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Comparison of PEG 4000 and 6000 in Solid Dispersion of Tadalafil Prepared by Melting Method

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Abstract: Tadalafil is a BCS Class II drug with very low aqueous solubility, limiting its oral bioavailability. Solid dispersion technology using polyethylene glycol (PEG) is an effective strategy to enhance solubility. This study aimed to compare the effectiveness of PEG 4000 and PEG 6000 as carriers in amorphous solid dispersions of tadalafil prepared by the melting method. Solid dispersions were prepared at weight ratios (tadalafil:polymer) of 1:1, 1:2, 1:3, and 1:4 for both PEG 4000 and PEG 6000 using the fusion technique (70 °C). The formulations were characterized by Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), and Fourier Transform Infrared (FTIR) spectroscopy. Solubility studies were conducted in distilled water and phosphate buffer (pH 6.8) and analyzed via a validated HPLC method. Solid dispersions with PEG 6000 at a 1:3 ratio (F7) exhibited the highest solubility enhancement, reaching 16.08 ± 0.6 µg/mL in water. For PEG 4000, the 1:2 ratio (F2) was optimal (8.20 ± 1.3 µg/mL). PXRD and DSC analyses confirmed the transformation of crystalline tadalafil into an amorphous state within the polymer matrix. FTIR spectra indicated shifts in N-H and C=O bands, suggesting hydrogen bond formation. In conclusion, PEG 6000 produced a superior solid dispersion for tadalafil compared to PEG 4000. The primary mechanism is the formation of an amorphous system stabilized by hydrogen bonding. This study provides a formulation basis for improving the oral delivery of tadalafil.

Introduction

Tadalafil, a phosphodiesterase-5 inhibitor, is characterized by very low aqueous solubility and a high melting point (~300 °C), placing it in Biopharmaceutics Classification System (BCS) Class II. This poor solubility leads to a slow dissolution rate in the gastrointestinal tract, resulting in limited oral bioavailability, delayed onset of action, inter-patient response variability, and the need for relatively high doses to achieve therapeutic effects in erectile dysfunction (1, 2, 3). Various formulation strategies have been explored to enhance the solubility and dissolution rate of tadalafil, including solid dispersions (SD), self-nanoemulsifying systems, inclusion complexes, and supercritical anti-solvent techniques (4, 5, 6). Among these, solid dispersion with hydrophilic polymers is one of the most widely used approaches due to its simple concept, scalability, and ability to generate a more soluble amorphous form with a faster dissolution rate (7, 8, 9).

Amorphous solid dispersion (ASD) technology is designed to transform a crystalline drug into a higher-energy, more soluble amorphous state, stabilized within a polymeric matrix (10). Various ASD manufacturing methods have been developed, such as melting/fusion, solvent evaporation, spray-drying, hot-melt extrusion (HME), freeze-drying, and supercritical fluid techniques (11, 12). The choice of method significantly influences particle size, degree of amorphicity, drug-polymer interactions, and the physical stability of the final product (13, 14, 15). Some studies indicate that melting-based methods (fusion or HME) can produce relatively more stable dispersions compared to some solvent-based formulations, although they carry a risk of thermal degradation if process temperatures are not controlled (16). For tadalafil, which has a high melting point and relative thermal stability, a melting-based approach is highly relevant for systematic investigation (17). Recent studies continue to explore innovative approaches for tadalafil solubility enhancement, including Type IV lipid-based formulations that achieved over 95% dissolution within 5 minutes (27).

Polyethylene glycol (PEG) is the most extensively used hydrophilic carrier in solid dispersions, with various molecular weights (e.g., PEG 1500, 4000, 6000, 8000, 10000) offering different solubility and physical characteristics (18, 19). PEG enhances the dissolution of hydrophobic drugs through several mechanisms: improved wetting and solubility, reduced crystallite size, potential partial/total conversion to an amorphous form, and prevention of drug crystal aggregation in the dissolution medium (20, 21). Various poorly soluble drugs such as haloperidol, simvastatin, atorvastatin, rivaroxaban, lansoprazole, glibenclamide, flurbiprofen, and amiodarone have shown significant improvements in solubility and dissolution rate when formulated as solid dispersions with PEG 4000 or PEG 6000, via either melting or solvent evaporation methods (22, 23, 24). This confirms PEG's role as a versatile carrier for enhancing the biopharmaceutical performance of BCS Class II drugs.

A comparison of the performance of different PEG molecular weights in solid dispersions shows that polymer chain length can affect dissolution characteristics, powder flow, compressibility, and tablet disintegration (19, 20). Some reports suggest that higher molecular weight PEG (e.g., 6000 or 10000) may provide slower hydration but greater film-forming and solubilizing capacity, sometimes resulting in higher dissolution compared to PEG 4000 at specific compositions (20, 21). The molecular weight of PEG critically influences its interaction with drug molecules, with higher molecular weight polymers potentially offering more interaction sites for hydrogen bonding (26). Studies on amiodarone and atorvastatin indicate that increasing PEG molecular weight and polymer ratio can enhance dissolution efficiency (DE) by 20–30% compared to formulations with lower molecular weight PEG, although effects on disintegration time and tablet hardness are also significant (19, 22). Conversely, some systems show that PEG 4000 can lead to faster disintegration or a more immediate dissolution profile, which may be advantageous for rapid-release dosage forms (19, 21, 23). These differences underscore the need for targeted comparative studies between PEG 4000 and PEG 6000 within the context of a specific drug and processing method.

The melting (fusion) method is a classic solid dispersion technique that avoids organic solvents and is relatively simple from an industrial standpoint. However, it is highly influenced by the melting points of the drug and polymer, the viscosity of the molten phase, and the cooling rate (25). Various studies demonstrate that PEG 4000 or 6000-based solid dispersions prepared by the melting method can increase drug dissolution more than twofold compared to the pure drug, provided heating and cooling conditions are controlled to prevent recrystallization (18, 20). The use of the melting method for haloperidol and rivaroxaban with PEG 4000, and for atorvastatin with PEG 4000, 10000, and poloxamer 188, resulted in significantly faster dissolution profiles and higher dissolution efficiency compared to the crystalline drug form (18, 21). A study on glibenclamide with a ternary system indicated that combining PEG 4000 with an anionic surfactant could improve physical stability and maintain enhanced dissolution for at least 12 months (23). The absence of long-term stability data under ICH conditions (e.g., 40 °C and 75% RH) means that the physical stability of the amorphous form during storage requires further investigation. Nevertheless, the specific influence of PEG molecular weight (4000 vs. 6000) in solid dispersions prepared purely by the melting method has not been adequately explored for tadalafil. The melting method for drugs with high melting points does not require melting the drug, but rather dispersing the drug in a liquid polymer.

To date, the development of carrier systems for tadalafil has focused more on non-PEG polymers such as poloxamers, copovidone, Soluplus, and self-nanoemulsifying systems, which have been shown to improve solubility, dissolution, and bioavailability by several fold (1, 17). Formulations of tadalafil solid dispersion with modern hydrophobic-hydrophilic polymers have shown solubility increases of up to several hundred-fold and plasma AUC increases of up to 10-fold, but often involve more complex processes and excipients, as well as higher costs (1, 3). On the other hand, there are few reports specifically comparing PEG 4000 and PEG 6000 as carriers in tadalafil solid dispersions prepared by the melting method, even though both polymers are inexpensive, widely available, and have proven effective for various BCS Class II drugs (18, 19). Therefore, a comparative study to evaluate the influence of PEG type (4000 vs. 6000) on the micromeritic properties, degree of amorphicity, dissolution rate, and potential bioavailability of tadalafil is essential for designing an effective, stable, and economical oral solid dosage form based on solid dispersion technology. A comparison of the performance of different PEG molecular weights in solid dispersions shows that polymer chain length can affect dissolution characteristics. Although PEG has been widely used, there has been no systematic comparative study between PEG 4000 and PEG 6000 for tadalafil with the melting method at various ratios and providing practical guidance for selecting the most optimal and economical polymer.

Methodology

Materials

Pure tadalafil (USP grade) was obtained from PT. Galenium. PEG 4000 and PEG 6000 (pharmaceutical grade) were from Bratachem. Acetonitrile (HPLC grade) was from Supelco. Trifluoroacetic acid and water for injection (WFI) were from CV. General Labora. Potassium dihydrogen phosphate (KH_2PO_4) and sodium hydroxide (NaOH) were of analytical grade.

Preparation of Solid Dispersions

Tadalafil ASDs were prepared using the melting method. Tadalafil and the polymer (PEG 4000 or PEG 6000) were accurately weighed in weight-to-weight (w/w) ratios of 1:1, 1:2, 1:3, and 1:4. The polymer was melted first in a beaker on a hot plate at 70 °C with gentle magnetic stirring. Once fully molten, tadalafil was added, and stirring continued at 70 °C for 10 minutes until a homogeneous molten mixture was obtained. It is important to emphasize that the processing temperature of 70 °C is far below the melting point of crystalline tadalafil (~300 °C). Therefore, the formation mechanism relies on the dissolution and molecular dispersion of the drug within the molten polymer carrier, rather than co-melting of the two

components. Complete dissolution of tadalafil in the molten PEG was visually confirmed by the formation of a clear, transparent, and homogeneous melt for the optimal formulations (F2 and F7). Although the exact saturation solubility of tadalafil in molten PEG 4000 and PEG 6000 at 70 °C was not experimentally determined in this initial screening study, the subsequent solid-state characterization (PXRD and DSC) provided indirect evidence. The complete absence of characteristic tadalafil diffraction peaks and melting endotherms in the final solid dispersions, as presented in Figures 3–4, confirmed that the drug was successfully maintained in a molecularly dispersed or amorphous state within the polymer matrix upon solidification. This observation suggests that the drug loadings employed (ratios up to 1:4) were within the miscibility limit for these systems under the specified processing conditions. The processing temperature of 70 °C was selected because it is approximately 10-15 °C above the melting point of both PEG grades, ensuring complete polymer melting while remaining well below the degradation temperature of tadalafil (>250 °C), thus maintaining drug stability throughout the process. The melt was rapidly poured into a pre-cooled glass plate and immediately transferred to a freezer (-20 °C) for 48 h to facilitate rapid solidification and inhibit the recrystallization of tadalafil, thereby promoting the formation of a metastable amorphous dispersion (9, 11). The solidified mass was gently ground in a mortar and pestle, passed through an 80-mesh sieve, and stored in a desiccator until use. The formulations were designated as F1-F4 (PEG 4000 ratios 1:1 to 1:4) and F5-F8 (PEG 6000 ratios 1:1 to 1:4).

Preliminary Screening: Melting Point

The melting behavior of pure tadalafil and the ASDs was assessed using a Melting-Temp Electrothermal Apparatus. Samples were placed in capillary tubes and heated at a rate of 2 °C/min from 50 °C to 320 °C. The temperature range at which sample collapse or melting occurred was noted.

Solubility Studies

Hplc Method Development and Validation

Tadalafil quantification was performed using a Shimadzu LC-20AT HPLC system with a UV detector. Separation was achieved on a Nucleosil C-18 column (150 x 4.6 mm, 5 µm) using an isocratic mobile phase of acetonitrile and 0.1% trifluoroacetic acid in WFI (45:55, v/v) at a flow rate of 1,5 mL/min. The column temperature was 40 °C, injection volume was 20 µL, and detection wavelength was 285 nm. The method was validated for selectivity, linearity (1-200 µg/mL), accuracy, precision (intra-day and inter-day), and robustness per ICH Q2(R1) guidelines.

Solubility Measurement

An excess amount of each ASD (equivalent to 50 mg tadalafil) was added to 50 mL of dissolution medium (distilled water or phosphate buffer pH 6.8) in a conical flask. The suspensions were agitated on a magnetic stirrer at 100 rpm at room temperature (25 ± 1 °C). Aliquots (2 mL) were withdrawn at predetermined time intervals (3, 24, 48 h), filtered immediately through a 0.45 µm membrane filter, and analyzed by HPLC. Samples equivalent to 10 mg of tadalafil were accurately weighed and directly introduced into the dissolution vessel to simulate powder dispersion behavior. The 3-hour time point was selected for primary comparison as it represented the plateau phase in preliminary kinetics studies. All tests were performed in triplicate

In Vitro Dissolution Study

The dissolution profiles of pure tadalafil and the optimal solid dispersions (F2 and F7) were determined using the paddle method (Logan UDT 804). The test was performed in 900 mL of phosphate buffer pH 6.8, maintained at 37 ± 0.5 °C with a paddle rotation speed of 50 rpm. Samples equivalent to 10 mg of tadalafil were introduced into the vessel. Aliquots (5 mL) were withdrawn at 5, 10, 15, 30, 45, 60, and 90 minutes, filtered through a 0.45 µm membrane filter, and suitably diluted. The concentration of tadalafil was determined using the validated HPLC method. The dissolution efficiency at 60 minutes (DE60) and mean dissolution time (MDT) were calculated to quantitatively compare the profiles.

Solid-state Characterization

Powder X-ray Diffraction (PXRD)

PXRD patterns were recorded using a Panalytical Xpert Pro diffractometer with Cu-Kα radiation (λ = 1,5406 Å). Samples were scanned from 4° to 40° (2θ) with a step size of 0.02° and a scan speed of 2°/min.

Differential Scanning Calorimetry (DSC)

Thermal analysis was performed using a Thermo plus EVO DSC 8230. Samples (3-5 mg) were sealed in aluminum pans and heated under a nitrogen purge (50 mL/min). The heating protocol was from 25 °C to 350 °C at a rate of 10 °C/min.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were obtained using a Bruker Alpha II spectrometer in ATR mode. Scans were performed from 4000 to 400 cm^{-1} with a resolution of 4 cm^{-1}.

Statistical Analysis

Data are presented as mean ± standard deviation (SD). Statistical analysis was performed using SPSS 16.0. One-way ANOVA followed by Tukey's post-hoc test was used to compare solubility among different formulations within each polymer group. An independent samples t-test was used to compare the best-performing formulation from each polymer group (F2 vs. F7) for both solubility and dissolution parameters (DE60, MDT). A p-value < 0.05 was considered statistically significant. For dissolution profiles, pairwise comparisons at each time point were also performed using t-tests with Bonferroni correction for multiple comparisons.

Results and Discussion

Preparation and Characterization of Amorphous Solid Dispersions

The preparation of tadalafil solid dispersions began by weighing the active ingredient and the polymers PEG 4000 and PEG 6000 in varying weight-to-weight (w/w) ratios. The formulations were designated as follows: F1 (1:1 PEG 4000), F2 (1:2 PEG 4000), F3 (1:3 PEG 4000), F4 (1:4 PEG



Figure 1. Photograph of tadalafil solid dispersion powders with PEG.

Table 1. Melting point analysis of pure tadalafil and solid dispersion formulations.

Formulation	Melting Range (°C)	Description
Tadalafil	298–301	Crystalline
F1–F8	Not observed	Amorphous

4000), F5 (1:1 PEG 6000), F6 (1:2 PEG 6000), F7 (1:3 PEG 6000), and F8 (1:4 PEG 6000). The variation in polymer ratios aimed to identify the optimal composition for enhancing tadalafil solubility and forming the most effective amorphous solid dispersion.

PEG is a widely used hydrophilic carrier in solid dispersion technology due to its ability to inhibit crystal growth and phase transformation, thereby improving drug solubility (1, 2). Both PEG 4000 and PEG 6000 are commonly employed in solid dispersions because of their high aqueous solubility, low melting points, low toxicity, and hydrophilic nature (7). The melting method was selected for its simplicity and cost-effectiveness (8). The hygroscopic nature suggests that appropriate packaging with desiccants would be necessary to ensure long-term physical stability by preventing moisture uptake and potential recrystallization.

The solid dispersions were prepared by melting the physical mixtures on a hot plate, followed by rapid cooling in a freezer for 48 h. The resulting solids were ground into fine, yellowish-brown, hygroscopic powders, as shown in **Figure 1**.

Initial Screening: Melting Point Analysis

The melting point is a critical physical property that indicates the transition from a solid to a liquid state. For crystalline substances, melting occurs at a sharp, defined temperature, while amorphous materials typically show a broad or indistinct melting range due to their disordered molecular structure (9).

The melting point of pure tadalafil was determined to be 298–301 °C, consistent with literature values for its crystalline form (6). In contrast, all solid dispersion formulations (F1–F8) showed no distinct melting point, suggesting the transformation of crystalline tadalafil into

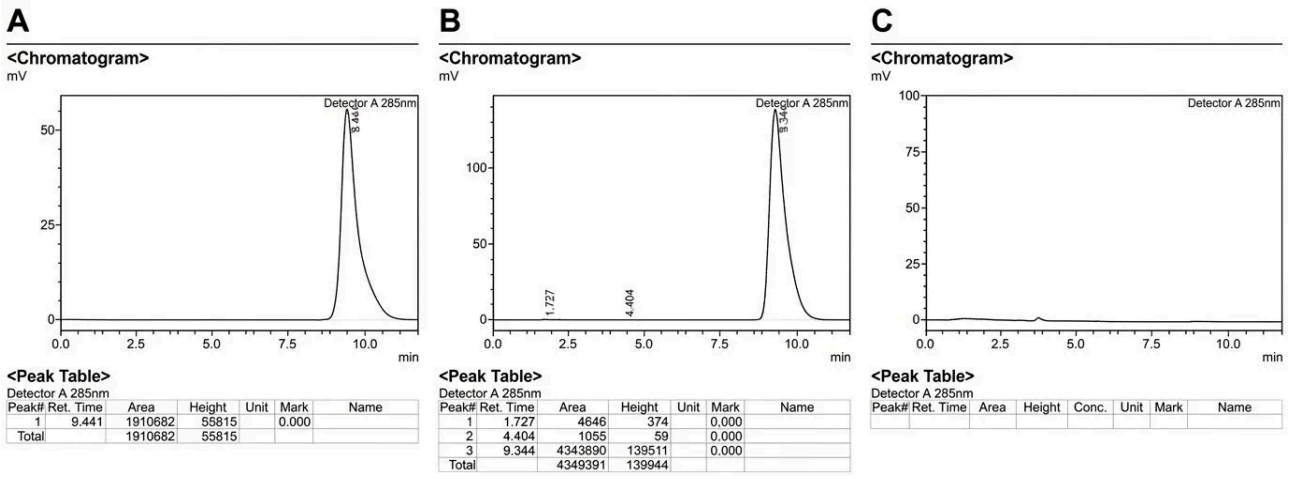


Figure 2. HPLC chromatograms of pure tadalafil, TDL:PEG solid dispersion, and the blank solution. (A) Pure tadalafil; (B) TDL:PEG solid dispersion; (C) Blank solution. Chromatographic conditions: C-18 Nucleosil column (150 x 4.6 mm, 5 µm); mobile phase of acetonitrile:0.1% TFA in WFI (45:55, v/v); flow rate of 1.5 mL/min; column temperature of 40 °C; injection volume of 20 µL; and detection wavelength of 285 nm.

Table 2. Representative HPLC chromatograms: (A) tadalafil standard, (B) solid dispersion sample (TDL:PEG), (C) mobile phase blank.

Solution	Peak Upper	
	Retention Time	**Peak**
Tadalafil Standard (TDL)	9.441	1910682
Solid dispersion sample	9.344	12503195
Mobile phase blank	ND	ND

an amorphous state within the PEG matrix (**Table 1**). This loss of crystallinity is a key indicator of successful solid dispersion formation and is expected to enhance dissolution and solubility (7).

Validation of HPLC Analytical Method

A reliable HPLC method was validated to ensure accurate quantification of tadalafil in solubility studies.

Selectivity: Chromatograms of the tadalafil standard and sample solutions showed single, well-resolved peaks with retention times of 9.44 and 9.34 minutes, respectively (**Figure 2**). No interfering peaks were detected from the blank mobile phase, confirming the method's selectivity (8).

Linearity: The method demonstrated excellent linearity over a concentration range of 1–200 µg/mL. The calibration curve yielded a correlation coefficient (R) of 0.9998, which exceeds the acceptance criterion of ≥0.999, indicating a robust linear relationship between concentration and detector response (9).

Solubility Studies

The solubility of tadalafil from various solid dispersions was evaluated in distilled water and phosphate buffer pH 6,8. Samples were analyzed at 3, 24, and 48 hours. The 3-hour time point was selected for primary comparison as it represents the initial dissolution phase and showed peak solubility before a gradual decline, a phenomenon also observed in prior studies (9).

The results demonstrated a significant increase in tadalafil solubility for all solid dispersion formulations compared to the pure drug, which was practically insoluble (**Table 2**). For PEG 4000-based dispersions, the highest solubility in water was achieved with the 1:2 ratio (F2: 8.20 ± 1.3 µg/mL). For PEG 6000-based dispersions, the 1:3 ratio (F7) yielded the optimal solubility in both water (16.08 ± 0.6 µg/mL) and buffer (14.23 ± 0.8 µg/mL).

The sharp decline in tadalafil concentration between 3 and 48 h points to precipitation from a supersaturated state, a phenomenon commonly observed in amorphous solid dispersions (28). This precipitation process is governed by the kinetics of nucleation and crystal growth, which can be significantly retarded by the presence of polymeric inhibitors that adsorb onto crystal surfaces or increase the energy barrier for nucleation (29, 30). The superior performance of PEG 6000 over PEG 4000 in maintaining higher solubility at later time points can be attributed to its longer polymer chains, which provide more hydrogen bonding sites and greater viscous resistance, thereby more effectively delaying the onset of crystallization (31).

In Vitro Dissolution

Statistical comparison of dissolution profiles revealed that F7 showed significantly higher ($p < 0.05$) drug release than F2 at all time points from 10 minutes onward. The differences in DE60 ($t = 5.23$, $df = 4$, $p = 0.006$) and MDT ($t = -6.18$, $df = 4$, $p = 0.003$) were also statistically significant.

Solid-state Characterization

Powder X-ray Diffraction (PXRD)

PXRD analysis was conducted to assess changes in the

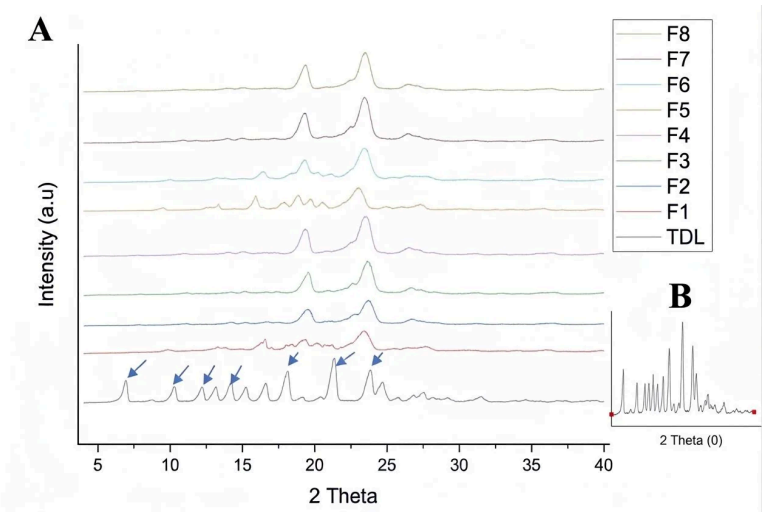


Figure 3. X-ray diffraction analysis of pure tadalafil and its solid dispersions with PEG. (A) XRD diffraction patterns of pure Tadalafil (TDL) and its solid dispersions with PEG 4000 and PEG 6000 at various ratios. (B) PXRD test results for pure Tadalafil and amorphous solid dispersions.

crystallinity of tadalafil. The diffractogram of pure tadalafil displayed sharp, intense peaks characteristic of a crystalline structure (**Figure 3**). In contrast, the diffractograms of formulations F2, F3, F4, F7, and F8 exhibited a significant reduction in the characteristic tadalafil peaks. Instead, they showed broad, halo-like patterns indicative of an amorphous state. This confirms that the crystalline tadalafil was molecularly dispersed or converted to an amorphous form within the PEG matrix, a change directly linked to improved solubility (8, 9). While the PXRD patterns are presented qualitatively, the complete absence of characteristic tadalafil diffraction peaks in the solid dispersion formulations strongly supports the conclusion of amorphization. Quantitative analysis of crystallinity, while valuable, was beyond the scope of this initial formulation screening study.

Differential Scanning Calorimetry (DSC)

DSC thermograms provided thermal behavior insights. Pure tadalafil showed a sharp endothermic melting peak at 304 °C (**Figure 4**). All solid dispersion thermograms displayed only the endothermic peak corresponding to PEG melting (~60 °C) (13). The complete absence of the distinct tadalafil melting peak in these formulations strongly indicates the loss of its crystalline lattice and the formation of a homogeneous amorphous solid solution or dispersion (9). The absence of the tadalafil melting endotherm in the DSC thermograms, when interpreted in conjunction with the PXRD data obtained at ambient temperature (which is not subject to thermal artifacts), provides strong evidence that the drug was already in the amorphous state prior to the thermal scan. Although it remains theoretically possible that trace crystalline residues could dissolve into the molten PEG matrix during the DSC heating ramp, the PXRD patterns recorded at room temperature definitively rule out the presence of significant crystallinity in the raw solid dispersions. Therefore, the combined PXRD and DSC data support the conclusion that molecular dissolution of tadalafil occurred during the fusion preparation step at 70 °C, and that the

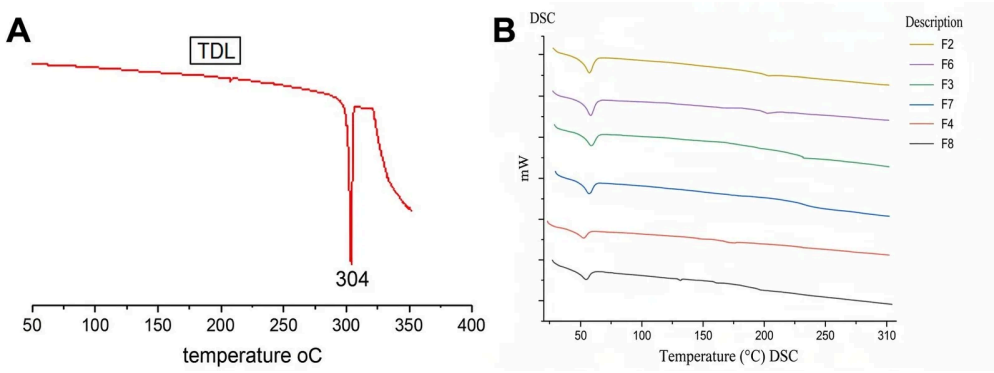


Figure 4. Differential scanning calorimetry (DSC) analysis of pure tadalafil and its solid dispersion formulas. (A) DSC test results for pure Tadalafil. (B) DSC thermograms of solid dispersions using different polymers and ratios: F2 (PEG 4000, 1:2), F6 (PEG 6000, 1:2), F3 (PEG 4000, 1:3), F7 (PEG 6000, 1:3), F4 (PEG 4000, 1:4), and F8 (PEG 6000, 1:4.5).

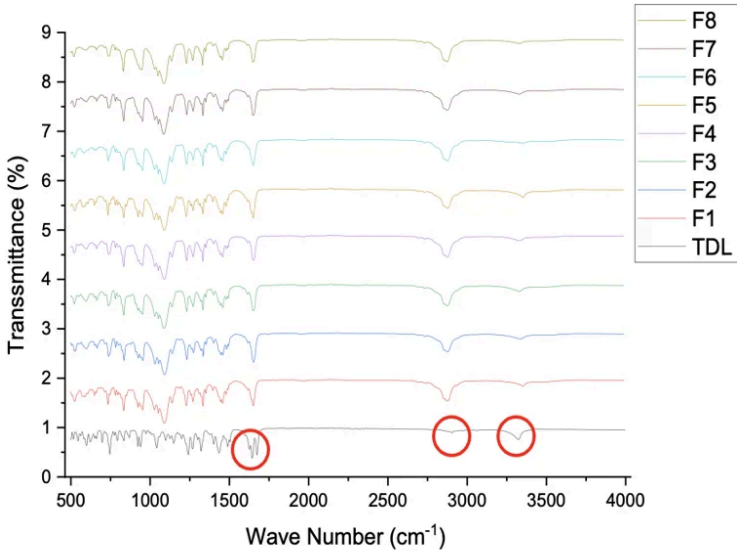


Figure 5. Fourier-transform infrared (FTIR) spectroscopy analysis of pure tadalafil and its solid dispersions. (A) FTIR spectra of pure Tadalafil and its dispersions using PEG 4000 polymers at ratios of F1 (1:1), F2 (1:2), F3 (1:3), and F4 (1:4). (B) FTIR spectra of Tadalafil dispersions using PEG 6000 polymers at ratios of F5 (1:1), F6 (1:2), F7 (1:3), and F8 (1:4).

amorphous state was kinetically trapped upon rapid cooling.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR analysis was performed to investigate potential molecular interactions between tadalafil and PEG. The spectrum of pure tadalafil showed characteristic absorption bands for N-H stretching (3328 cm^{-1}), C=O amide (1677 cm^{-1}), and aromatic C=C (1649 cm^{-1}) (**Figure 5**). In the solid dispersion spectra, all principal tadalafil peaks were present but with reduced intensity and slight shifts. Notably, shifts were observed in the N-H and C=O regions, suggesting the involvement of these functional groups in hydrogen bonding interactions with the ether oxygen of PEG (15). The N-H stretching band shifted from 3328 cm^{-1} to approximately 3310 cm^{-1} and broadened significantly, while the C=O amide band at 1677 cm^{-1} also showed broadening. These spectral changes are characteristic of hydrogen bond formation (15). Specifically, the shift to lower wavenumber for N-H stretching indicates that this proton is involved in hydrogen bonding, acting as a donor to an electronegative atom—in this case, the ether oxygen (C-O-C) of the PEG chain. The broadening of the C=O band suggests that the carbonyl group may also participate as a hydrogen bond acceptor or that its environment is altered by the interaction. Importantly, these hydrogen bonding interactions were more pronounced in the F7 (PEG 6000, 1:3) spectrum compared to F2, suggesting that the longer PEG 6000 chains may provide more opportunities for drug-polymer interactions. This difference could explain the superior stabilization and enhanced dissolution observed with PEG 6000. The absence of new peaks indicates the interactions are physical (hydrogen bonding) rather than chemical.

The combined PXRD, DSC, and FTIR data conclusively demonstrate the successful conversion of crystalline tadalafil into an amorphous state within the PEG-based solid dispersions. This amorphization, facilitated by hydrogen bonding, is the primary mechanism responsible for the observed enhancement in aqueous solubility.

Conclusion

This study successfully developed and characterized amorphous solid dispersions of tadalafil using PEG 4000 and PEG 6000 as hydrophilic carriers via the melting method, aiming to enhance its aqueous solubility. A comprehensive evaluation of solubility and solid-state properties led to the conclusion that this study successfully developed amorphous solid dispersions of tadalafil using PEG 4000 and PEG 6000 as hydrophilic carriers via the fusion (melting) method. The results demonstrated that the tadalafil:PEG 6000 ratio of 1:3 (Formulation F7) was the most optimal formulation, exhibiting the highest solubility enhancement of up to 16.08 ± 0,6 µg/mL in water, substantially surpassing the PEG 4000-based dispersion which was optimal at a 1:2 (Formulation 2) 8.20 ± 1.3 µg/mL. PXRD and DSC characterization confirmed the transformation of crystalline tadalafil into an amorphous state, while FTIR analysis revealed hydrogen bonding interactions between the N-H and C=O groups of tadalafil and the ether oxygen of PEG, which played a critical role in stabilizing the amorphous system and enhancing the dissolution rate (17).

These findings provide a clear formulation basis for further development of tadalafil oral dosage forms; however, the actual improvement in oral bioavailability cannot be confirmed from the present in vitro data alone. To substantiate the therapeutic advantage of this solid dispersion system, future studies must include intestinal permeability assays (e.g., Caco-2 cell models or ex vivo gut sac studies) as well as in vivo pharmacokinetic evaluations in appropriate animal models to demonstrate enhanced systemic absorption and pharmacodynamic efficacy.

Abbreviations

PXRD = Powder X-Ray Diffraction; DSC = Differential Scanning Calorimetry; FTIR = Fourier Transform Infrared; PEG = Polyethylene glycol; TDL = Tadalafil F= Formula; ASD= Amorphous solid dispersion; HME = hot-melt extrusion; BCS = Biopharmaceutics Classification System

Declaration

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Conflict of Interest
The authors declare no conflict of interest.

Data Availability
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Additional Information

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