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Formulation and Evaluation of Danazol Tablets Using Cyclodextrin Complexation for Improved Oral Bioavailability

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Abstract- Danazol, a BCS Class II synthetic isoxazole derivative of 17α-ethinyl testosterone, exhibits extremely poor aqueous solubility (< 1 µg/mL) and characteristically low, highly variable oral bioavailability (2–6%) from conventional formulations, necessitating high daily doses of 200–800 mg and predisposing patients to dose-dependent androgenic adverse effects. This study investigated cyclodextrin inclusion complexation as a solubility and dissolution enhancement strategy for danazol tablet development.

Danazol–cyclodextrin inclusion complexes were prepared using β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) at drug-to-cyclodextrin molar ratios of 1:1 and 1:2 by three methods: physical mixing, kneading, and solvent evaporation, yielding eight formulations (F1–F8). Complexes were characterized by Fourier Transform Infrared spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC), and Powder X-Ray Diffraction (PXRD). Phase solubility studies were conducted following the Higuchi–Connors method. Tablet formulations (T1–T6) were prepared by direct compression and evaluated for pharmacopoeial quality attributes and in-vitro dissolution performance.

Phase solubility studies confirmed AL-type profiles for both cyclodextrins, with HP-β-CD demonstrating superior stability constants (Ks = 2847.3 M^{-1} vs 685.4 M^{-1} for β-CD) and 22.3-fold solubility enhancement at 10 mM. FT-IR, DSC, and PXRD analyses converged in identifying F8 (danazol:HP-β-CD, 1:2, solvent evaporation) as the optimally amorphized complex, exhibiting complete loss of danazol crystallinity. The optimized tablet T6 achieved 93.8% drug dissolution within 90 minutes — a 5.9-fold improvement over pure danazol control (16.8%) — with T50% reduced from >90 to 10.4 minutes (87% reduction). All tablet formulations met pharmacopoeial quality specifications. Drug release followed Fickian diffusion (Korsmeyer–Peppas $R^2 = 0.9882$, n = 0.428).

Cyclodextrin inclusion complexation, particularly with HP-β-CD via solvent evaporation, represents a scientifically validated, pharmaceutically viable, and industrially scalable strategy for dramatically improving danazol oral bioavailability. The direct compression tablet manufacturing approach further enhances commercial feasibility.

Keywords: Danazol; Cyclodextrin inclusion complex; β-Cyclodextrin; Hydroxypropyl-β-cyclodextrin; BCS Class II; Solubility enhancement; Oral bioavailability; Direct compression; In-vitro dissolution

I. INTRODUCTION

The oral route of drug administration remains the preferred, most widely employed, and most extensively investigated pathway for delivering therapeutic agents to achieve systemic pharmacological effects, accounting for more than 85 percent of all pharmaceutical dosage forms prescribed globally. However, oral drug delivery faces a central physicochemical challenge: poor aqueous solubility. Between 40 and 70 percent of newly identified chemical entities in contemporary drug development pipelines exhibit insufficient aqueous solubility to support adequate gastrointestinal dissolution and reliable oral bioavailability (Amidon et al., 1995; Yalkowsky et al., 2004).

Danazol, the subject of the present investigation, is a synthetic isoxazole derivative of 17α-ethinyl testosterone widely employed in the clinical management of endometriosis, fibrocystic breast disease, hereditary angioedema, and menorrhagia. Despite well-established therapeutic efficacy, the clinical utility of danazol is substantially limited by its extremely poor aqueous solubility (< 1 µg/mL), high partition coefficient (log P ≈ 3.3–4.0), and highly variable oral bioavailability estimated at only 2–6% from conventional formulations. The Biopharmaceutics Classification System (BCS) categorizes danazol as a Class II drug — characterized by high membrane permeability but very poor aqueous solubility — in which dissolution, rather than permeation across the intestinal epithelium, constitutes the primary rate-limiting barrier to gastrointestinal absorption.

The pharmacokinetic variability of danazol necessitates administration of high doses (200–800 mg/day) to achieve therapeutic plasma concentrations, which in turn increases the incidence and severity of androgenic adverse effects including acne, weight gain, hirsutism, voice alterations, and hepatotoxicity. These limitations create a compelling pharmacological rationale for formulation strategies capable of overcoming the solubility barrier: if dissolution and absorption of danazol can be improved through superior formulation, lower doses may achieve equivalent therapeutic plasma concentrations, proportionally reducing the androgenic and hepatotoxic adverse effect burden.

Cyclodextrin inclusion complexation represents a scientifically validated, pharmaceutically accepted, and industrially scalable approach for enhancing the aqueous solubility and dissolution rate of BCS Class II drugs. Cyclodextrins are cyclic oligosaccharides with a distinctive molecular architecture comprising a hydrophobic internal cavity and a hydrophilic external surface, enabling formation of non-covalent inclusion complexes with lipophilic drug molecules. Among available cyclodextrins, β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) have been most extensively investigated and utilised in pharmaceutical formulations.

The present study was designed to formulate and evaluate danazol tablets incorporating cyclodextrin inclusion complexes, with the primary objective of enhancing aqueous solubility, accelerating the dissolution rate, and ultimately improving oral bioavailability. Danazol–cyclodextrin inclusion complexes were prepared using β-CD and HP-β-CD at molar ratios of 1:1 and 1:2 by three established methods, comprehensively characterized for physicochemical properties, and formulated into immediate-release tablets by direct compression.

II. MATERIALS AND METHODS

2.1 Materials

Danazol (purity ≥ 99.0%) was obtained as a generous gift sample from a reputed pharmaceutical manufacturing company. β-Cyclodextrin (β-CD, purity ≥ 98.0%) and Hydroxypropyl-β-cyclodextrin (HP-β-CD, average degree of substitution 0.65, purity ≥ 98.0%) were procured from Sigma-Aldrich (St. Louis, USA). Microcrystalline cellulose (Avicel PH 102) was obtained from FMC BioPolymer, USA. Polyvinylpyrrolidone K-30 (PVP K-30), croscarmellose sodium, magnesium stearate, and talc were procured from S.D. Fine Chemicals, India. All reagents and solvents including ethanol (99.9%), methanol (HPLC grade), acetone, potassium dihydrogen phosphate, and sodium hydroxide were of analytical or HPLC grade.

2.2 Analytical Method Development

A UV-spectrophotometric analytical method was developed and validated for quantitative estimation of danazol in dissolution samples. The UV absorption spectrum of danazol dissolved in phosphate buffer (pH 6.8) displayed a well-resolved absorption maximum (λmax) at 286 nm. A ten-point calibration curve was constructed over the 2–20 μg/mL range, yielding the regression equation $A = 0.0471C + 0.0001$ ($R^2 = 0.9999$), with precision (%RSD < 2%) and accuracy (% recovery 98.8–101.2%) fully within acceptable analytical limits.

2.3 Phase Solubility Studies

Phase solubility studies were performed according to the classical method of Higuchi and Connors (1965) to evaluate the interaction between danazol and cyclodextrins (β-CD and HP-β-CD) and to determine the apparent stability constants. Aqueous solutions of β-CD and HP-β-CD were prepared at concentrations ranging from 0 to 10 mM. An excess quantity of danazol (10 mg) was added to 10 mL of each cyclodextrin solution in sealed glass vials, equilibrated at 25 ± 0.5°C and 100 rpm for 72 hours, filtered through 0.45 μm membrane filters, and analyzed at λmax 286 nm. The apparent stability constants (Ks) of 1:1 complexes were calculated using: $K_s = \text{slope} / [S_0 \times (1 - \text{slope})]$, where S_0 is the intrinsic solubility of danazol.

2.4 Preparation of Danazol–Cyclodextrin Inclusion Complexes

Eight danazol–cyclodextrin binary systems (F1–F8) were prepared based on a formulation design matrix involving two cyclodextrin types (β-CD and HP-β-CD), two molar ratios (1:1 and 1:2), and three preparation techniques. Physical mixtures (F1, F2) served as reference controls. Kneading complexes (F3–F6) were prepared by wetting the cyclodextrin with a water–ethanol mixture (1:1 v/v) and adding danazol with continuous manual kneading for 45 minutes, followed by drying at 40°C for 12 hours. Solvent evaporation complexes (F7, F8) were prepared by dissolving danazol in ethanol, dissolving HP-β-CD in distilled water, combining the solutions with stirring at 400 rpm, and removing solvent using a rotary evaporator at 40°C under reduced pressure (200 mbar).

2.5 Physicochemical Characterization

FT-IR spectra of pure danazol, pure cyclodextrins, physical mixtures, and complexes were recorded using a Shimadzu IRTracer-100 spectrophotometer (4000–400 cm^{-1}, KBr pellet method, 16 scans). DSC analysis was performed using a TA Instruments Q2000 differential scanning calorimeter calibrated with indium (heating rate 10°C/minute, 30–320°C, nitrogen atmosphere). X-ray powder diffraction analysis was conducted using a Bruker D8 Advance diffractometer with CuKα radiation ($\lambda = 1.5406$ Å, 2θ range 5–50°, step size 0.02°).

2.6 Tablet Formulation by Direct Compression

Six tablet formulations (T1–T6) were designed incorporating pure danazol (control) and danazol–cyclodextrin inclusion complexes (F1, F3, F5, F7, F8). Each tablet delivered 100 mg equivalent of danazol. All ingredients were accurately weighed, passed through a 60-mesh sieve, geometrically blended, and compressed on a 10-station rotary tablet compression machine (Cadmach CMS-10) to a target hardness of 6–8 kg/cm^2. Tablet excipients included Avicel PH 102 as diluent, lactose monohydrate as filler, PVP K-30 as binder, croscarmellose sodium (4%) as superdisintegrant, magnesium stearate (1%) as lubricant, and talc (2%) as glidant.

2.7 Tablet Evaluation and In-Vitro Dissolution

All tablets were evaluated for pre-compression powder parameters (bulk density, tapped density, Carr's compressibility index, Hausner's ratio, angle of repose) and post-compression pharmacopoeial quality attributes (weight variation, thickness, hardness, friability, disintegration time, drug content uniformity). In-vitro dissolution studies were performed using a USP Type II (paddle) dissolution apparatus (Electrolab TDT-08L) at 50 rpm in 900 mL phosphate buffer pH 6.8, maintained at 37 ± 0.5°C. Samples of 5 mL were withdrawn at 5, 10, 15, 20, 30, 45, 60, and 90 minutes, filtered through 0.45 μm in-line filters, and analyzed by UV spectrophotometry at 286 nm. Dissolution data were analyzed statistically using one-way ANOVA with Tukey's post-hoc test ($p < 0.05$). The similarity factor (f2) was calculated to compare dissolution profiles between test formulations and the control.

III. RESULTS AND DISCUSSION

3.1 Preformulation and Solubility Profile

Physical examination confirmed danazol as a white to off-white crystalline powder with a faint characteristic odour, consistent with pharmacopoeial specifications. The melting point was determined at 225 ± 1°C, confirming identity and adequate purity. The partition coefficient ($\log P = 3.68 \pm 0.12$, $n = 3$) confirmed the pronounced lipophilic character of danazol, consistent with its BCS Class II classification.

Danazol displayed extremely poor aqueous solubility across all aqueous media tested: 0.82 ± 0.06 μg/mL in distilled water and 1.24 ± 0.08 μg/mL in phosphate buffer pH 6.8, classifying it unambiguously as practically insoluble. In contrast, organic solvents demonstrated orders-of-magnitude higher solvation capacity: acetone (42.8 ± 1.8 mg/mL), ethanol (28.4 ± 1.2 mg/mL), and methanol (18.6 ± 0.9 mg/mL), validating the use of ethanol as co-solvent in the kneading and solvent evaporation complexation procedures.

Table 1. Solubility of danazol in various solvents at 25 ± 1°C (n = 3)

Solvent / Medium	Solubility (Mean ± SD)	Classification
Distilled water	0.82 ± 0.06 μg/mL	Practically insoluble
Phosphate buffer pH 6.8	1.24 ± 0.08 μg/mL	Practically insoluble
0.1 N HCl (pH 1.2)	0.95 ± 0.07 μg/mL	Practically insoluble
Ethanol (99%)	28.4 ± 1.2 mg/mL	Freely soluble
Methanol	18.6 ± 0.9 mg/mL	Freely soluble
Acetone	42.8 ± 1.8 mg/mL	Very freely soluble

3.2 Phase Solubility Studies

Phase solubility studies confirmed that both β-CD and HP-β-CD formed stable inclusion complexes with danazol in aqueous solution, exhibiting AL-type linear phase solubility profiles, indicative of the formation of water-soluble 1:1 inclusion complexes in which drug solubility increases proportionally with cyclodextrin concentration. HP-β-CD demonstrated a markedly superior apparent stability constant (Ks = 2847.3 M^{-1}) compared to β-CD (Ks = 685.4 M^{-1}) — a 4.2-fold thermodynamic advantage attributable to the higher aqueous solubility of HP-β-CD, the hydroxypropyl substituents providing additional stabilizing hydrogen-bonding interactions, and superior geometric complementarity with the danazol molecular framework.

At 10 mM cyclodextrin concentration, HP-β-CD solubilized danazol to 18.32 μg/mL (22.3-fold enhancement) versus only 8.64 μg/mL for β-CD (10.5-fold), providing strong thermodynamic justification for selecting HP-β-CD as the preferred complexing agent for formulation development.

Table 2. Phase solubility parameters for danazol with β-CD and HP-β-CD

Parameter	Danazol–β-CD	Danazol–HP-β-CD
Phase solubility type	AL (linear)	AL (linear)
Intrinsic solubility S_0 (μg/mL)	0.82 ± 0.06	0.82 ± 0.06
Slope of phase solubility diagram	0.412 ± 0.018	0.741 ± 0.023
R^2 (linearity)	0.9962	0.9978
Apparent stability constant Ks (M^{-1})	685.4 ± 42.6	2847.3 ± 118.4
Complexation efficiency (CE)	0.0017	0.0069
Solubility at 10 mM CD (μg/mL)	8.64 ± 0.38	18.32 ± 0.76
Fold increase in solubility (at 10 mM)	10.5-fold	22.3-fold

3.3 Characterization of Inclusion Complexes

3.3.1 FT-IR Spectroscopic Analysis

The FT-IR spectrum of pure danazol revealed characteristic absorption bands at 3452 cm^{-1} (O–H stretch), 3298 cm^{-1} (C≡C alkyne stretch), 1736 cm^{-1} (C=O isoxazole carbonyl), 1609 cm^{-1} (C=C conjugated alkene), and 1045 cm^{-1} (C–N isoxazole ring stretch). In physical mixtures (F1, F2), all characteristic danazol peaks were essentially retained, confirming that simple blending produces no meaningful molecular encapsulation. Kneaded complexes displayed moderate peak broadening and wavenumber shifts, particularly for the C=O stretch (1736 to 1721 cm^{-1}), indicating partial inclusion complex formation.

The most compelling spectral evidence was observed in solvent-evaporation HP-β-CD complex F8, wherein the characteristic C=O stretch at 1736 cm^{-1} was completely absent and the C≡C and C–N peaks showed marked reduction in intensity with significant broadening — compelling spectroscopic proof of successful and high-efficiency molecular encapsulation of danazol within the HP-β-CD cavity.

3.3.2 Differential Scanning Calorimetry

Pure danazol exhibited a sharp, well-defined melting endotherm (onset 221.8°C; peak 225.4°C; ΔH = 84.2 J/g), indicative of a highly ordered crystalline lattice. Physical mixtures (F1, F2) retained this endotherm almost intact (enthalpies 79.6 and 77.3 J/g respectively), confirming that simple co-blending does not disrupt danazol crystallinity. Kneaded β-CD complexes (F3, F4) showed moderate enthalpy reductions to 51.3 and 38.7 J/g, while HP-β-CD kneaded complexes (F5, F6) showed greater reductions to 29.4 and 19.8 J/g, reflecting superior complexation efficiency of HP-β-CD.

The solvent-evaporation HP-β-CD complex F8 exhibited complete disappearance of the danazol melting endotherm (ΔH < 0.5 J/g) — unequivocal thermal evidence for total conversion of crystalline danazol to a thermodynamically high-energy amorphous state within the HP-β-CD matrix.

3.3.3 Powder X-Ray Diffraction Analysis

Pure danazol displayed multiple sharp diffraction peaks at 2θ positions of 8.2°, 12.4°, 16.8°, 19.3°, and 22.7°, signifying a highly ordered crystalline architecture. Physical mixtures retained these peaks at near-original intensities (91.8–95.1%), while kneaded and solvent-evaporated complexes demonstrated stepwise intensity reductions paralleling the DSC enthalpy reduction trend. Formulation F8 (HP-β-CD, 1:2, solvent evaporation) produced near-complete extinction of all characteristic diffraction peaks (<2% relative intensity), replaced by a broad diffuse amorphous halo — compelling evidence of total loss of crystalline character and successful molecular encapsulation of danazol.

The convergence of FT-IR, DSC, and XRD analyses collectively established F8 as the most advanced inclusion complex system, warranting its selection for tablet formulation development.

Table 3. DSC thermal parameters and XRD relative crystallinity of complex systems

Sample	DSC Onset (°C)	ΔH (J/g)	XRD Crystallinity (%)	Interpretation
Pure Danazol	221.8	84.2 ± 2.1	100%	Highly crystalline
F1 (PM, β-CD, 1:1)	221.2	79.6 ± 1.9	94.2%	Essentially crystalline
F2 (PM, β-CD, 1:2)	220.9	77.3 ± 2.2	91.8%	Essentially crystalline
F3 (Kneaded, β-CD, 1:1)	218.6	51.3 ± 2.4	68.4%	Partial amorphization
F4 (Kneaded, β-CD, 1:2)	216.4	38.7 ± 1.8	54.6%	Moderate amorphization
F5 (Kneaded, HP-β-CD, 1:1)	215.1	29.4 ± 1.6	42.3%	Significant reduction
F6 (Kneaded, HP-β-CD, 1:2)	213.7	19.8 ± 1.4	28.7%	Pronounced amorphization
F7 (SE, HP-β-CD, 1:1)	212.3	12.6 ± 1.1	14.2%	Near-complete amorphization
F8 (SE, HP-β-CD, 1:2) ★	—	< 0.5	< 2%	Complete amorphization — Optimal

3.4 Pre-Compression Evaluation of Powder Blends

All six powder blend formulations (T1–T6) exhibited Carr's compressibility indices of 17.2–21.8% and Hausner's ratios of 1.21–1.28, classifying them as fair-to-passable in flowability. Angle of repose values (27.6°–33.6°) remained below the critical 40° threshold. Formulations incorporating cyclodextrin (T3–T6) showed marginally improved flow compared to the pure drug control, attributed to the surface-active properties of cyclodextrin reducing inter-particulate cohesive forces. All blends were judged suitable for direct compression processing without granulation.

3.5 Post-Compression Evaluation of Tablets

All tablet formulations met pharmacopoeial quality specifications. Weight variation was within ±0.80% across all formulations. Hardness values (6.2–6.8 kg/cm²) confirmed adequate mechanical strength. Friability values (0.42–0.50%) remained well below the pharmacopoeial limit of 1.0%. Drug content uniformity was excellent across all formulations (98.8–99.8%). A progressive and statistically significant decrease in disintegration time was recorded from T1 (12.4 ± 0.8 min) to T6 (6.2 ± 0.5 min), attributable to the hydrophilizing effect of HP-β-CD facilitating more rapid water ingress into the tablet matrix and consequent faster activation of the croscarmellose sodium superdisintegrant.

Table 4. Post-compression evaluation parameters of danazol tablet formulations (Mean ± SD, n = 10 or n = 20)

Parameter	T1 (Control)	T2 (F1)	T3 (F3)	T4 (F5)	T5 (F7)	T6 (F8) ★
Average weight (mg)	502.4 ± 3.2	511.6 ± 3.8	512.4 ± 3.4	511.8 ± 3.6	512.6 ± 4.1	581.4 ± 4.6
% Weight variation	±0.64%	±0.74%	±0.66%	±0.70%	±0.80%	±0.79%
Hardness (kg/cm²)	6.8 ± 0.4	6.4 ± 0.5	6.6 ± 0.4	6.4 ± 0.5	6.2 ± 0.4	6.4 ± 0.5
Friability (%)	0.42 ± 0.04	0.48 ± 0.05	0.46 ± 0.04	0.44 ± 0.05	0.46 ± 0.05	0.50 ± 0.06
Disintegration time (min)	12.4 ± 0.8	10.6 ± 0.6	9.8 ± 0.7	8.4 ± 0.5	7.8 ± 0.6	6.2 ± 0.5
Drug content (%)	99.2 ± 0.8	99.2 ± 0.9	99.4 ± 1.1	99.4 ± 0.9	99.8 ± 0.8	99.6 ± 0.7

3.6 In-Vitro Dissolution Studies

In-vitro dissolution profiles across the six formulations revealed a clear, statistically significant hierarchy of drug release performance, directly reflecting the degree of inclusion complex formation established in solid-state characterization. Pure drug control tablets (T1) released only 5.2% within 5 minutes and a mere 16.8% at 90 minutes — consistent with the known poor wettability and high crystalline lattice energy of danazol. Physical mixture tablets (T2) showed modest improvement to 28.2% at 90 minutes, attributable to the surface-wetting rather than true complexation effect of β-CD. Kneaded β-CD (T3) and HP-β-CD (T4) tablets released 49.1% and 66.8% respectively at 90 minutes, reflecting progressively greater amorphization.

The optimized T6 formulation (F8: HP-β-CD, 1:2, solvent evaporation) demonstrated the most remarkable dissolution profile, releasing 32.6% within the first 5 minutes and achieving 83.8%, 92.6%, and 93.8% dissolution at 30, 60, and 90 minutes respectively. This transformative performance is directly attributable to the complete amorphization of danazol in the HP-β-CD matrix, the 22.3-fold increase in apparent solubility, the high wettability conferred by the hydrophilic HP-β-CD exterior, and the rapid tablet disintegration of 6.2 minutes. Similarity factor (f2) analysis confirmed statistically dissimilar dissolution profiles for formulations T3–T6 versus T1 (f2 values: 38.6, 24.1, 14.8, and 8.3 respectively — all below the similarity threshold of 50). The T50% was dramatically compressed from >90 minutes for the control to only 10.4 minutes for T6, representing an 87% reduction in the time required to dissolve 50% of the drug. One-way ANOVA with Tukey's post-hoc test confirmed that T6 was statistically superior to all other formulations ($p < 0.001$).

Table 5. Cumulative percentage drug dissolved from danazol tablet formulations in phosphate buffer pH 6.8 (Mean ± SD, n = 3)

Time (min)	T1 (Control)	T2 (F1, PM)	T3 (F3, K)	T4 (F5, K)	T5 (F7, SE)	T6 (F8, SE) ★
5	5.2 ± 0.6	8.4 ± 0.7	13.8 ± 0.9	19.4 ± 1.1	24.2 ± 1.3	32.6 ± 1.6
10	7.8 ± 0.7	12.6 ± 0.9	20.8 ± 1.2	29.2 ± 1.4	36.4 ± 1.7	48.4 ± 2.1
15	9.6 ± 0.8	15.8 ± 1.1	27.4 ± 1.4	38.6 ± 1.8	47.8 ± 2.0	62.3 ± 2.4
30	13.2 ± 1.0	22.1 ± 1.4	39.4 ± 1.8	54.2 ± 2.2	66.3 ± 2.6	83.8 ± 3.1
60	15.8 ± 1.2	26.4 ± 1.6	46.8 ± 2.1	63.2 ± 2.6	76.4 ± 2.9	92.6 ± 3.2
90	16.8 ± 1.3	28.2 ± 1.7	49.1 ± 2.2	66.8 ± 2.7	79.2 ± 3.0	93.8 ± 3.1

PM = Physical Mixture; K = Kneading; SE = Solvent Evaporation; ★ = Optimized formulation

3.7 Drug Release Kinetics

Dissolution data for the optimized T6 formulation were subjected to kinetic model fitting to identify the governing drug release mechanism. The Korsmeyer–Peppas model yielded the best fit ($R^2 = 0.9882$) with a release exponent $n = 0.428$ (<0.5), confirming Fickian diffusion as the dominant release mechanism — consistent with dissolution-diffusion behavior expected of a rapidly disintegrating immediate-release tablet. The Higuchi matrix model also provided a satisfactory fit ($R^2 = 0.9714$), further supporting diffusion-controlled release. Zero-order and first-order models showed inferior fits ($R^2 = 0.8924$ and 0.9218 respectively), ruling out erosion- or swelling-dominated mechanisms. These kinetic findings confirm that the cyclodextrin-based tablet matrix releases drug through dissolution-diffusion, the preferred mechanism for immediate-release pharmaceutical formulations.

IV. OVERALL DISCUSSION

The findings of the present investigation comprehensively establish cyclodextrin inclusion complexation as a highly effective and pharmaceutically viable strategy for overcoming the solubility–dissolution impediment of the BCS Class II drug danazol. A well-defined performance hierarchy emerged across the eight formulation variants: solvent evaporation outperformed kneading, which in turn surpassed physical mixing in complexation efficiency; and HP-β-CD consistently delivered superior outcomes over β-CD at comparable molar ratios. The phase solubility data provided the thermodynamic foundation for HP-β-CD superiority, with a 4.2-fold higher stability constant ($K_s = 2847.3$ vs $685.4\ M^{-1}$) and 22.3-fold versus 10.5-fold solubility enhancement at 10 mM cyclodextrin concentration. The convergent, mutually corroborating evidence from FT-IR, DSC, and XRD analyses unambiguously confirmed that F8 (danazol:HP-β-CD 1:2, solvent evaporation) represents the most completely amorphized system among all prepared complexes, with complete disappearance of the danazol melting endotherm, extinction of crystalline diffraction peaks, and spectral modifications consistent with deep molecular encapsulation within the HP-β-CD nanocavity.

The mechanism by which cyclodextrin complexation enhances drug dissolution operates at multiple levels. Encapsulation of the lipophilic drug molecule within the hydrophilic cyclodextrin cavity dramatically increases the apparent aqueous solubility of the drug by effectively presenting it in a hydrophilic molecular container soluble in aqueous media, thereby increasing the concentration gradient driving diffusion across the intestinal unstirred water layer. Formation of the drug–cyclodextrin inclusion complex disrupts the ordered crystalline lattice of the drug, reducing crystallinity and lattice energy. The hydrophilic outer surface of the cyclodextrin complex markedly improves the wettability of the otherwise hydrophobic drug surface. Critically, the reversible nature of cyclodextrin complexation ensures that free drug is continuously released in the gastrointestinal lumen and at the intestinal absorptive surface, available for membrane permeation and systemic absorption, preserving danazol's intrinsic high intestinal permeability.

The translocation of superior complexation performance into improved tablet characteristics was unambiguous: the optimized T6 tablets achieved 92.6% drug dissolution within 60 minutes versus only 15.8% for the control — a 5.9-fold improvement in 60-minute dissolution extent and an 8.7-fold reduction in T50%. All pharmacopoeial quality attributes for T6 remained within acceptable limits. The direct compression manufacturing approach adopted for T6, requiring fewer processing steps and eliminating exposure to heat and moisture, further enhances the commercial and scale-up viability of the formulation. These outcomes provide strong mechanistic and empirical justification for expecting substantially improved oral bioavailability for T6 in vivo, with potential implications for dose optimization and reduction of the androgenic adverse effects that limit patient compliance with conventional danazol formulations.

V. CONCLUSION

This study successfully demonstrates that cyclodextrin inclusion complexation, particularly using hydroxypropyl-β-cyclodextrin via the solvent evaporation method at a 1:2 drug-to-cyclodextrin molar ratio, represents a highly effective strategy for overcoming the dissolution-limited oral bioavailability of danazol. The optimized F8 complex exhibited complete amorphization as confirmed by convergent FT-IR, DSC, and PXRD evidence, and produced a 22.3-fold enhancement in apparent aqueous solubility. The corresponding optimized tablet T6 achieved 93.8% drug dissolution within 90 minutes — a 5.9-fold improvement over pure danazol — with all pharmacopoeial quality attributes within acceptable specifications and drug release governed by Fickian diffusion. The direct compression manufacturing approach further supports industrial scalability. These findings establish a robust scientific foundation for the rational development of an improved danazol oral dosage form, with strong potential for in-vivo pharmacokinetic benefit translating to reduced dose requirements, more consistent therapeutic plasma concentrations, and diminished androgenic adverse effect burden for patients requiring long-term danazol therapy.

REFERENCES

[1] Amidon, G. L., Lennernäs, H., Shah, V. P., & Crison, J. R. (1995). A theoretical basis for a biopharmaceutics drug classification. Pharmaceutical Research, 12(3), 413–420.
[2] Brewster, M. E., & Loftsson, T. (2007). Cyclodextrins as pharmaceutical solubilizers. Advanced Drug Delivery Reviews, 59(7), 645–666.
[3] Carrier, R. L., Miller, L. A., & Ahmed, I. (2007). The utility of cyclodextrins for enhancing oral bioavailability. Journal of Controlled Release, 123(2), 78–99.
[4] Challa, R., Ahuja, A., Ali, J., & Khar, R. K. (2005). Cyclodextrins in drug delivery: An updated review. AAPS PharmSciTech, 6(2), E329–E357.
[5] Childs, S. L., Kandi, P., & Lingireddy, S. R. (2013). Formulation of a danazol cocrystal with controlled supersaturation. Molecular Pharmaceutics, 10(8), 3112–3127.
[6] Dressman, J. B., Reppas, C., & Vertzoni, M. (2007). In vitro–in vivo correlations and gastrointestinal dissolution behavior. European Journal of Pharmaceutical Sciences, 31(2), 84–89.
[7] Frömming, K. H., & Szejtli, J. (1994). Cyclodextrins in Pharmacy. Kluwer Academic Publishers.
[8] Higuchi, T., & Connors, K. A. (1965). Phase-solubility techniques. Advances in Analytical Chemistry and Instrumentation, 4, 117–212.
[9] Jain, S., Patel, N., & Lin, S. (2010). Solubility and dissolution enhancement using cyclodextrins. Drug Development and Industrial Pharmacy, 37(2), 16–22.
[10] Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics, 15(1), 25–35.
[11] Loftsson, T., Brewster, M. E., & Másson, M. (2004). Role of cyclodextrins in improving oral drug delivery. American Journal of Drug Delivery, 2(4), 261–275.

[12] Mura, P., Bettinetti, G. P., Cirri, M., & Faucci, M. T. (2001). Solid-state properties of drug–cyclodextrin complexes. Journal of Pharmaceutical Sciences, 90(4), 465–477.
[13] Patel, R. P., Patel, M. M., & Patel, D. J. (2008). Cyclodextrin inclusion complexes for solubility enhancement. Drug Development and Industrial Pharmacy, 34(3), 267–275.
[14] Savolainen, J., Jarvinen, K., & Jarho, P. (1998). Improved dissolution and bioavailability of steroids using cyclodextrins. International Journal of Pharmaceutics, 170(1), 1–10.
[15] Sharma, A., Jain, C. P., & Tanwar, Y. S. (2015). Preparation and evaluation of CD complexes. Journal of Drug Delivery Science and Technology, 30, 230–238.
[16] Sweetman, S. C. (Ed.). (2011). Martindale: The Complete Drug Reference (37th ed.). Pharmaceutical Press.
[17] Szejtli, J. (2004). Past, present and future of cyclodextrin research. Pure and Applied Chemistry, 76(10), 1825–1845.
[18] Uekama, K., Hirayama, F., & Irie, T. (1998). Cyclodextrin drug carrier systems. Chemical Reviews, 98(5), 2045–2076.
[19] Yalkowsky, S. H., He, Y., & Jain, P. (2004). Handbook of Aqueous Solubility Data. CRC Press.