Solubility Enhancement of Carvedilol by Solid Dispersion Technique Using Sodium Alginate, Guar Gum, Xanthan Gum, and Locust Bean Gum as Polymers

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Abstract: *Carvedilol (CVD) is a non-selective β-blocker. CVD is included in BCS class II. It has low water solubility. In this research, solid dispersion was used to increase the solubility and dissolution profile of CVD.* In silico *study using the ligand-ligand docking method. The preparation of solid dispersion using the kneading method with a weight ratio of 1:1, 1:2, 1:3, and 1:4, evaluation of solid dispersion includes solubility and dissolution. The best solid dispersion was characterized using FTIR, DSC, and PXRD.* In silico *study showed complexes CVD-SA, CVD-GG, CVD-XG and CVD-LBG have a hydrogen interaction. SA and XG were chosen as carriers in solid dispersion. CVD solid dispersion showed increased solubility in all samples, with the highest increase at 90.63 times at CVD: XG (1:4). The results of the dissolution profile obtained at 60 min are 64.95 ± 0.45% at pure CVD, 83.32 ± 1.19% at CVD:SA (1:4), and 72.56 ± 3.62% at CVD: XG (1:4). The FTIR spectrum indicates an interaction between CVD and SA. The thermogram indicated the amorphous drug, and the diffractogram showed a decrease in crystallinity. Solid dispersion is proven to increase the solubility and dissolution profile of CVD. Solid dispersion CVD: SA (1:4) showed the highest solubility and dissolution profile.*

Keywords: *carvedilol; BCS class II; solid dispersion*

■ INTRODUCTION

Oral administration is the most common and convenient method of drug administration. The drug concentration in the blood must be reached for oral drugs to work effectively. The drug concentration depends on its bioavailability, which is strongly influenced by the rate and extent of drug absorption [1-2]. More than 70% of active pharmaceutical ingredients in formulation development have solid hydrophobic characteristics. As a result, inadequate bioavailability is a significant difficulty in the design of oral dosage forms. When it comes to poorly soluble drugs in water, substantial doses are frequently required to achieve therapeutic plasma concentrations following oral administration [3].

Cardiovascular disease is the leading cause of death globally. In 2019, an estimated 17.9 million individuals died from cardiovascular disease. And it is estimated that around 1.28 billion adults aged 30–79 years worldwide suffer from hypertension. Carvedilol (CVD) is a non-selective beta blocker with alpha-1 receptor blocking activity commonly used to treat cardiovascular diseases such as hypertension, ischemic heart disease, post-myocardial infarction, left ventricular dysfunction, and congestive heart failure [4]. The carvedilol structure (Fig. 1) shows various functional groups as donor and acceptor proton. With such a structure, CVD has several issues with its pharmaceutical formulations.

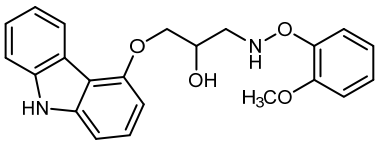


Fig 1. Chemical structure of carvedilol (CVD) [5]

CVD has a minimal bioavailability of about 25–30% due to its practically insoluble solubility in water (10.42 mg/L) and exhibits a pH-dependent solubility and its dissolution limits absorption from the gastrointestinal tract. CVD undergoes extensive first-line metabolism, contributing to its low bioavailability [2]. CVD is classified as BCS class II by the Biopharmaceutics Classification System (BCS) because it has a high membrane permeability but poor solubility [6].

There have been several studies conducted to increase the solubility and bioavailability of CVD, some of which are micronization techniques, complex inclusion techniques [7–8], carbon dioxide supercritical techniques [9], hydrotropic techniques [10], nanotechnology [11], but these techniques are still inefficient in overcoming the problem of CVD solubility so that other efforts need to be made, including the solid dispersion approach. Solid dispersions are solid products in which the hydrophobic drug is dispersed in a hydrophilic polymer, which might be in an amorphous and molecularly microcrystalline form. The characteristics of the solid dispersion formulation are influenced by these hydrophilic polymers, also known as carriers. Due to the ease of preparation, optimization, and reproducibility of the production procedure, the solid dispersion technique is an excellent way to enhance solubility [7].

Determination of polymers as carriers in solid dispersions can be done by conducting in-silico studies. This computational technique is used to see the interactions between the drug and each candidate polymer. Using natural polymers as carriers in solid dispersions is an excellent choice to increase solubility because natural polymers are low in toxicity, biocompatible, biodegradable, and widely available. Natural polymers that can be used are sodium alginate (SA), guar gum (GG), xanthan gum (XG), and locust bean gum (LBG) [11-13].

SA is a hydrophilic polymer extracted from brown seaweed cell walls. As a hydrophilic polysaccharide, SA can improve the wettability of poorly soluble pharmaceuticals in water, reducing agglomeration and increasing surface area [14]. It has been demonstrated that SA, a carrier of telmisartan's solid dispersion (an antihypertensive and member of BCS class II), can boost solubility up to 16.7 times more than pure telmisartan. Additionally, SA works well as an anti-plasticizer to avoid the recrystallization of drugs [11].

GG and XG have been shown to increase the dissolution of solid dispersion of valsartan (antihypertensive and belongs to BCS class II) up to 4.62 times compared to pure valsartan [15]. The solid dispersion of domperidone (an antiemetic and belongs to BCS class II drugs) using modified locust bean gum (MLBG) as a carrier showed an increase in solubility up to 12.62 times compared to pure drugs. The ability of MLBG to increase drug wettability and reduce drug particle size in solid dispersion leads to increased drug dissolution and results in increased drug bioavailability [16]. Therefore, SA, GG, XG, and LBG polymers allow an increase in the solubility of CVD through the solid dispersion method. Although it has been reported to increase the solubility of CVD using some of the techniques previously mentioned, it is still not efficient to increase the solubility of CVD, so in this study, an increase in the solubility of CVD was carried out utilizing the solid dispersion techniques with selected polymers based on the results of in silico studies. So far, there have not been many developed.

■ EXPERIMENTAL SECTION

Materials

The materials used in this study were Hydrochloric acid (Merck), potassium bromide (Merck), carvedilol (Kalbe), ethanol (Merck), sodium alginate (Kimica), and xanthan gum (Qingdao ICD Biochemistry).

Instrumentation

The instrumentations used in this study were UV-Vis spectrophotometer (Specord 205 Analytical Jena), USP dissolution apparatus type 2 (SotaX AT7 Smart dissolution tester), Fourier-Transformed Infrared Spectrophotometer (FTIR) (Specord 100), Differential Scanning Calorimetry (DSC) (Linseis PTA ST 1600), and X-ray diffractometer (PanAnaltycal).

Procedure

In silico *simulation*

2D structures of CVD and polymer were drawn using ChemDraw. Ligand preparation was performed using AutoDockTools, and ligand-ligand docking was performed using the Vina Wizard on PyRX. Observation of interactions formed between drugs and polymers was carried out using AutoDockTools [17].

Solid dispersion preparation

The solid dispersion was prepared by kneading method with the ratio of drug and polymer w/w 1:1, 1:2, 1:3, and 1:4. The drug and polymer are mixed with a sufficient amount of methanol to form a paste. The mixture was dried at 40 °C in an oven, then ground into a fine powder and sieved using a mesh no. 80. A physical mixture of CVD and polymer was also prepared in a ratio of 1:4 [15].

Saturated solubility test

Pure CVD and solid dispersion in excess were each dissolved in 10 mL of distilled water and stirred for 24 h at room temperature (25 °C). Then, filtered using Whatman paper No. 42 and analyzed using a UV-Vis spectrophotometer at 286 nm [18].

Dissolution test

The dissolution test was carried out using USP apparatus II (paddle method) using HCl pH 1.45 (900 mL), a speed of 50 rpm at 37 °C. Pure CVD and solid dispersion were weighed as much as 25 mg or the equivalent amount of solid dispersion. The test sample was put into the media, and 10 ml of the sample solution was taken at certain time intervals, 10, 20, 30, 40, 50, and 60 min and was refilled with the same amount using new media. The samples were then analyzed using a UV-Vis spectrophotometer at a wavelength of 286 nm [19].

Fourier transform infrared (FTIR)

The readings of the FTIR spectra on samples of pure CVD, polymer, physical mixture, and CVD solid dispersion were carried out separately using an FTIR spectrophotometer. FTIR spectrum readings are seen in the 4000–400 cm^{-1} at a resolution of 4 cm^{-1} [20].

Differential scanning calorimetry (DSC)

The phase transitions of pure CVD, physical mixture, and CVD solid dispersion were analyzed using the DSC method. Approximately 2 mg of the sample is heated over a temperature range of 25–180 °C at a rate of 10 °C /min under a nitrogen atmosphere (50 mL/min) [21-22].

Powder X-ray diffraction (PXRD)

The diffractogram pattern of pure CVD, physical mixture and solid dispersion of CVD was performed using an X-ray diffractometer with copper Kα radiation (wavelength = 1.54060), a voltage of 40 kV and a current of 20 mA. 100-200 mg samples were scanned in the range of 5–60° (2θ) at a speed of 0.02°/sec [20].

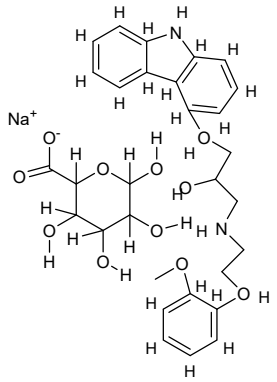
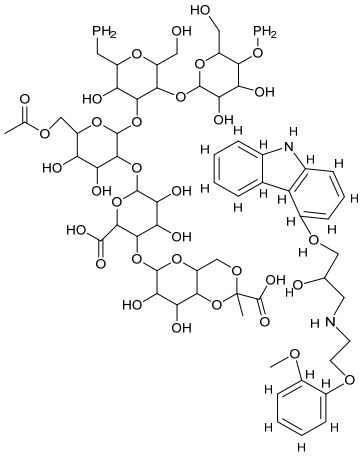
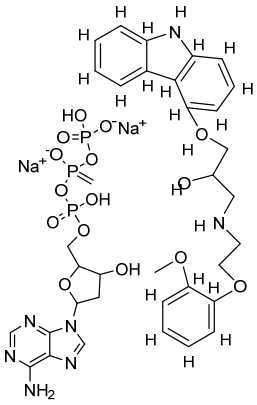
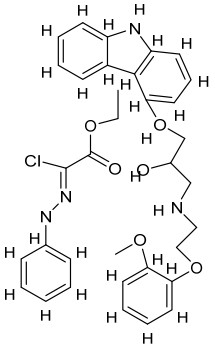
■ RESULTS AND DISCUSSION

In Silico Simulation

In silico studies between drugs and polymers were conducted to examine possible interactions. The polymers used include sodium alginate (SA), Xanthan Gum (XG), Guar Gum (GG), and Locust Bean Gum (LBG). These polymers have a hydroxyl group (-O-H) in their chemical structure, making it possible to form hydrogen bonds with CVDs having hydroxyl (-O-H) and amine (-N-H) groups. The results of the in-silico study can be seen in Table 1. Hydrogen bonding has an essential role in influencing the physicochemical properties of an active pharmaceutical ingredient, one of which is solubility and dissolution rate [23]. The binding energy or also known as binding affinity indicates the ability of the drug to bind to the receptor (in this case, the drug and the polymer). The bond affinity between the drug and the polymer increases when the bond energy value decreases and vice versa [24].

Hydrogen bonds are included in polar interactions, so they have a high water-attracting ability. Therefore, it is expected that the presence of hydrogen bonds can increase the contact between the drug and water, increasing the solubility of the drug. Two polymers were selected for solid dispersion; considering the convenience and availability of resources, the polymer chosen was the one that formed the most and the fewest hydrogen bonds. For the creation of CVD solid dispersions, SA and XG were chosen as the polymers.

Table 1. Results of in silico studies of drugs and polymers

Compound	Complex structure	Interaction	Binding energy (kcal/mol)
Carvedilol-Sodium Alginate (CVD-SA)		2 hydrogen bonds, 5 hydrophobic interactions	-2.4
Carvedilol-Xanthan Gum (CVD-XG)		1 hydrogen bond, 2 hydrophobic interactions, π-π interactions	-2.6
Carvedilol-Guar Gum (CVD-GG)		2 hydrogen bonds, 4 hydrophobic interactions, π-π interactions	-2.9
Carvedilol-Locust Bean Gum (CVD-LBG)		1 hydrogen bond, 2 hydrophobic interactions, π-π interactions	-2.9

Saturated Solubility Test Results

The solubility test was carried out in aqueous media for 24 h at room temperature to reach saturation, and the solubility results can be seen in Fig. 2. The saturated solubility of CVD in water was 2.46 ± 0.03 mg/L. An increase in the saturated solubility of CVD was observed in all variations of solid dispersion with both SA and XG polymers. The solid dispersion with SA polymer showed an increase in saturated solubility from the highest at CVD:SA (1:4) of 27.48 ± 1.59 mg/L (11.17 times), CVD:SA (1: 3) of 25.40 ± 0.34 mg/L (10.32 times), CVD:SA (1:2) of 17.39 ± 0.13 mg/L (7.07 times), and CVD:SA (1:1) of 12.34 ± 0.14 mg/L (5.01 times). This finding shows that the greater the number of polymers used, the higher the solubility increase. This fact can be related to the hydrogen bonds formed between CVD and polymer caused by the addition of polymer ratio. The tendency of increasing solubility, which increases with the high ratio between drug and polymer, has also occurred in several previous studies [25-26].

The solid dispersion with XG polymer showed an increase in saturated solubility from the highest at CVD: XG (1:4) of 222.95 ± 3.53 mg/L (90.63 times), CVD:XG (1:1) of 168.40 ± 5.69 mg/L (68.46 times), CVD:XG (1:3) of 165.48 ± 5.62 mg/L (67.27 times), and CVD:XG (1:2) of 150.11 ± 0.70 mg/L (61.02 times).

The increase in solubility of the solid dispersion can occur because the drug is dispersed molecularly in the hydrophilic polymer. The decrease in particle size also facilitates the formation of new surfaces, thereby causing an increase in the effective surface area. This new surface allows for an increase in wettability so that the solubility of the drug increases [24,27].

Statistical tests were also carried out and showed a significance value of 0.000 ($p < 0.05$), so it can be said that there was a significant difference between the solubility of pure CVD and CVD solid dispersion. Two solid dispersions with the highest increase in solubility of each polymer were then continued for dissolution test, solid dispersion CVD:SA (1:3), CVD:SA (1:4), CVD-XG (1:1), and CVD-XG (1:4).

Dissolution Test Results

The dissolution test results can be seen in Fig. 3. At 60 min, the pure CVD that can be dissolved is 64.95 ± 0.45%. The solid dispersion CVD:SA (1:4) and CVD:XG (1:4) showed an increase in the dissolution profile at 60 min, respectively, which was 83.32 ± 1.19% and 72.56 ± 3.62%. Several mechanisms can cause the increase in the dissolution profile in the solid dispersion system due to a decrease in the particle size of the drug, the drug being in an amorphous state, the particles in the solid dispersion having high porosity, and particles with increased wettability.

The statistical test results showed a significance value of 0.448 ($p > 0.05$), so it can be said that there was no significant difference between pure CVD dissolution

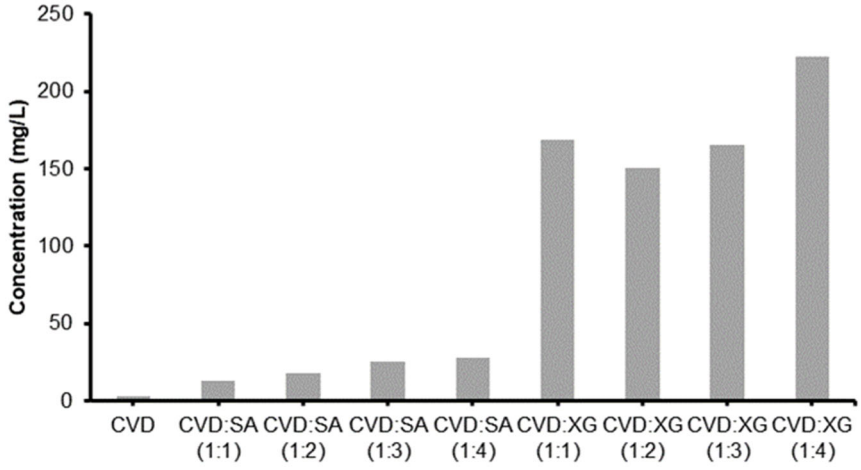


Fig 2. Graph of pure CVD and CVD solid dispersion saturated solubility test

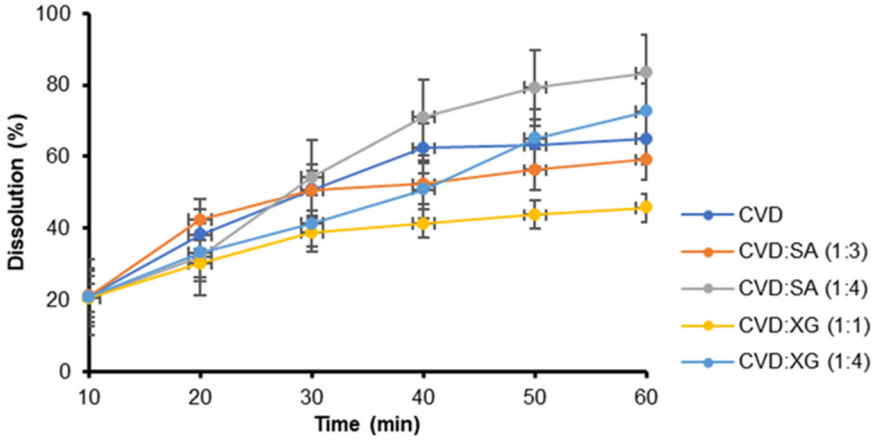


Fig 3. Graph of pure CVD and CVD solid dissolution test results

and CVD solid dispersion. Therefore, one solid dispersion variation with the highest dissolution profile at 60 min was selected for the characterization, namely CVD:SA (1:4) solid dispersion.

Fourier Transform Infrared (FTIR)

The results of the characterization using FTIR can be seen in Fig. 4. In the pure CVD IR spectrum, it can be seen that there are two N-H groups with stretching vibrations at 3342 and 3305 cm^{-1} and stretching vibration of an O-H group at 3343 cm^{-1}. Other peaks were also observed at wavenumbers 2923 cm^{-1} (C-H stretch), 1214 cm^{-1} and 1257 cm^{-1} (C-O), and 1592 cm^{-1} (C=C) [28].

The FTIR results on the SA polymer showed a peak at a wavenumber of 1419 cm^{-1} caused by the presence of a carboxylate group. The absence of a peak associated with the COOH group at 1700 cm^{-1} indicates that the carboxylic acid is converted to a carboxylic acid in the presence of sodium (COO-Na). The broad peak at wave number 3415 cm^{-1} indicates the presence of an O-H stretch. The peak formed at 1363 cm^{-1} indicates the presence of carbonyl (-C=O) starching [21,29].

The FTIR spectra of the physical mixture (PM) and CVD:SA (1:4) solid dispersion (SD) present overlapping characteristics of the drug and carrier at a lower intensity, indicating an interaction between CVD and SA and showing that the drug is evenly dispersed in the polymer [23,28]. Peaks of SA dominated the spectrum of the physical mixture and solid dispersion, but peaks of pure CVD were still found. A shift in the wavenumber of the

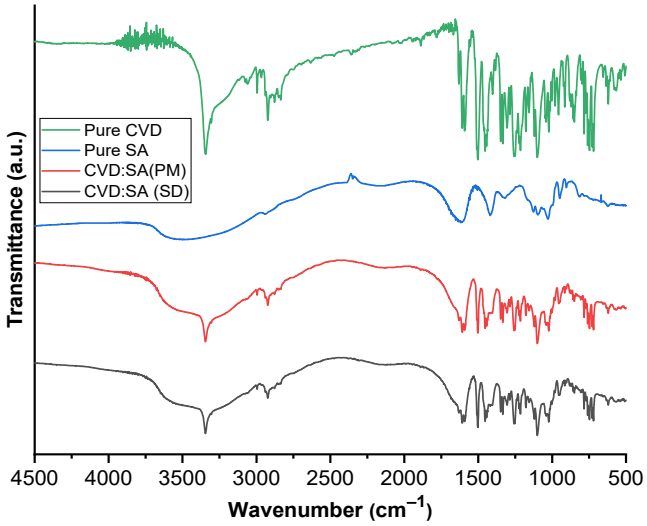


Fig 4. FTIR spectrum overlay of pure CVD, SA, CVD:SA physical mixture (PM), and CVD:SA solid dispersion (SD)

C-O functional group in solid dispersion was also observed, namely from 1257 (pure CVD) to 1251 cm^{-1}; this is following the results of in silico studies where there is the formation of hydrogen bonds on the O atom in fragment 2-methoxyphenyl of CVD.

Differential Scanning Calorimetry (DSC)

Characterization with DSC aims to assess the physical state of the drug and see the phase transition of CVD, physical mixture, and solid dispersion of CVD. The thermogram of each sample can be seen in Fig. 5.

The thermogram results of CVD showed a single and sharp maximum endothermic peak at a temperature

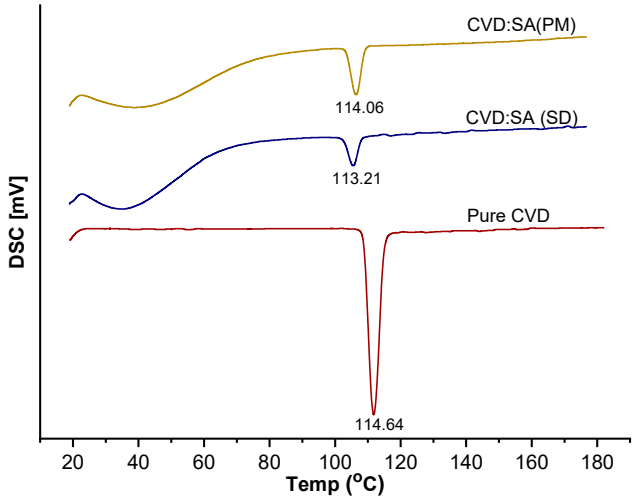


Fig 5. Thermogram overlay of pure CVD, CVD:SA physical mixture (PM), and CVD:SA solid dispersion (SD)

of 111.76 °C, which is close to the melting point of CVD form II, which is at 114 °C, indicates that CVD is crystalline [29]. In the thermogram of the physical mixture and solid dispersion CVD:SA (1:4), sharp endothermic peaks of the pure drug were still observed. However, the reduced intensity of the endothermic peak on the thermogram of the physical mixture and solid dispersion indicates the amorphous state of the drug [2,7].

Melting point and enthalpy decreases also occur in pure CVD, physical mixtures and solid dispersions of CVD:SA (1:4) (Table 2). The shift in the relative energy needed to break bonds between solute molecules can be linked to this decreasing trend, meaning that the higher the solubility, the less energy is needed to break the solute bonds as the enthalpy value decreases.

Powder X-Ray Diffraction (PXRD)

Characterization with PXRD aims to identify the crystalline phase and see changes in the state of drug molecules. The diffractogram of pure CVD, physical mixture, and solid dispersion of CVD:SA (1:4) can be seen in Fig. 6. The characterization results show that the pure CVD used in the test has a degree of crystallinity of 90.7%. The 2θ characteristics observed in the pure CVD diffractogram pattern are 5.77°, 11.59°, 12.94°, 14.74°, 16.42°, 17.47°, 18.37 °, 24.25°, 26.15°, 29.37° according to the CVD diffractogram pattern form II [29].

The diffractogram of the physical mixture and solid dispersion shows the formation of a diffractogram halo. However, the 2θ characteristic of CVD can still be observed as less than pure CVD. A decrease in the intensity of the diffractogram was also observed, both of which indicate that the crystallinity of the pure drug has decreased and shows the amorphous nature of the drug [11]. The formation of the amorphous phase is also supported by the calculation results, which show the degree of crystallinity in the CVD:SA (1:4) physical mixture is 37.5% and the CVD:SA (1:4) solid dispersion is 34.8%.

Compared to crystalline compounds, which tend to be more rigid in structure, amorphous compounds have

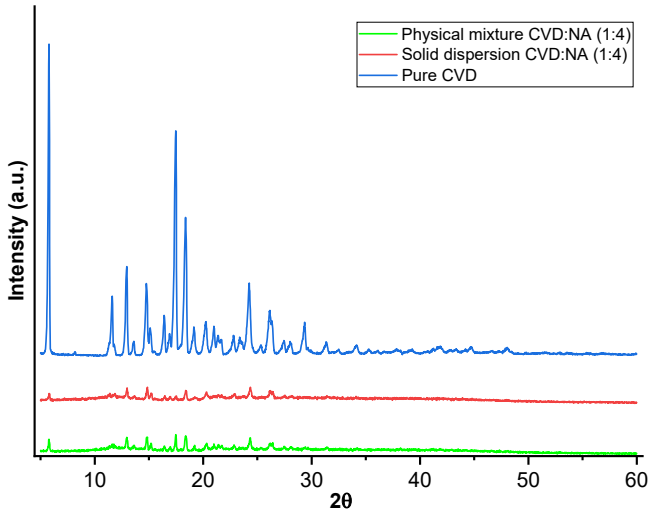


Fig 6. Diffractogram overlay of pure CVD, CVD:SA physical mixture (PM) and CVD:SA solid dispersion (SD)

Table 2. DSC characterization results

No	Sample	Melting point (°C)			Enthalpy (J/g)
		Onset	Endset	Maximum peak	
1	Pure CVD	108.91	114.64	111.76	-60.69
2	CVD:SA (1:4) physical mixture	108.82	114.06	111.52	-14.89
3	CVD:SA (1:4) solid dispersion	108.25	113.21	110.87	-8.35

a more irregular molecular arrangement and more excellent intermolecular interactions, resulting in faster solubility and dissolution rates. Furthermore, this amorphous state has the benefit of improved wettability and smaller particle size, which can increase solubility.

■ CONCLUSION

Based on the *in silico* study results, there was an interaction between CVD and each candidate polymer. Sodium alginate (SA) and xanthan gum (XG) were selected as carriers in solid dispersion. The results of the *in silico* study showed that there were two hydrogen bonds and five hydrophobic interactions in the CVD-SA complex, and one hydrogen bond, two hydrophobic interactions, and π-π interactions in the CVD-XG complex. The results of the saturation solubility test and the dissolution rate of CVD increased; solid dispersion CVD:SA (1:4) showed the best results, namely an increase of 11.17 times in the saturated solubility test and an increase in the dissolution profile from 64.95 to 83.32%. Changes in the physicochemical properties of the CVD:SA (1:4) solid dispersion also occurred, which can be seen from the characterization results. The decrease in intensity and shift in wavenumber in the FTIR spectrum indicates an interaction between CVD and SA. The reduced intensity of the endothermic peak on the DSC thermogram indicates the amorphous state of the drug, and this is also supported by the PXRD results, which show a decrease in the crystallinity of the drug.

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