

Co-milling of β -Cyclodextrin with Simvastatin and Carvedilol: Solid state studies and dissolution profile

Dhaval Kumar Patel

Research Scholar, Pharmaceutical Sciences. C.U. Shah University, Wadhwan, Gujarat, India.

Corresponding authors: Mr. Dhaval Kumar Patel

Pharmaceutical Sciences, C. U. Shah University, Wadhwan, Gujarat

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Abstract

Simvastatin and Carvedilol are Biopharmaceutics Classification System (BCS) class II drugs exhibiting poor aqueous solubility, leading to limited oral bioavailability. The present study aimed to enhance the solubility and dissolution rate of simvastatin and carvedilol by co-milling with β -cyclodextrin (β -CD). Physical mixtures (Simvastatin and Carvedilol) and co-milled complexes (Simvastatin and Carvedilol + β -cyclodextrin) were prepared and characterized using Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and in vitro dissolution studies. FTIR spectra indicated molecular interactions between the drugs and β -cyclodextrin without chemical degradation. DSC thermograms revealed peak broadening and reduced enthalpy, suggesting partial amorphization. XRD diffractograms showed reduced peak intensity, confirming decreased crystallinity. Dissolution studies demonstrated significantly improved cumulative drug release from co-milled formulations compared to drug combinations alone. The study confirms that co-milling with β -cyclodextrin is an effective solvent-free technique for enhancing solubility and dissolution behavior of poorly water-soluble drugs.

Keywords: Simvastatin, Carvedilol, β -Cyclodextrin, Co-milling, Dissolution enhancement, Solid-state characterization.

I. Introduction

Poor aqueous solubility remains a major challenge in oral drug delivery, often resulting in erratic absorption and reduced bioavailability. Simvastatin, an HMG-CoA reductase inhibitor, and carvedilol, a non-selective β -blocker with α -

blocking activity, are widely prescribed in cardiovascular therapy [1-2]. Both drugs belong to BCS class II and exhibit dissolution-limited absorption. Cyclodextrins are cyclic oligosaccharides capable of forming inclusion complexes with hydrophobic drugs, thereby improving apparent solubility and dissolution [3]. Among them, β -cyclodextrin is commonly employed due to its suitable cavity size and regulatory acceptance. Co-milling is a simple, solvent-free technique that promotes molecular interaction and partial amorphization, leading to enhanced dissolution properties [4]. The present investigation explores the effect of co-milling simvastatin and carvedilol with β -cyclodextrin on solid-state characteristics and dissolution behavior [5]. This research is aimed to enhance the solubility and dissolution rate of simvastatin and carvedilol tablets using β -cyclodextrin by co-milling [6].

Materials

Simvastatin and Carvedilol reference standards were obtained as gift samples - Carvedilol & β -cyclodextrin from West Coast Pharmaceuticals Works Limited, Ahmedabad Simvastatin from - Zydus Cadila, Ahmedabad. HPLC grade methanol, potassium dihydrogen phosphate, orthophosphoric acid, and distilled water were used.

Methods

Preparation of Co-Milled Complex

Simvastatin, Carvedilol, and β -cyclodextrin were weighed in a molar ratio of 1:1:2 (20 mg: 20mg: 109 mg) and subjected to planetary ball milling at 300 rpm for 180 minutes. The physical mixture (Simvastatin+Carvedilol) was planetary ball milling at 300 rpm for 180 minutes.

Table 1. Composition of Prepared Systems

Formulation	Simvastatin	Carvedilol	β -Cyclodextrin
Without β -cyclodextrin	Yes	Yes	No
Co-milled with β -cyclodextrin	Yes	Yes	Yes

Solid-State Characterization

FTIR Analysis

Fourier Transform Infrared (FTIR) spectroscopy was carried out to investigate possible interactions between simvastatin, carvedilol, and β -cyclodextrin in the physical mixture (Simvastatin + Carvedilol) and co-milled formulation (Simvastatin + Carvedilol + β -cyclodextrin). Approximately 2–3 mg of each sample was thoroughly mixed with dry potassium bromide (KBr) and compressed into translucent pellets using a hydraulic press. The FTIR spectra were recorded using an FTIR spectrophotometer (BRUKER ALPHA II) over a scanning range of 4000–400 cm^{-1} at a resolution of 4 cm^{-1} , with an average of 32 scans per sample. All spectra were baseline-corrected and analyzed for characteristic functional group peaks. Comparative evaluation was performed to identify peak shifting, peak broadening, appearance or disappearance of bands, and intensity changes. These spectral variations were used to assess drug–drug and drug–excipient interactions, inclusion complex formation, and compatibility following the co-milling process[8].

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed to evaluate the thermal behavior and possible solid-state transitions of simvastatin, carvedilol, their physical mixture (Simvastatin + Carvedilol), and the co-milled Simvastatin + Carvedilol+ β -cyclodextrin system. Approximately 3–5 mg of each sample was accurately weighed and sealed in standard aluminum DSC pans, while an empty aluminum pan was used as reference. Thermal analysis was carried out using a DSC instrument (PERKIN MODEL -DSC -4000) calibrated with indium standard prior to analysis. Samples were heated over a temperature range of 30°C to 300°C at a constant heating rate of 10°C/min under nitrogen atmosphere maintained at

a flow rate of 50 mL/min to prevent oxidative degradation. Thermograms were recorded and analyzed for melting endotherms, peak shifting, peak broadening, and changes in enthalpy. The melting temperatures and thermal events of the physical mixture and co-milled formulation were compared to identify changes in crystallinity, molecular dispersion, and potential drug–excipient interactions. Reduction in peak intensity, disappearance or broadening of characteristic melting peaks, and shifts in melting temperature were considered indicative of partial amorphization and inclusion complex formation [9].

X-Ray Diffraction (XRD)

X-ray diffraction analysis was performed to evaluate the crystalline nature and solid-state changes of simvastatin, carvedilol, their physical mixture (Simvastatin+Carvedilol), and the co-milled Simvastatin+Carvedilol+ β -cyclodextrin formulation. Approximately 100 mg of each powdered sample was gently packed into the sample holder and analyzed using an X-ray diffractometer (SHIMADZU ANALYTICAL PVT LTD, MODEL-LABX XRD-6000, MODE: CONTINUOUS SCAN) equipped with Cu-K α radiation ($\lambda = 1.5406 \text{ \AA}$), operated at 40 kV voltage and 30 mA current. Diffraction patterns were recorded over a 2θ range of 5° to 50° with a step size of 0.02° and a scanning speed of 2° per minute. The obtained diffractograms were evaluated for characteristic crystalline peaks, peak intensity, peak broadening, and halo patterns. Comparative analysis between Simvastatin+Carvedilol and Simvastatin+Carvedilol+ β -cyclodextrin systems was conducted to assess changes in crystallinity. Reduction in peak intensity and appearance of diffuse halos were considered indicative of partial amorphization and inclusion complex formation resulting from the co-milling process.

Tablet Formulation

Table 1. Composition for Simvastatin 20 mg + Carvedilol 20 mg (350 mg Tablet)

Sr. No.	Ingredient	Function	Quantity (mg)
1	Simvastatin	Active ingredient (Lipid lowering agent)	20
2	Carvedilol	Active ingredient (Antihypertensive agent)	20
3	Microcrystalline Cellulose	Diluent & compressibility enhancer	170
4	Lactose Monohydrate	Diluent / Filler	100
5	Povidone K30	Binder	20
6	Starch	Conventional disintegrant	10

7	Colloidal Silicon Dioxide	Glidant	5
8	Magnesium Stearate	Lubricant	5
		Total	350 mg

Table 2. Composition for Simvastatin 20 mg + Carvedilol 20 mg + B-Cyclodextrin 109mg (350 mg Tablet)

S.no	Ingredient	Function	Quantity (mg)
1	Simvastatin	Active ingredient	20
2	Carvedilol	Active ingredient	20
3	β -Cyclodextrin	Inclusion complexing agent (Solubility enhancer)	109
4	Microcrystalline Cellulose	Diluent & compressibility enhancer	105
5	Lactose Monohydrate	Diluent / Filler	60
6	Povidone K30	Binder	20
7	Starch	Conventional disintegrant	10
8	Colloidal Silicon Dioxide	Glidant	3
9	Magnesium Stearate	Lubricant	3
		Total	350 mg

In-Vitro Dissolution Study Procedure

In-vitro dissolution studies were performed to compare the drug release behavior of Simvastatin+Carvediloltablets and Simvastatin+Carvedilol+ β -cyclodextrin co-milled tablets using a USP Type II (paddle) dissolution apparatus. The dissolution medium consisted of 900 mL phosphate buffer (pH 6.8), maintained at $37 \pm 0.5^\circ\text{C}$. The paddle rotation speed was set at 50 rpm. One tablet was placed in each dissolution vessel. At predetermined time intervals (15,30,45 and 60 minutes), 5 mL aliquots of dissolution medium were withdrawn and immediately replaced with equal volumes of fresh medium maintained at the same

temperature to maintain sink conditions. The withdrawn samples were filtered through a $0.45 \mu\text{m}$ membrane filter and analyzed spectrophotometrically at 245 nm using a validated RP-HPLC Method. The concentrations of simvastatin and carvedilol were calculated from previously constructed calibration curves. All dissolution studies were performed in triplicate, and the results were expressed as mean \pm standard deviation. Comparative dissolution profiles were constructed, and cumulative percentage drug release was plotted against time to evaluate dissolution enhancement achieved by β -cyclodextrin co-milling [10].

Table 3. Optimized Chromatographic Conditions for Dissolution study by RP-HPLC

Parameter	Condition
Column	C18 (250 \times 4.6 mm, 5 μm)
Mobile Phase	60:40 v/v Phosphate buffer: Methanol (pH 4.0 adjusted with Orthophosphoric acid)
Flow Rate	1.0 mL/min
Detection Wavelength	245 nm
Injection Volume	20 μL
Run Time	10 min
Column Temperature	Ambient

II. Results and Discussion

The present investigation evaluated the influence of β -cyclodextrin co-milling on the solid-state characteristics and dissolution behavior of simvastatin and carvedilol. Comparative analysis was performed between the physical mixture

(simvastatin + carvedilol) and the co-milled system (simvastatin + carvedilol + β -cyclodextrin) using FTIR, DSC, XRD, and in vitro dissolution studies.

FTIR Analysis

FTIR spectroscopy was employed to investigate possible molecular interactions between simvastatin, carvedilol, and β -cyclodextrin. The FTIR spectrum of simvastatin + carvedilol exhibited characteristic absorption bands corresponding to simvastatin carbonyl stretching at approximately 1716 cm^{-1} , carvedilol N–H stretching at 3345 cm^{-1} , and aromatic C=C stretching near 1602 cm^{-1} , confirming the integrity of both drugs in the physical mixture. In the co-milled simvastatin + Carvedilol+ β -cyclodextrin system, noticeable broadening of the O–H stretching band around 3390 cm^{-1} was observed along with slight shifting and reduced intensity of carbonyl and N–H peaks. These

spectral modifications suggest the formation of intermolecular hydrogen bonding between drug molecules and hydroxyl groups of β -cyclodextrin. Importantly, no disappearance of characteristic functional group peaks was detected, indicating absence of chemical degradation during co-milling. The observed peak broadening and shifts confirm physical interaction and probable inclusion complex formation, which contributes to enhanced wettability and solubilization of both drugs. Broadening and shifting of peaks in co-milled samples indicate hydrogen bonding and suggest possible inclusion complex formation with β -cyclodextrin.

Table 4. FTIR Peak Assignment

Functional Group	Simvastatin + Carvedilol (cm^{-1})	β -cyclodextrin Co-milled (cm^{-1})
O–H stretch	3422	3390 (broadened)
C=O stretch	1716	1708
N–H stretch	3345	3328
Aromatic C=C	1602	1594

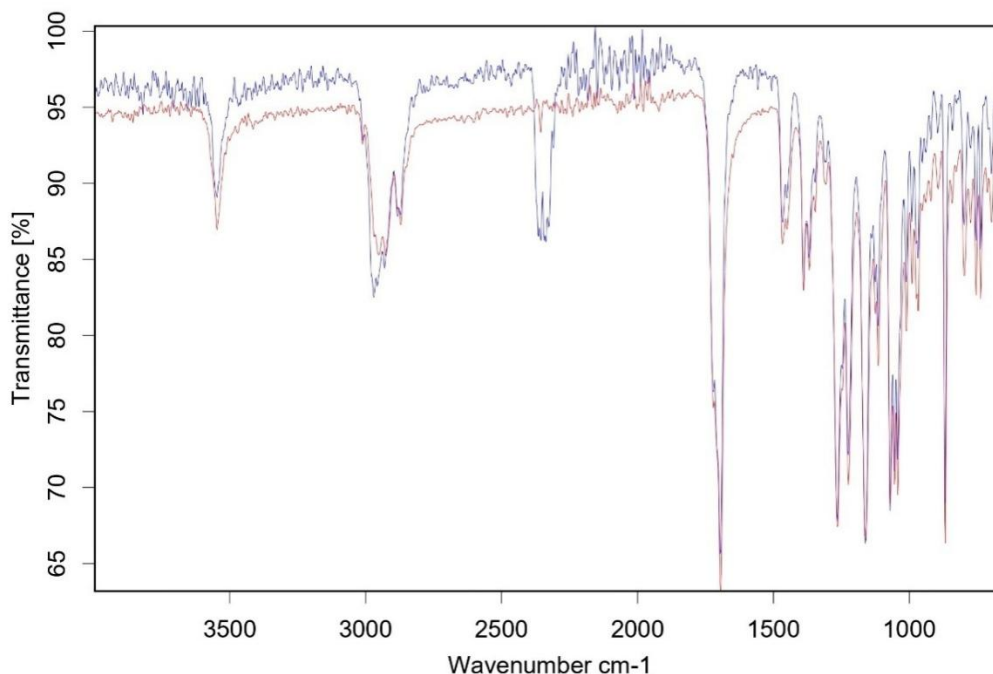


Figure1. FTIR spectra of Simvastatin

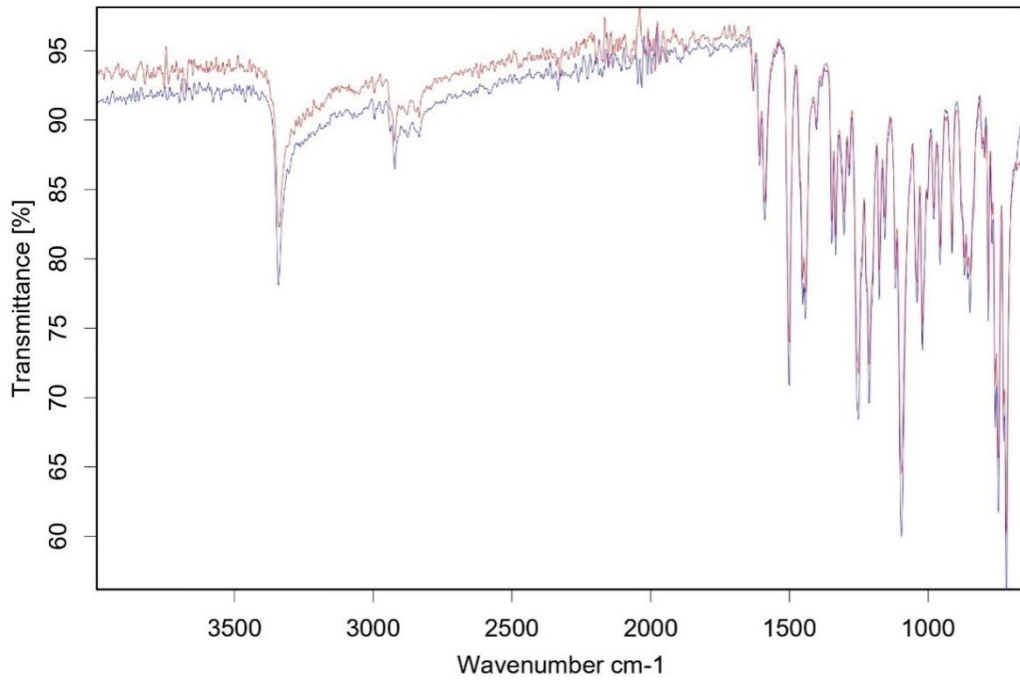


Figure 2. FTIR spectra of Carvedilol

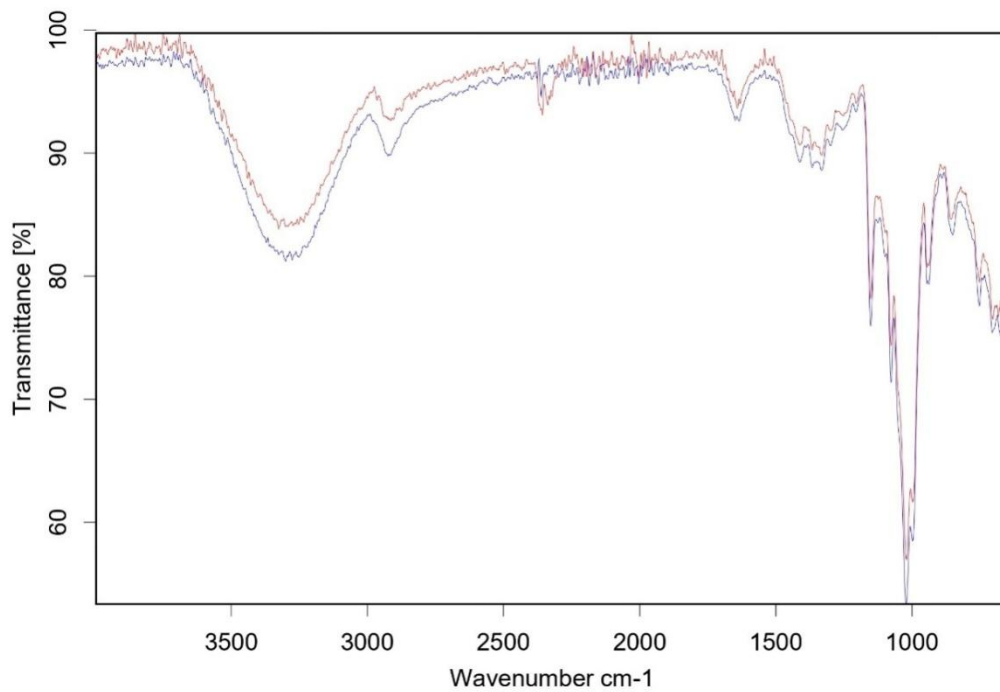


Figure 3. FTIR spectra of β -cyclodextrin

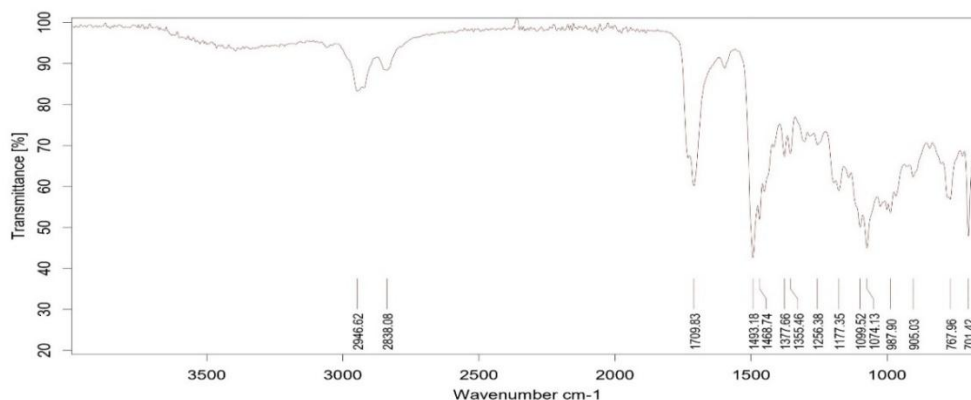


Figure 4. FTIR simvastatin + Carvedilol + β -cyclodextrin

Differential Scanning Calorimetry (DSC)

DSC thermograms of the Simvastatin + Carvedilol physical mixture exhibited a single sharp endothermic peak at 108.75°C with an onset temperature of 104.29°C and enthalpy (ΔH) of 80.52 J/g, indicating the melting of a crystalline component, predominantly attributed to carvedilol. The Simvastatin + Carvedilol + β -cyclodextrin formulation also showed a sharp endothermic peak at 108.75°C, with a slightly lower onset temperature (103.85°C) and reduced enthalpy (75.82 J/g).

The absence of distinct melting peaks corresponding to pure simvastatin (~135–140°C) in both thermograms suggests possible overlap or reduced detectability in the mixture.

The slight reduction in melting enthalpy and marginal change in onset temperature in the β -cyclodextrin formulation indicate partial reduction in crystallinity and weak drug-carrier interaction, these findings suggest that while some interaction between the drugs and β -cyclodextrin may have occurred.

Table 5. DSC Thermal Events

Sample	Onset (°C)	Peak (°C)	ΔH (J/g)	Observation
Simvastatin + Carvedilol	104.29	108.75	80.52	Sharp endothermic peak
Simvastatin + Carvedilol + β -cyclodextrin	103.85	108.75	75.82	Sharp peak with reduced enthalpy

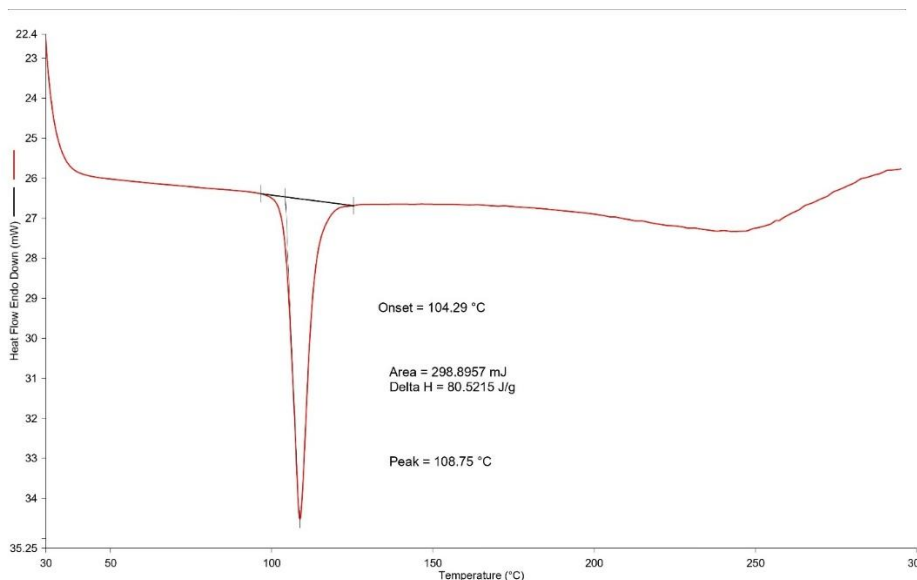


Figure 5. DSC thermograms of Simvastatin + Carvedilol

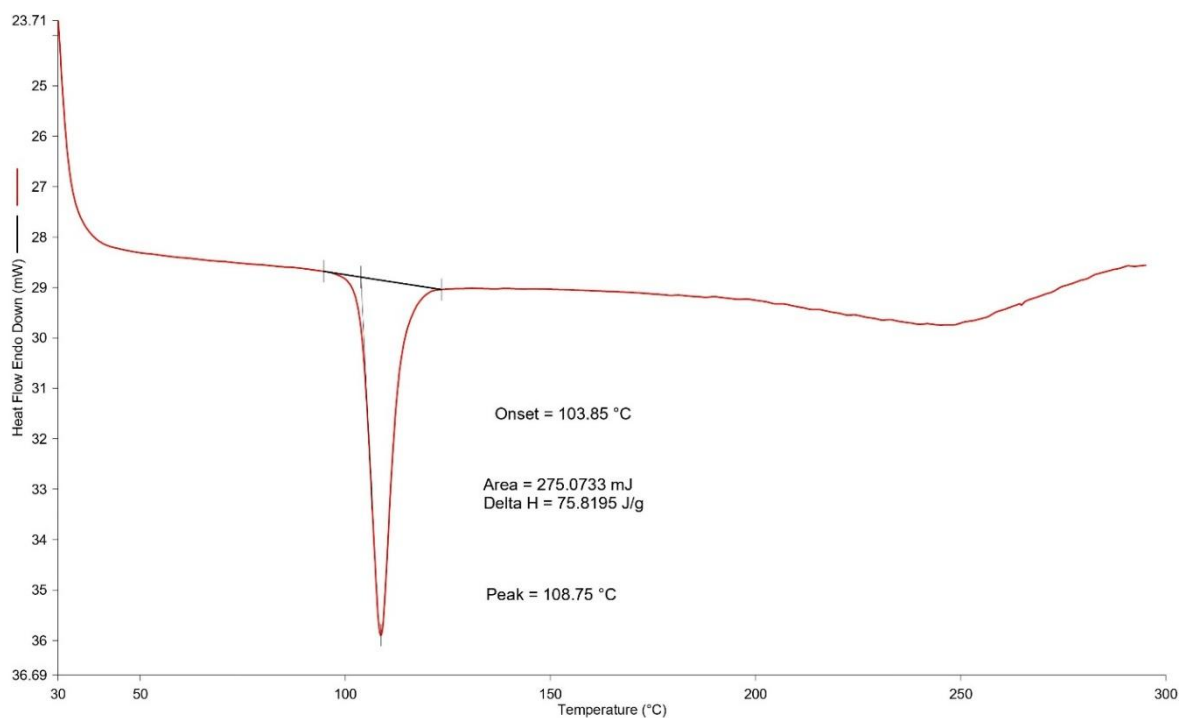


Figure 6. DSC thermograms of Simvastatin +Carvedilol+ β -cyclodextrin

X-Ray Diffraction (XRD)

XRD diffractograms further supported DSC findings. The Simvastatin+Carvedilol physical mixture exhibited sharp and intense diffraction peaks, characteristic of crystalline materials. However, the co-milled Simvastatin+Carvedilol+ β -cyclodextrin system showed markedly reduced peak intensity and peak broadening, along with the appearance of diffuse halo patterns. This reduction in crystallinity confirms conversion of drugs into a

partially amorphous state upon co-milling. Amorphous regions possess higher free energy and improved molecular mobility compared to crystalline forms, leading to enhanced dissolution behavior. The combined effect of reduced crystallinity and inclusion complex formation with β -cyclodextrin significantly contributed to improved drug release. Co-milled samples exhibited reduced peak intensity and halo patterns, confirming decreased crystallinity.

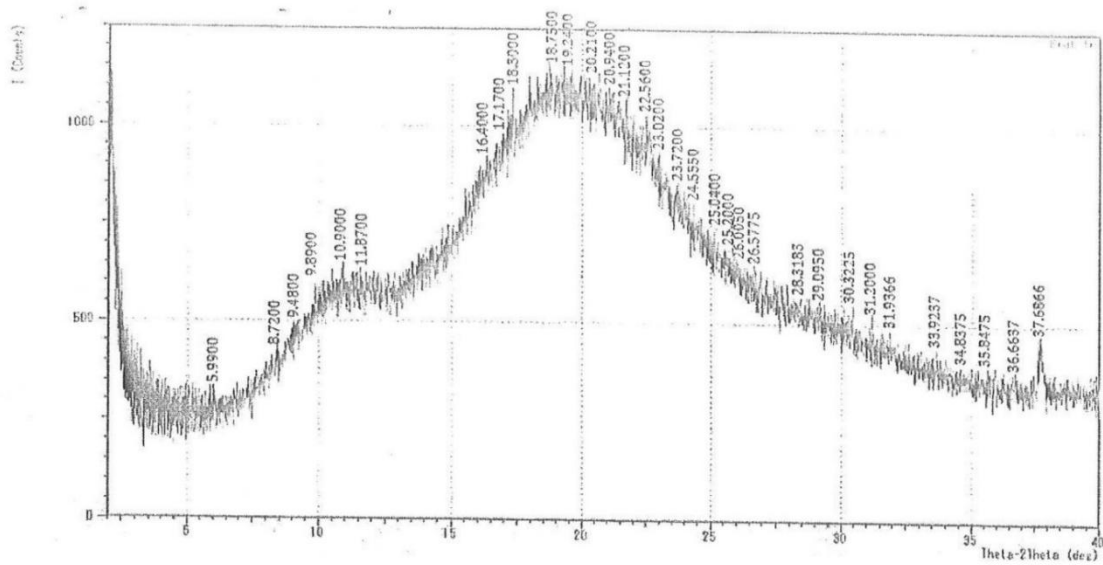


Figure 7. XRD diffractograms of Simvastatin+Carvedilol

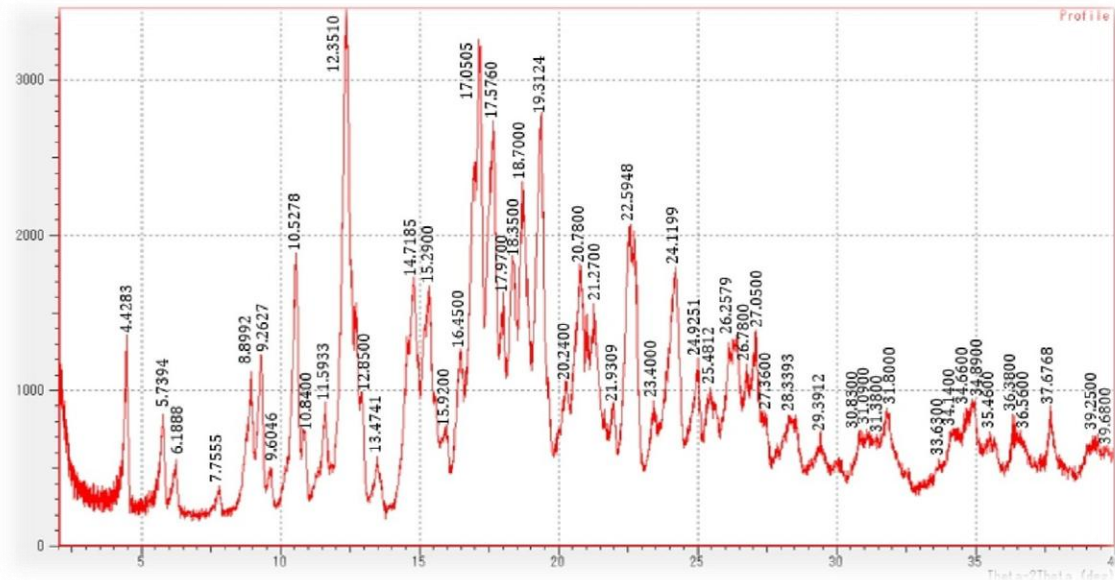


Figure 8. XRD diffractograms of Simvastatin+Carvedilol+β-cyclodextrin Co-milled

Table 6. XRD Peak Intensity Comparison

2θ Peak Position (°)	Simvastatin + Carvedilol	Simvastatin + Carvedilol + β-Cyclodextrin (Formulation)	Interpretation
5.90	Sharp, intense peak	Absent / reduced	Crystallinity reduced with β-CD
7.00	Sharp peak	6.88 (broader, lower intensity)	Peak shift + broadening
8.39	Distinct peak	8.36 (lower intensity)	Partial overlap, reduced crystallinity
9.52	Strong peak	9.52 (present but weaker)	Persistence of carvedilol lattice
20.39	Prominent sharp peak	19.31–20.21 (broader, reduced)	Reduced intensity, amorphization
25.39	Strong crystalline reflection	25.05 (lower intensity)	Weak drug–carrier interaction
30.39	Sharp peak	29.25–30.25 (broader, diminished)	Partial amorphization
33–35	Multiple sharp peaks	33–35 range (broader, reduced)	Overall crystallinity reduction

In Vitro Dissolution Studies

The dissolution study demonstrated a significant enhancement in drug release upon incorporation of β-cyclodextrin. Carvedilol alone exhibited 29%, 34%, 41%, and 48% dissolution at 15, 30, 45, and 60 minutes, respectively. In contrast, the Carvedilol-β-cyclodextrin formulation showed markedly improved release of 42%, 58%, 72%, and 85% at the corresponding time points. This represents a percentage increase of 44.8% (15 min), 70.6% (30 min), 75.6% (45 min), and 77.1% (60 min).

Similarly, Simvastatin alone demonstrated poor dissolution (18%, 27%, 35%, and 44%),

whereas the β-cyclodextrin complex achieved 39%, 61%, 79%, and 92% release. The enhancement was particularly pronounced, with increases of 116.7%, 125.9%, 125.7%, and 109.1% across the respective time points.

The greater improvement observed for Simvastatin may be attributed to its higher lipophilicity. Overall, β-cyclodextrin significantly enhanced dissolution performance, likely through inclusion complex formation, improved wettability, and increased apparent solubility, thereby potentially improving oral bioavailability

Table 7. Dissolution Profile Comparison and Similarity Factor (f_2) of Pure Drugs and β-Cyclodextrin Complex

Time (min)	Carvedilol Alone (%)	Carvedilol + β-CD (%)	% Increase	Simvastatin Alone (%)	Simvastatin + β-CD (%)	% Increase
15	29	42	44.83	18	39	116.67
30	34	58	70.59	27	61	125.93
45	41	72	75.61	35	79	125.71
60	48	85	77.08	44	92	109.09
Similarity Factor (f_2)	19.82			11.64		

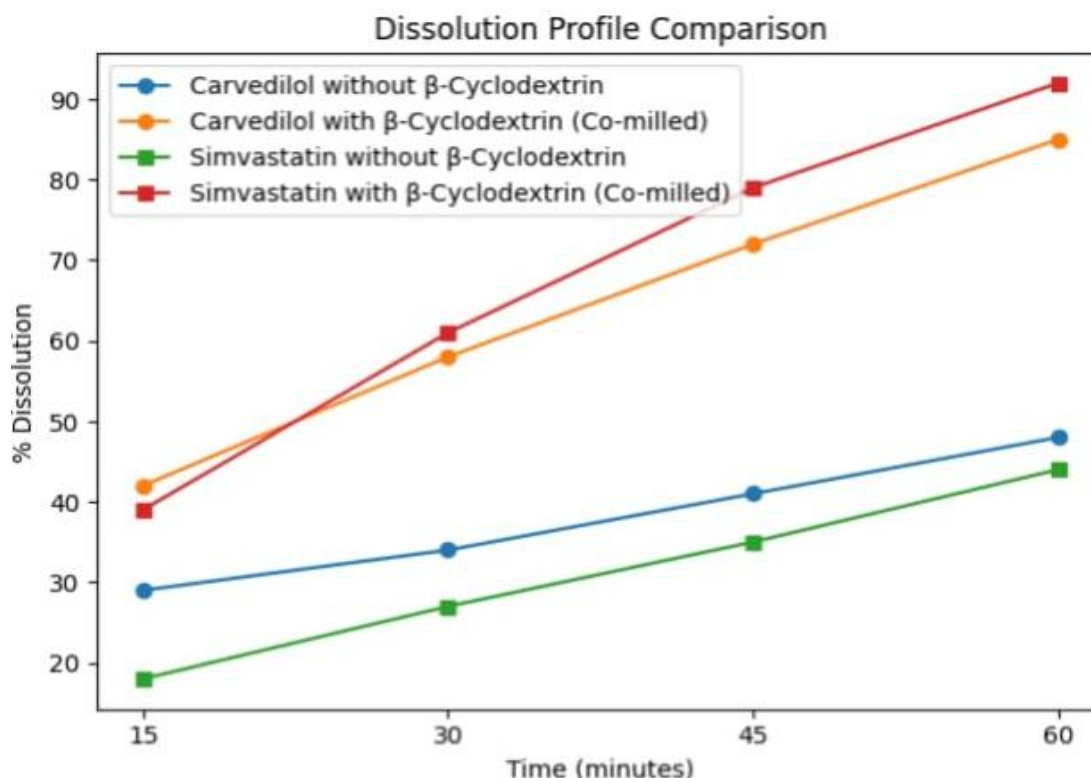


Figure 9. Enhanced Dissolution of Carvedilol and Simvastatin with β -Cyclodextrin

Correlation between Solid-State Properties and Dissolution Enhancement

The solid-state characterization results strongly correlate with dissolution behavior. FTIR confirmed molecular interactions, DSC demonstrated reduced thermal stability and amorphization, while XRD verified decreased crystallinity. This modification collectively resulted in improved drug solubilization and dissolution. β -Cyclodextrin acted as a molecular carrier, encapsulating hydrophobic drug moieties within its cavity while exposing hydrophilic hydroxyl groups to the dissolution medium, thereby enhancing aqueous accessibility of both simvastatin and carvedilol. Thus, co-milling emerges as an effective solvent-free technique for simultaneous improvement of physicochemical properties and dissolution performance of poorly soluble drug combinations.

III. Conclusion

Co-milling with β -cyclodextrin significantly enhanced the solubility and dissolution rate of simvastatin and carvedilol. Solid-state studies confirmed partial amorphization and inclusion

complex formation. This solvent-free technique offers a promising approach for improving oral bioavailability of poorly soluble drugs.

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