the complex. This structural transformation from crystalline to partially amorphous state contributes to the enhanced dissolution properties, as amorphous forms generally exhibit higher apparent solubility [29].

The dissolution profiles demonstrated clear superiority of the inclusion complexes over pure tadalafil. The initial dissolution rate (DR30min) increased from 0.142%/min for pure drug to 0.827%/min for the TF/HP-β-CD microwave complex. This enhancement can be attributed to:

- The improved wettability of the drug surface due to the hydrophilic exterior of the complex
- Reduced particle size (from 77.89 μm to 42.80 μm) increasing the surface area available for dissolution
- Local solubilization effects in the microenvironment of the dissolving surface
- The formation of readily soluble inclusion complexes at the drug-medium interface

The stability studies indicated physicochemical properties of the optimized formulation (F10) under both normal and accelerated conditions. The dissolution profiles and chemical integrity suggests that the inclusion complex effectively protects the drug from environmental factors while preserving its enhanced solubility characteristics. When compared to other solubility enhancement techniques reported in literature, such as solid dispersions (2.8-fold increase) and lipid-based formulations (3.2-fold increase), the current technique using microwave-assisted cyclodextrin complexation (3.7-fold increase) shows better performance while offering advantages in terms of processing simplicity and stability [30].

5. Conclusion

The present work showed the potential of microwave-assisted cyclodextrin complexation in improving the aqueous solubility and dissolution of tadalafil. The microwave irradiation method found to be superior to conventional preparation techniques. The TF/HP-β-CD complex exhibited a 3.7-fold increase in aqueous solubility and achieved nearly complete drug release (97.82%) within 120 minutes, compared to only 42.75% release from pure tadalafil. The physicochemical characterization confirmed the formation of true inclusion complexes, with DSC, FTIR, and PXRD data supporting the molecular encapsulation of tadalafil within the cyclodextrin cavity. The stability studies confirmed the stability of the optimized formulation under various storage conditions, indicating its potential for commercial development.

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