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Hydroxypropyl-β-Cyclodextrin for Delivery of Sinapic Acid via Inclusion Complex Prepared by Solvent Evaporation Method

Abdul Ahad *, Yousef A. Bin Jardan, Mohammad Raish, Abdullah M. Al-Mohizea and Fahad I. Al-Jenoobi

Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
* Correspondence: abdulahad20@yahoo.com or aahad@ksu.edu.sa

Abstract: The goal of this study was to increase the aqueous solubility and dissolution rate of sinapic acid (SA) by formulating binary inclusion complex (BIC) of SA with hydroxypropyl-β-cyclodextrin (HPβCD) using solvent evaporation (SE) technology. The phase solubility and dissolution studies were conducted to determine the solubility and in vitro release rate of SA. In addition, the prepared inclusion complex was characterized for solid state characterization using techniques such as DSC, PXRD, SEM, and FTIR. Moreover, the prepared SA-BIC was evaluated for its antioxidant activity. Results revealed that the SA solubility can be shown to improve with a change in HPβCD concentration. About 2.59 times higher solubility of SA in water was noticed in the presence of HPβCD (10 mM). Dissolution study demonstrated that the 34.11 ± 4.51% of SA was released from binary physical mixture (BPM), while the maximum release of 46.27 ± 2.79% of SA was observed for SA-BIC prepared by SE method. The prepared SA-BIC demonstrated distinctive properties when compared to pure SA, which was demonstrated by different analytical methods, such as DSC, PXRD, SEM, and FTIR, as evidence of SA inclusion into HPβCD cavity. Further, it was observed that SA-BIC displayed stronger DPPH radical scavenging activity than SA. In conclusion, SE technology considerably enhanced the complexity of SA with HPβCD, and these observations could help to heighten the SA solubility, which may lead to a better bioavailability.

Keywords: antioxidant activity; binary inclusion complex; cyclodextrins; hydroxypropyl-β-cyclodextrin; sinapic acid; solubility

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1. Introduction

Hydroxycinnamic acids refer to the category of phenolic acids containing bioactive carboxylic acids. They primarily consist of sinapic acid (SA, Figure 1A), caffeic acid, and ferulic acid [1–3]. SA may be present in free form but also in the ester forms. It is yellow-brown crystalline powder with the molecular weight of 224.21 g/mol [2]. It is a phytochemical that is present in various plant sources, such as berry fruits, cereals, citrus, oilseed crops, spices, and vegetables [4–7]. Previously, SA has shown activity against different conditions, such as oxidative stress [8], inflammation [9,10], anxiety [10], infections [11], diabetes [12], neurodegeneration [13], and cancer [14]. SA is a poorly soluble bioactive compound in water and, due to its limited dissolution rate, it restricts its permeability via the biological membranes, leading to decreased bioavailability [15–17].

Cyclodextrin (CD) inclusion complex is among the most popular strategies for augmenting the solubility of poorly soluble drugs. CDs reflect the family of cyclic oligosaccharide, and the parent CDs are referred to as alpha, beta, and gamma CDs comprising of six, seven, and eight units of glucopyranose, respectively. The cone form of the CD has lipophilic cavity inside and hydrophilic surface on the outside [18]. Its distinctive configuration is capable of influencing drug molecules, which could improve the stability, solubility, and enhance the permeability of the drug to the biological membrane. CD derivatives have become much more focused as the parent CDs themselves have quite low aqueous solubility, in particular βCD [19,20]. It is generally documented that the

introduction of certain water-soluble polymers could considerably improve the solubility of drugs in aqueous solutions through the development of ternary complexes [21,22]. A beneficial increase in drug solubilization was observed using the combination of CDs and polymers [23]. Water-soluble polymers play a leading role in the stabilization of complex aggregates and numerous forms of pharmaceutical particulate systems. By modifying the hydration characteristics of CD molecules, they could also decrease CD mobility and enhance the solubility of complexes [24].

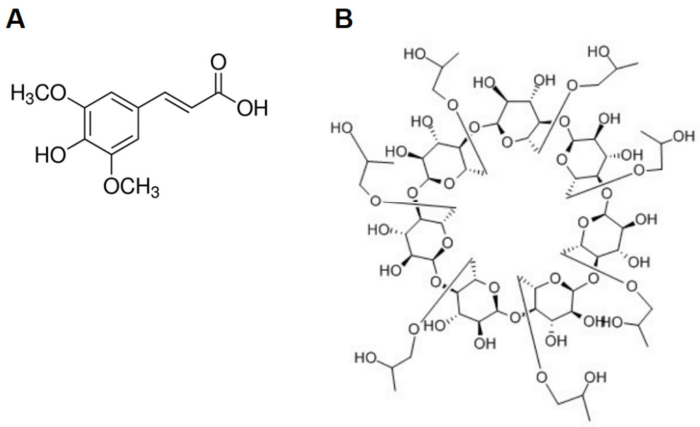

Figure 1. The chemical structure of (**A**) SA and (**B**) HPβCD.

It has been demonstrated that chemically modified CDs can be used for enriching the pharmaceutical properties of pharmaceuticals, food, and cosmetics [25]. Hydroxypropyl-β-CD (HPβCD, Figure 1B) is a derivate of β-CD and it possesses high water solubility, excellent stability, excellent absorption, strong solubilization, and low toxicity [26]. This makes it a common ingredient for pharmaceuticals as solubilizers, excipients, etc. [27]. HPβCD has attracted extensive research interest and has excessive application prospects in future [28].

In the present study, solvent evaporation (SE) procedure was applied to produce binary inclusion complex (BIC) of SA/HPβCD. The phase solubility of SA/HPβCD mixture and the in vitro dissolution profile of binary physical mixture (BPM) and BIC were assessed. In addition, the prepared inclusion complex was characterized for solid-state characterization and antioxidant property.

2. Materials and Methods

2.1. Materials

SA was acquired from "Carbosynth limited, Berkshire, UK". HPβCD was sourced from "Sigma-Aldrich, St. Louis, MO, USA". Analytical reagents were used for all other materials. Water from "Millipore (Molsheim, Cedex, France)" was used for preparing all solutions.

2.2. Formulation of Physical Mixture and Inclusion Complex

The binary physical mixture (BPM, 1:1 ratio) was prepared by proper mixing of each component of SA-BPM (SA:HPβCD) in mortar and pestle. The prepared PM mixture was stored in a desiccator for any further assessment. The SA-BIC (1:1 ratio) was prepared by SE method. In this procedure, the quantities of SA and HPβCD were precisely weighed for the preparation of binary complex, then SA and HPβCD were separately dissolved in organic phase (ethanol, 7 parts) and aqueous phase (water, 3 parts), respectively. Later, the solution of both SA and HPβCD were mixed slowly together with stirring [29]. Further, the solvent was evaporated at higher temperature with agitation till a damp mass was formed. Consequently, in order to remove the traces of solvent remaining in the mass, the formed damp mass was transferred to oven for 24 h, which was maintained at 50 °C. The dried mass was ground by mortar and pestle and passed through the sieve (#80). The prepared dried binary complex was stored in a well-sealed desiccator for further examination.

2.3. Measurements of Physical Properties

2.3.1. Differential Scanning Calorimetry (DSC)

Assessment of DSC was carried out by the "DSC, Perkin Elmer, Pyris 6 System, Shelton, CT, USA". As a reference, an empty aluminum pan was utilized. The test sample of 5 mg was mounted in a crimped aluminum pan and the DSC system heated throughout a range of temperatures of 50 °C to 300 °C at a steady rate of 10 °C/min.

2.3.2. Powder X-ray Diffraction (PXRD)

An X-ray diffractometer was used to determine the physical state of SA in the prepared inclusion complex. In the study, "Ultima IV Diffractometer (Rigaku Inc., Tokyo, Japan)" performed the PXRD analysis, and the PXRD trend of all tests samples was evaluated from the 3° to 60° 2-theta range.

2.3.3. Scanning Electron Microscopy (SEM)

The surface characteristics of pure SA, BPM, and prepared complex were analyzed using a "Zeiss EVO LS10 microscope". Each sample was initially mounted on a ribbon of carbon and applied to a vacuum for further examination and SEM photomicrographs were acquired [30,31].

2.3.4. Fourier Transform Infrared Spectroscopy (FTIR)

The prepared inclusion complex, BPM, and pure SA samples were analyzed by FTIR spectroscopy. The potassium bromide (KBr) and test sample mixture pellets were analyzed throughout a spectral region from 400 to 4000 cm^{-1} using "Bruker Alpha FTIR spectrometer".

2.4. Measurements of Phase Solubility and Dissolution Rate

A phase solubility analysis was performed to analyze the binary mixture's stability constant (K_c) and complexation efficiency (CE). The phase solubility analysis was conducted as reported by Higuchi and Connors [32]. A surplus quantity of SA was placed in aqueous solution of HPβCD (2–10 mM) [33]. The flasks were shaken continually at 25 °C for 3 days. Consequently, the samples were removed, filtered using a "0.45 µm membrane filter", and filtrate was "spectrophotometrically assayed at 322 nm (Jasco V 530, Tokyo, Japan)" [34,35]. The K_c and CE was determined using Equation (1) [36–39] and Equation (2) [37,40], respectively. S_0 was the equilibrium solubility of SA in water per se [41–43].

$$K_c = \frac{Slope}{Intercept\ (1 - Slope)} \quad (1)$$

$$CE = S_0 K_c \quad (2)$$

In vitro dissolution experiments were undertaken utilizing USP dissolution apparatus II paddle system. Dissolution profile was determined for SA per se, BPM, and for BIC (equivalent to 100 mg of SA). Phosphate-buffered pH 6.8 (900 mL) maintained at 37.0 ± 0.5 °C was used as the dissolution medium, which was agitated with a paddle rotating speed of 50 rpm. At each time interval of 5, 10, 20, 30, and 60 min, sample (5 mL) was pipetted out from each dissolution vessel and replenished with equivalent volume of fresh dissolution medium. The pipetted samples were filtered and analyzed for drug content using UV spectrophotometer at 322 nm. In order to identify the best drug release kinetic from inclusion complex, the dissolution data obtained were fitted to the "zero order, first order, Korsmeyer–Peppas, Hixson–Crowell, and the Higuchi drug release models" [43]. For the purpose of determining the best model, the r^2 (correlation coefficient) value was taken into consideration [44–46].

2.5. Assesment of Antioxidant Activity

The "DPPH (2,2-diphenyl-1-picrylhydrazyl)" assay process was employed in this study to evaluate the antioxidant activity of prepared SA-BIC (SE). The SA per se (control) and SA-BIC (SE) were separately dissolved in methanol to attain various concentrations in the range of 0–100 µg/mL. The resultant absorbance was noted down at 517 nm by

spectrophotometer [43]. The percentage scavenging of DPPH free radical by samples was calculated by the formula:

$$\text{Radical Scavenging } (\%) = \frac{(\text{Absorbance of control} - \text{Absorbance of sample})}{\text{Absorbance of control}} \times 100$$

2.6. Statistical Analysis

"The results of phase solubility and dissolution study were compared statistically using one-way ANOVA followed by Dunnett test and Tukey test while the unpaired *t*-test was used for comparing means of antioxidant activity. The GraphPad InStat® 3.06 (GraphPad Software, Inc., San Diego, CA, USA) was used for statistical analysis and $^{*,\#}$ $p < 0.05$ was considered significant".

3. Results and Discussion

3.1. Differential Scanning Calorimetry

Figure 2 illustrates the DSC graph for SA, BPM, and BIC prepared by SE method. The SA thermal curve demonstrated a strong endothermic melting peak at 193.52 °C, referring to the SA's transition temperature. The HPβCD DSC thermogram demonstrated a wide peak.

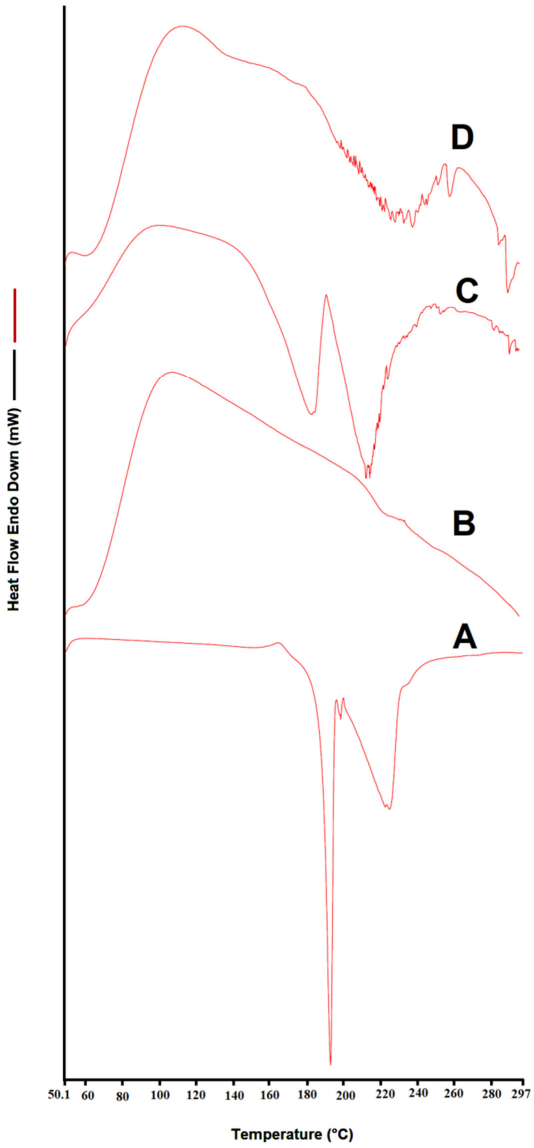

Figure 2. DSC thermogram of (**A**) SA, (**B**) HPβCD, (**C**) BPM, and (**D**) BIC.

The peak observed corresponding to the melting point of SA is very negligible in BIC; this could be due to the enclosure of the guest molecule into the cavity of the host. This indicated that the inclusion complex was established among the drug and CD [46,47].

3.2. Powder X-ray Diffraction

The PXRD graph of SA, BPM, and BIC are presented in Figure 3. On comparison of the PXRD pattern, it was noticed that the SA-BIC PRXD pattern (Figure 3D) is nearly comparable to that of the PXRD pattern of HPβCD (Figure 3B) and supports the possibility that the SA was contained in the HPβCD cavity, which fully obscured the SA molecule from X-rays.

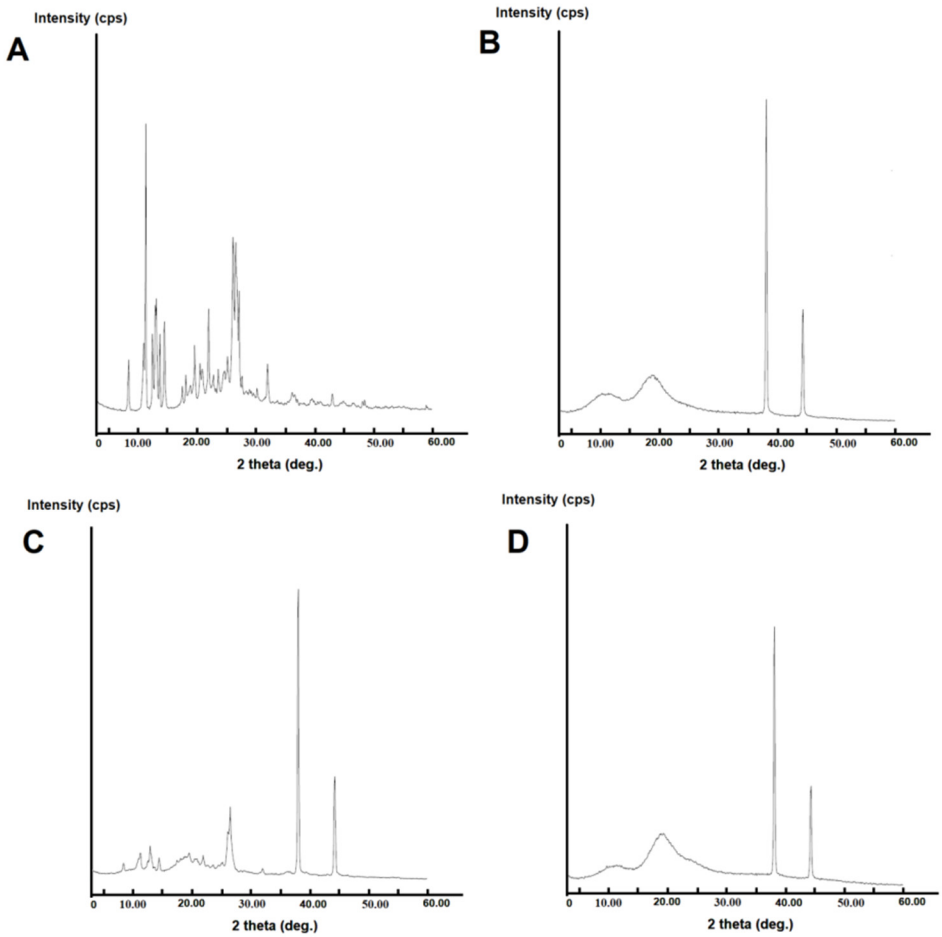

Figure 3. XRD patterns of (**A**) SA, (**B**) HPβCD, (**C**) BPM, and (**D**) BIC.

On the other hand, the pure SA sample had a high degree of crystallinity, as demonstrated by the much-defined peaks in its PXRD image. The PXRD pattern of the BPM (Figure 3C) indicates the existence of both the guest and host molecules of the mixture, and that was basically a mixture of SA/HPβCD. The peaks originating from SA were invisible from the BIC prepared by SE method. The X-ray diffraction pattern of BIC sample indicates that the guest molecule SA complexed in the grid of the host molecule, i.e., HPβCD. The outcomes are correlated with DSC's findings on the complexes.

3.3. Scanning Electron Microscopy

As seen from SEM images (Figure 4), pure SA particles identified as irregularly formed crystals, while HPβCD particles (Figure 4B) consisted of irregularly sized crystals.

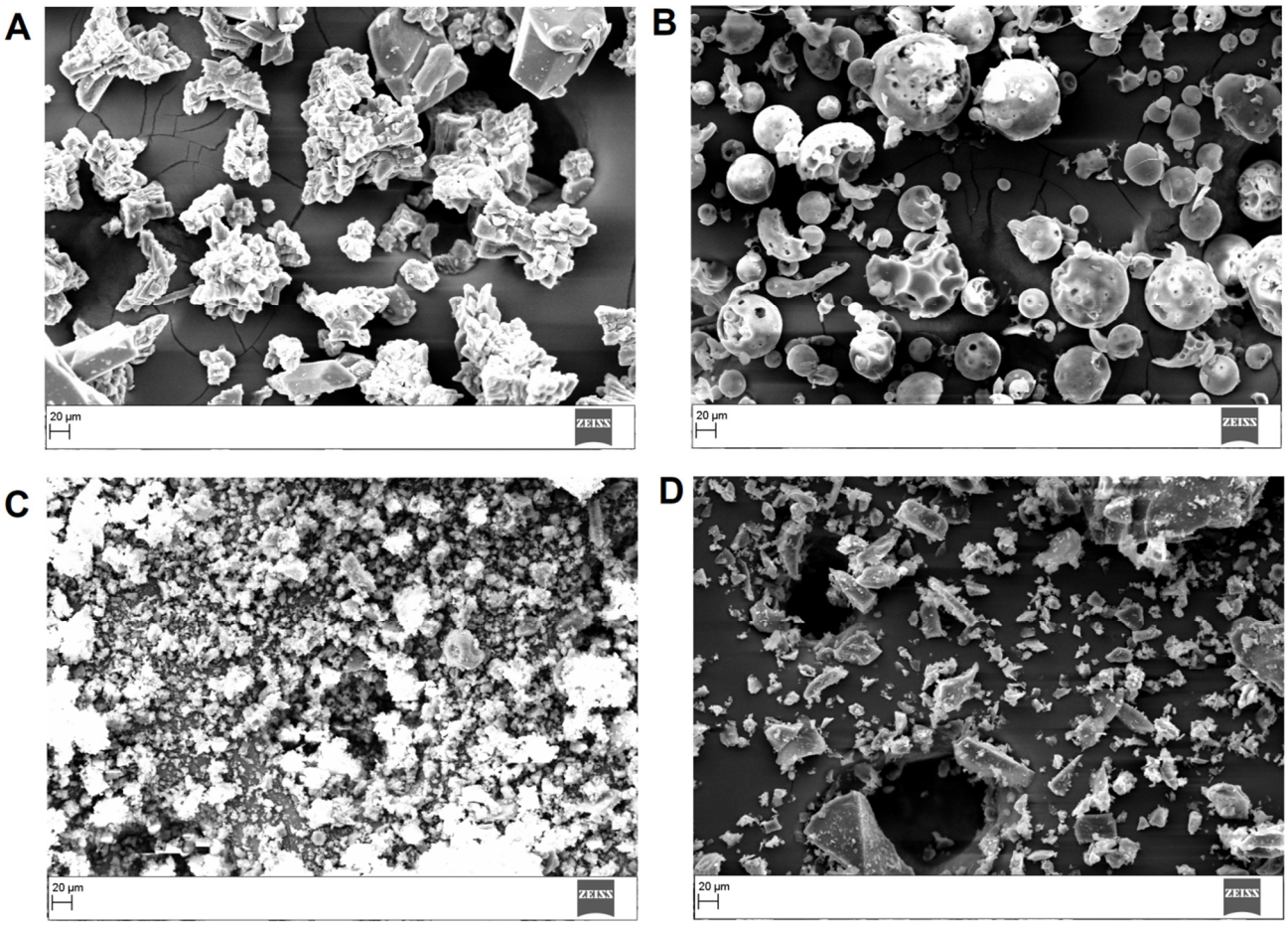

Figure 4. SEM image of (**A**) SA, (**B**) HPβCD, (**C**) BPM, and (**D**) BIC.

Analysis of BPM (SA/HPβCD) (Figure 4C) reported the existence of mixed and adhered SA crystals on the surface of HPβCD particles, showing no obvious solid-state interaction between the constituents of BPM. The products of BIC prepared by SE method (Figure 4D) demonstrated tiny and irregular pieces, with a transition from crystalline to amorphous form. It was reported earlier that a shift in drug particles' form was representative of a new solid state [45]. Consequently, modifications in the morphology of SA-BIC in comparison to the SA indicated an interaction among the SA and HPβCD.

3.4. Fourier-Transform Infrared Spectroscopy

Pure SA displayed a strong stretching at 620.84, 1107.99, 1208.45, and 1261.87 cm^{-1}. In addition to this, the typical vibrations also were detected at 819.33, 1426.45, 1511.17, 1657.41, and 2830.64 cm^{-1} (Figure 5A).

The displayed frequencies for HPβCD were identified at 3332.04 and 1020.70 cm^{-1} that represent the stretching vibration of the C-O-C and O-H moiety. Further, the stretching vibration at 848.35 and 703.82 cm^{-1} was the other main noticeable peak for HPβCD (Figure 5B). In the BIC, the HPβCD vibration bands concealed the absorption peaks of SA from 1261.87 to 1657.41 cm^{-1} (Figure 5D). The major spectra changes of C=O and C-H groups corresponding to SA could indicate the formation of hydrogen bonds among the carbonyl groups of SA and hydrogen groups located outside of HPβCD. It was noted that the distinctive band corresponding to SA at 620.84, 1107.99, and 1657.41 cm^{-1} is dramatically diminished and relocated for BIC system. Transitions and declines in carbonyl band strength imply the creation of hydrogen bonds between both the SA carbonyl groups and the HPβCD hydrogen groups. The findings indicate that there has been interaction

among SA and HPβCD, which could suggest the creation of complex formation by the SE approach used for the development of BIC.

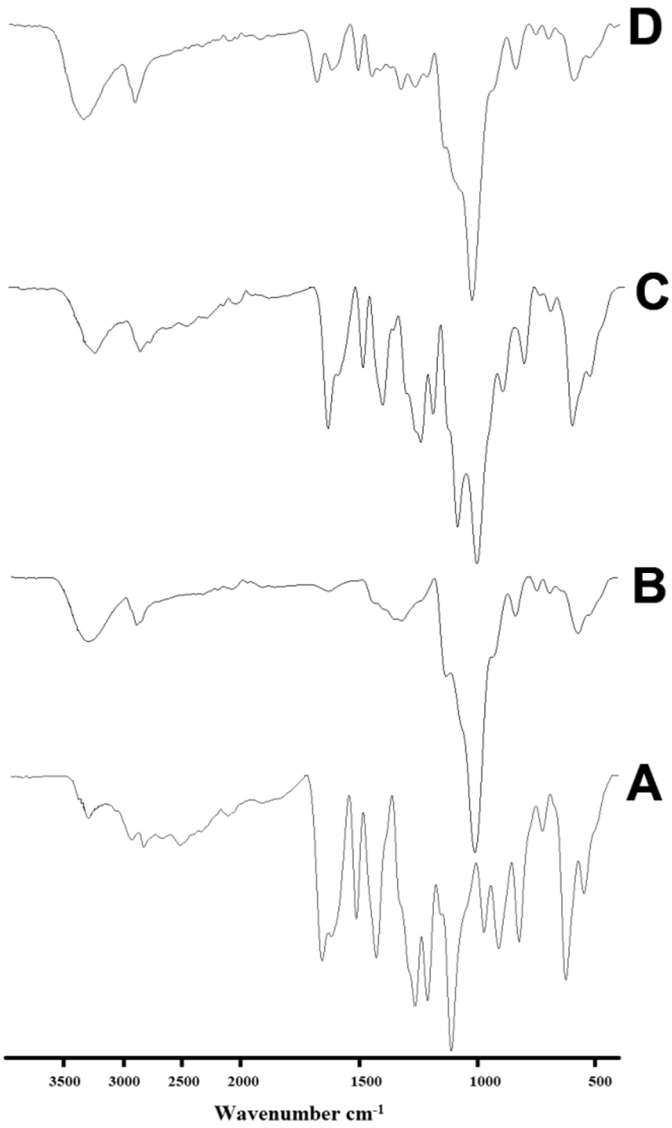

Figure 5. FTIR spectra of (**A**) SA, (**B**) HPβCD, (**C**) BPM, and (**D**) BIC.

3.5. Phase Solubility and Dissolution Rate

The phase solubility analysis was executed to examine the solubility of SA in HPβCD. The SA solubility can be shown to improve with a change in HPβCD concentration (Figure 6).

About 2.59 times higher solubility ($p < 0.05$) of SA in water was noticed in the presence of HPβCD (10 mM). The stability constant (K_c) and CE value was found to be 258.50 M^{-1} and 681.68, respectively [33,48–52]. The above results suggested the prepared binary complex of SA/HPβCD was found to be stable. It was reported that the stability constant (K_c) value from 50 to 5000 M^{-1} was more appropriate for enhancing the solubility and stability of poorly water-soluble drugs [53]. The findings suggest that the inclusion complex has been established, and it is evident from the calculated K_c value that such inclusion complex is relatively stable [44,45].

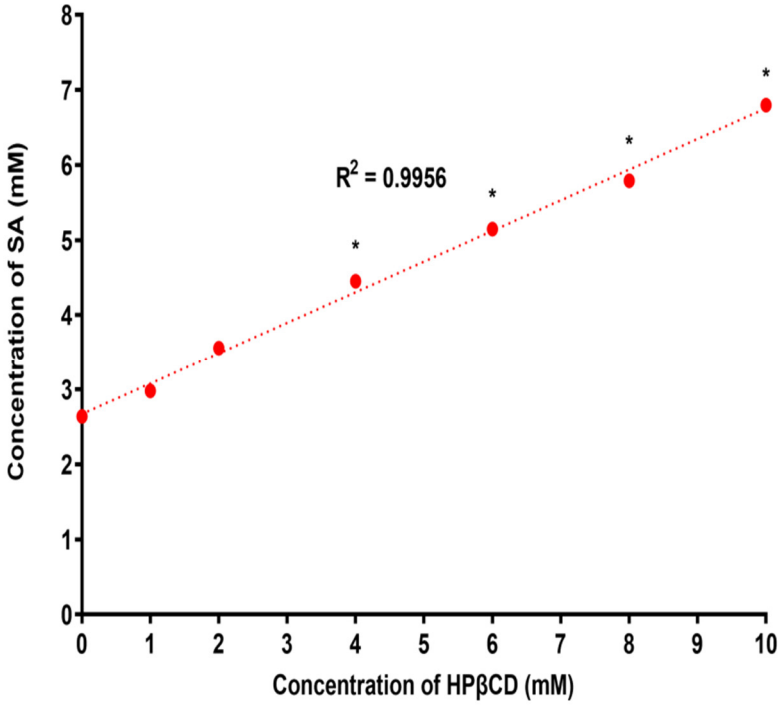

Figure 6. Phase solubility graph of SA in presence of HPβCD. * $p < 0.05$ as compared to S_0.

Figure 7 demonstrates the SA, SA-BPM, and SA-BIC dissolution profile. The SA showed the slowest rate of dissolution (28.01 ± 2.33%) in comparison to other formulations SA-BPM and SA-BIC, which could be owing to poor solubility of SA. The prepared BIC greatly increased ($p < 0.05$) the rate of dissolution of SA, as contrasted to pure SA dissolution. It was observed through the dissolution study that around 34.11 ± 4.51% of SA was released from BPM at 1 h.

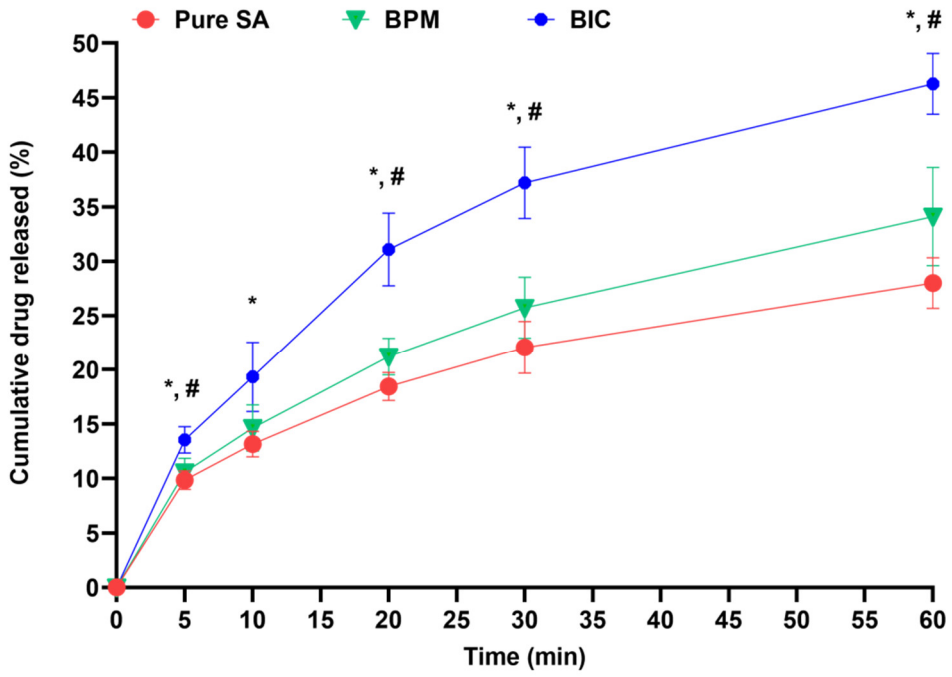

Figure 7. Dissolution profile of SA, BPM, and BIC. * $p < 0.05$ as compared to SA, # $p < 0.05$ as compared to BPM.

SA-BIC further improves the release of SA considerably ($p < 0.05$). The maximum release of 46.27 ± 2.79% of SA was observed for SA-BIC prepared by SE method (Figure 7).

As per Table 1, a Peppas type drug release model was found to be best suited for the release of SA from BIC prepared by SE method ($r^2 = 0.9807$).

Table 1. Correlation coefficients calculated by fitting in vitro data to different release models.

Release Model	SA	BPM	BIC
	r^2 Value	r^2 Value	r^2 Value
Zero order	0.9302	0.9457	0.8907
First order	0.9462	0.9647	0.9286
Higuchi's Model	0.9897	0.9952	0.9698
Korsmeyer-Peppas	0.9960	0.9974	0.9807
Hixon–Crowell	0.9410	0.9588	0.9166

3.6. Antioxidant Activity

It is reported that the antioxidants contribute hydrogen or electron to DPPH and transform it to DPPH-H in the DPPH radical scavenging process, so the antioxidant behavior of substances relies primarily on the electron or hydrogen donating potential.

In our study, the findings of the experiment revealed that the DPPH radical scavenging behavior of both SA and BIC increased considerably on increasing their concentrations. The DPPH radical scavenging activity demonstrated by SA and BIC at their maximum concentration was 93.65% and 97.73%, respectively ($p < 0.05$, Figure 8). It was observed that BIC sample displayed stronger DPPH radical scavenging activity than SA. The research finding indicates that the development of inclusion complex BIC demonstrated considerable radical scavenging and antioxidant properties, undoubtedly owing to the increment of SA solubility by BIC prepared by SE method. Antecedently, Jo et al. reported that the complexation of β-CD augmented the solubility of trans cinnamaldehyde, as well as upsurged its antioxidant activity [54]. In another study, the inclusion complex of mangiferin and β-CD exhibited higher antioxidant activity toward DPPH [55]. In another study, significant enhancement in the antioxidant activity of piperine inclusion complex was observed as compared to piperine alone. Authors concluded that the increase in antioxidant activity could be due to enhanced solubility of piperine in the presence of HPβCD and auxiliary substance [56].

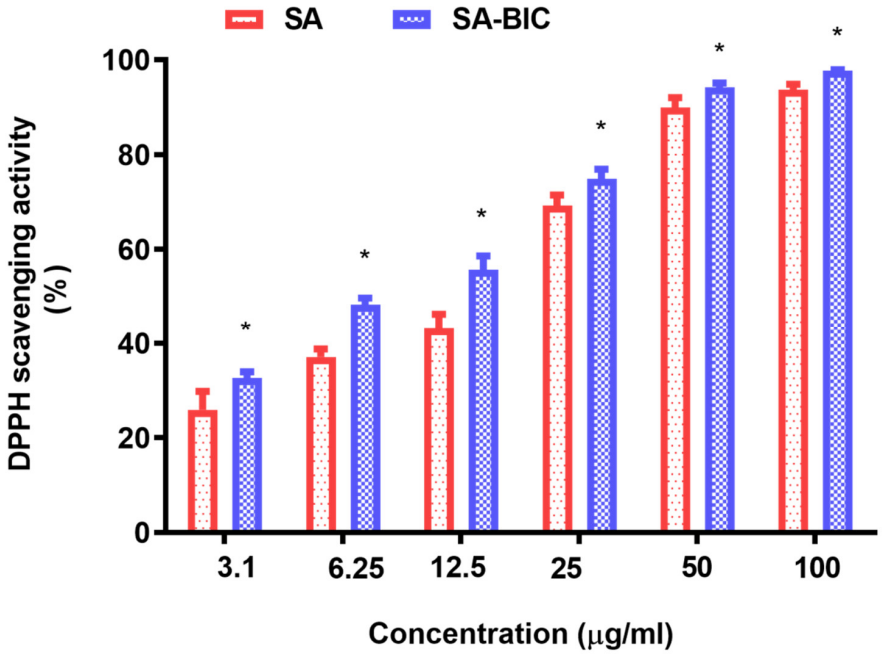

Figure 8. Antioxidant activity profile of pure SA and BIC. * $p < 0.05$ as compared to SA.

4. Conclusions

In this study, the SE was effectively used to prepare the inclusion complex of SA. Results showed that SA was solubilized more readily by HPβCD. The formation of inclusion complex was supported by solid characterization techniques, such as DSC, PXRD, SEM, and FTIR. Additionally, the in vitro dissolution profile of SA was enhanced by the binary complex. It was observed through the dissolution study that 34% of SA was released from BPM. The maximum release of 46.27% of SA was observed for SA-BIC prepared by SE method. Further, it was observed that SA-BIC displayed stronger DPPH radical scavenging activity than SA. In summary, SE technology considerably enhanced the complexity of SA and HPβCD, resulting in an improved solubility of SA in binary compound.

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Conflicts of Interest: The authors declare no conflict of interest.

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