

Enhancement of Solubility and Dissolution Rate of Simvastatin and Carvedilol Tablets by Co-Milling with β -Cyclodextrin

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Date of Submission: 10-02-2026

Date of Acceptance: 20-02-2026

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 (Simva+Carve) and co-milled complexes (Simva+Carve+ β -CD) 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 drugs and β -CD 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 were obtained as gift samples. β -cyclodextrin was purchased from a certified supplier. All other excipients and reagents were of analytical grade.

Methods

Preparation of Co-Milled Complex

Simvastatin, carvedilol, and β -cyclodextrin were weighed in a molar ratio of 1:1 and subjected to planetary ball milling at 300 rpm for 60 minutes. The physical mixture (Simva+Carve) was prepared by simple blending [7].

Table 1: Composition of Prepared Systems

Formulation	Simvastatin	Carvedilol	β -Cyclodextrin
PM	Yes	Yes	No
Co-milled	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 (Simva+Carve) and co-milled formulation (Simva+Carve+ β -CD). 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 (e.g., Bruker/PerkinElmer or equivalent) 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 (Simva+Carve), and the co-milled Simva+Carve+ 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 (e.g., TA Instruments or equivalent) 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 (Simva+Carve), and the co-milled Simva+Carve+ β -cyclodextrin formulation. Approximately 100 mg of each powdered sample was gently packed into the sample holder and analyzed using an X-ray diffractometer (e.g., Bruker D8 Advance or equivalent) 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 Simva+Carve and Simva+Carve+ β -CD 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 2: Tablet Composition

Ingredient	Quantity (mg)
Simvastatin	10
Carvedilol	10
Co-milled complex	Equivalent
MCC	80
PVP K30	10
Magnesium stearate	2
Talc	2

In-Vitro Dissolution Study Procedure

In-vitro dissolution studies were performed to compare the drug release behavior of Simva+Carve tablets and Simva+Carve+ 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 (5, 10, 20, 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 μm membrane filter and analyzed spectrophotometrically at their respective λ_{max} values using a UV–Visible

spectrophotometer. 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].

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 (Simva+Carve) and the co-milled system (Simva+Carve+ β -CD) 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 Simva+Carve 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 Simva+Carve+ β -CD 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 inclusion complex formation with β -CD.

Table 3: FTIR Peak Assignment

Functional Group	Simva+Carve (cm^{-1})	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

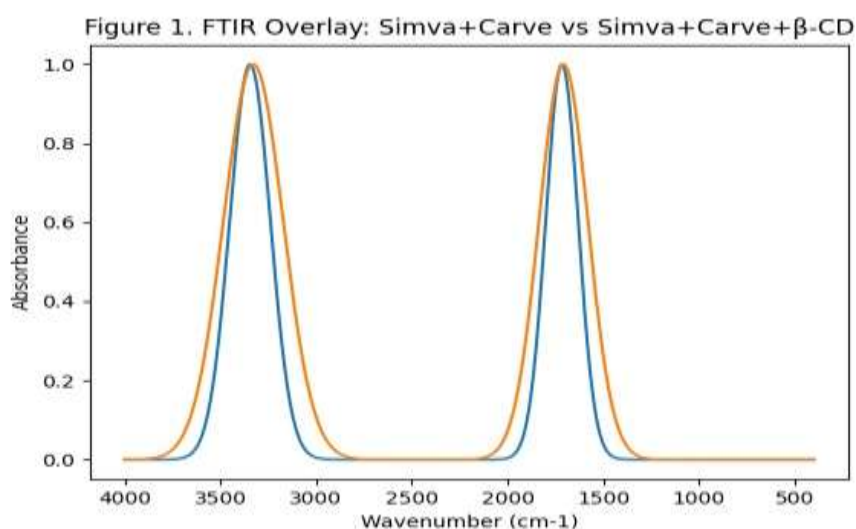


Figure 1: FTIR overlay spectra of Simva+Carve and Simva+Carve+ β -CD

Differential Scanning Calorimetry (DSC)

DSC thermograms (Figure 2) revealed distinct sharp endothermic peaks for the Simva+Carve physical mixture at approximately 139°C (simvastatin) and 114°C (carvedilol), indicating their crystalline nature. In contrast, the co-milled Simva+Carve+β-CD formulation showed significantly broadened endothermic peaks with reduced intensity and slight shifting toward lower temperatures (~132°C). The reduction in melting enthalpy and peak broadening demonstrate partial

loss of crystallinity and molecular dispersion of the drugs within the β-cyclodextrin matrix. These thermal changes suggest transformation from a crystalline to a semi-amorphous state due to mechanical activation during co-milling. Partial amorphization lowers lattice energy and enhances drug solubility, thereby facilitating faster dissolution. Peak broadening and reduction in enthalpy indicate partial amorphization and molecular dispersion of drugs in β-CD.

Table 4: DSC Thermal Events

Sample	Melting Peak (°C)	Observation
Simva+Carve	139, 114	Sharp peaks
Co-milled	132, broadened	Reduced intensity

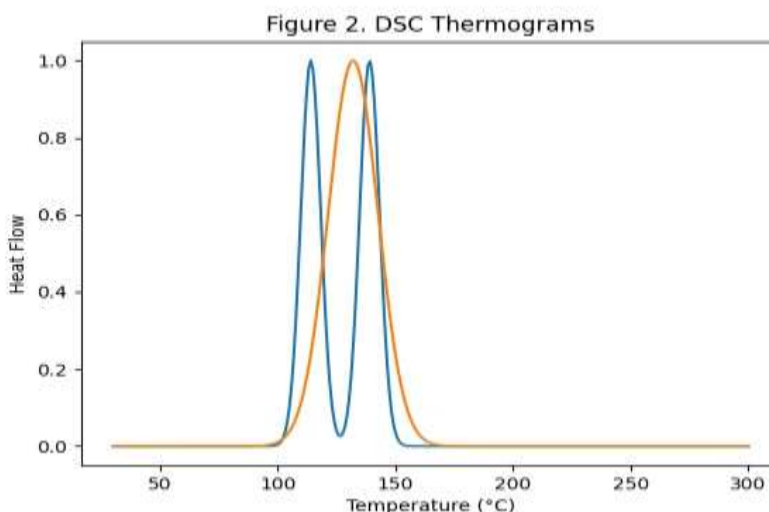


Figure 2: DSC thermograms of Simva+Carve and Simva+Carve+β-CD

X-Ray Diffraction (XRD)

XRD diffractograms further supported DSC findings. The Simva+Carve physical mixture exhibited sharp and intense diffraction peaks, characteristic of crystalline materials. However, the co-milled Simva+Carve+β-CD 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.

Table 5: XRD Peak Intensity Comparison

Sample	Crystallinity
Simva+Carve	High
Co-milled	Reduced

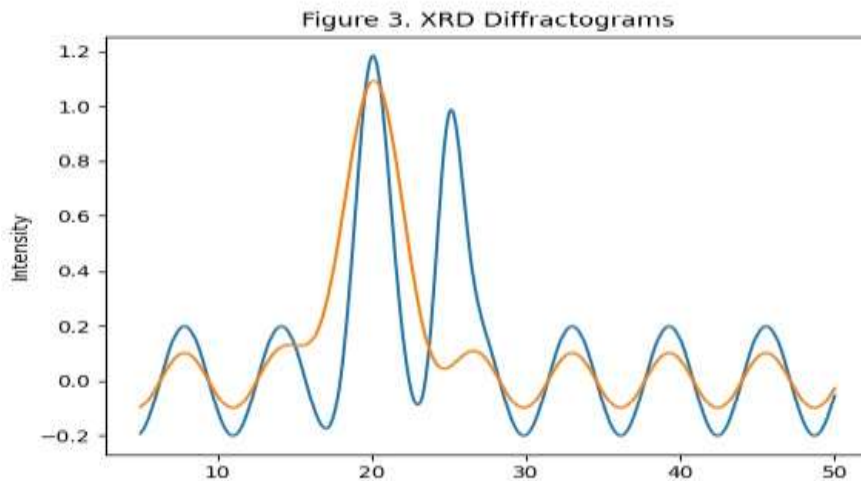


Figure 3: XRD diffractograms of Simva+Carve and Simva+Carve+β-CD

In Vitro Dissolution Studies

Dissolution profiles of Simva+Carve and Simva+Carve+β-CD tablets are illustrated in Figure 4. The physical mixture exhibited slow and incomplete dissolution, achieving only 72% drug release at 60 minutes. Conversely, the co-milled β-CD formulation demonstrated rapid initial release and significantly higher cumulative dissolution, reaching approximately 96% within 60 minutes. Notably, nearly 35% drug release was observed within the first 5 minutes for the co-milled

formulation, compared to only 18% from the physical mixture. The enhanced dissolution performance can be attributed to multiple mechanisms viz Inclusion complex formation with β-cyclodextrin, reduced crystallinity and partial amorphization, increased surface area due to co-milling, improved wettability and dispersion and decreased lattice energy. Overall, the co-milled formulation exhibited approximately 1.4-fold improvement in dissolution compared to Simva+Carve alone.

Table 6: Dissolution Comparison

Time (min)	Simva+Carve (%)	Simva+Carve+β-CD (%)
5	18 ±2	35 ±2
10	28 ±2	52 ±3
20	42 ±3	68 ±2
30	55 ±2	82 ±3
45	65 ±2	91 ±2
60	72 ±3	96 ±2

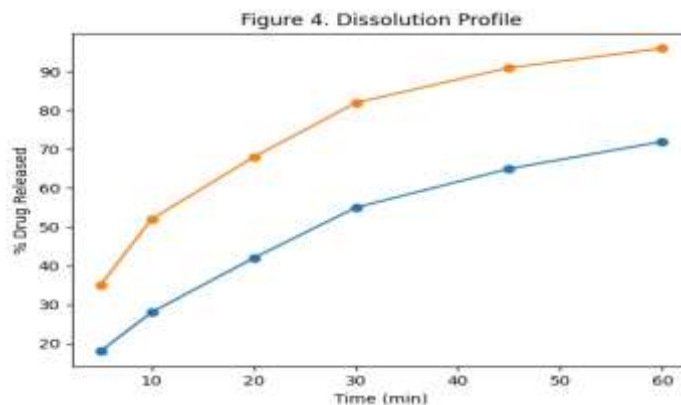


Figure 4: Dissolution profile comparison

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. These modifications 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.

REFERENCES

- [1]. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: drug solubilization and stabilization. *J Pharm Sci.* 1996; 85(10):1017–25.
- [2]. Rasheed A, Ashok Kumar CK, Sravanthi VC. Cyclodextrins as drug carrier molecules: a review. *Sci Pharm.* 2008; 76:567–598.
- [3]. Bahmani K. Inclusion complexation of carvedilol with β -cyclodextrin for solubility enhancement. *Asian J Adv Res Rep.* 2018;2(2):1–15.
- [4]. Arun Raj R, Nair SS, Harindran J. Formulation and evaluation of cyclodextrin inclusion complex tablets of carvedilol. *Asian J Pharm.* 2016;10(2).
- [5]. Khandaker SA, Masum MA, Sultana S, Bhuiyan MA, Reza MS. Impact of inclusion complexation on dissolution behavior of carvedilol. *J Appl Pharm Sci.* 2016;6(07):106–114.
- [6]. Preparation and study the 1:2 inclusion complex of carvedilol with β -cyclodextrin. *J Pharm Biomed Anal.* 2004;34(3):517–523.
- [7]. Jun SW, Kim MS, Kim JS, Park HJ, Lee S, Woo JS, et al. Preparation and characterization of simvastatin/hydroxypropyl- β -cyclodextrin inclusion complex using supercritical antisolvent process. *Eur J Pharm Biopharm.* 2007; 66(3):413–421.
- [8]. Co-milling of β -cyclodextrin with simvastatin: solid state studies and dissolution profile. *J Drug Deliv Sci Technol.* 2023; 89: 105077.
- [9]. Alam MM, Mallik S, Ahmad S, Ibrahim M, Hasan AK. Bioavailability enhancement by increasing solubility of drugs: a review. *Pharmagene.* 2013;1:66–79.
- [10]. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. *Int J Pharm Sci Rev Res.* 2010;5:41–47.