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Research Article

Carvedilol solubility enhancement by multicomponent crystallization with coformers of benzoic acid, isonicotinamide, and saccharin

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Abstract

Multicomponent crystallization is a method that can modify the physicochemical properties of Carvedilol (CVD), thereby increasing its solubility. Based on *in silico* screening the coformers (Benzoic Acid, Isonicotinamide, and Saccharin) showed non-covalent interactions with CVD, so the multicomponent crystal preparation of CVD by solvent evaporation method used these coformers with mole ratios of 1:1, 1:2, and 2:1. Multicomponent CVD:Isonicotinamide (1:2) exhibits increased saturation solubility of up to 140 mg/L and increased dissolution of up to 99.48%. The infra-red (IR) spectrum showed a peak shift, a thermogram pattern that was different from the DSC results, and a new peak on the XRD multicomponent crystal diffractogram indicating the formation of a new solid phase compared to pure Carvedilol. Therefore, the formation of multicomponent crystals can increase the solubility and dissolution rate of CVD, and all characteristics indicate the presence of interaction between CVD and Isonicotinamide, and the formation of a new solid phase.

Keywords

Carvedilol, BCS Class II, multicomponent crystal, coformer

Introduction

The most popular method of medicine administration is through oral ingestion. According to the Biopharmaceutical Classification System (BCS), around 75% of drug candidates that are reported to be taken orally have low solubility, which may have an impact on how well these medications work when taken orally. One of the medications with limited solubility is carvedilol. This medication is in BCS class II and has a 0.093 mg/mL water solubility, although it has good permeability and a 25–30% bioavailability rate (Soleha 2014; Fernandes et al. 2019).

Carvedilol is a non-selective beta-blocker drug that can block α-1, β-1, and β-2 adrenergic receptors. Carvedilol is widely used as a long-term oral antihypertensive therapy (Ahad et al. 2015). However, poor solubility is a major obstacle in the development of Carvedilol formulations because it affects its low bioavailability and causes repeated oral administration, which can reduce patient compliance to taking the drug (Stafylas and Sarafidis 2008; Ahad et

al. 2015; Eesam et al. 2020). At the same time, cardiovascular disease is the leading cause of death globally, where around 17.9 million people die from this disease (World Health Organization 2021a). In addition, about 1.13 billion people worldwide have hypertension, and it is reported to be the leading cause of premature death in the world (World Health Organization 2021b).

There have been several studies conducted to increase the solubility and bioavailability of Carvedilol, that is through solid dispersion methods (Yarraguntla et al. 2016), Liquidsolid compacts (Meer et al. 2012), nanocrystals (Janakiraman et al. 2017), and nanoemulsion (Chidi et al. 2017). However, some of the methods mentioned above are still considered less practical and economical, mainly when applied on a laboratory scale, pilot scale and have low reproducibility.

Crystal engineering is a component of pharmaceuticals. With the help of crystal engineering, it is possible to change the physical, chemical, and mechanical characteristics of active medicinal components (Weyna et al. 2012). One of the most often employed crystal engineering procedures is the production of multicomponent crystals. According to (Aakeröy and Salmon 2005), a multicomponent crystal is a homogeneous solid phase that contains two molecules and/or ions in stoichiometric amounts within the same crystal lattice. The three types of multicomponent crystals are salt, cocrystal, and salt cocrystal. In cocrystals, the component placement is determined by weak interactions such hydrogen bonds, van der Waals, or π-π stacking (Aakeröy and Salmon 2005; Kiguchiya et al. 2019). In salt, the component placement is determined by ion pairs in the same crystal lattice.

Cocrystal is a solid form of multicomponent crystal that has been widely applied in the pharmaceutical field, especially in increasing drug solubility (Eesam et al. 2020; Thenge et al. 2020; Wang et al. 2021). The formation of multicomponent crystals successfully increases the solubility and dissolution rate of BCS class II drugs. In a study conducted by Al-Kazemi et al. (2019), the application of co-crystallization to atorvastatin calcium using nicotinamide and glucosamine as coformers showed an increase in solubility of 86.19 and 31.05% compared to pure atorvastatin calcium. Other studies have also been carried out on Nefiracetam cocrystals with oxalic acid, increasing solubility (Buol et al. 2020).

Solubility will thus be improved in this work using a multicomponent crystal method using coformers, particularly isonicotinamide, benzoic acid, and saccharin, which have not before been employed with carvedilol. These coformers have been demonstrated to increase solubility, dissolving rate, and other physicochemical qualities, and they are known to be safe based on generally recognized as safe (GRAS) standards (Gozali et al. 2012; Hairunnisa et al. 2019; Dutt et al. 2021) Isonicotinamide was reported to increase the dissolution rate of quercetin:isocotinamide cocrystals (1:1) and the solubility of atorvastatin calcium:isocotinamide (1:1) (Gozali et al. 2016; Wisudyaningsih et al. 2019). Benzoic Acid is reportedly used as a coformer to form cocrystals of aspirin and fenofibrate, which shows an increase in the dissolution rate (Dutt et al. 2021). In addition, Saccharin was also reported to increase the solubility of simvastatin: Saccharin cocrystals (Sopyan et al. 2017).

Through *in silico* research or chemical calculations, coformers can be identified and the solubility of the active ingredient complex with these coformers can be predicted. where interactions between drug and coformers, particularly non-covalent bonds and their strengths, can be examined through *in silico* experiments. (Siswandi et al. 2015). Based on the background provided, a study was done to see if the multicomponent crystal formation method may increase the solubility of the BCS class II drug carvedilol. By creating multicomponent crystals of carvedilol, the drug's solubility and bioavailability are intended to be increased, and drug development is anticipated to become more creative.

Materials and methods

Materials

The materials used in this study were aquades, Benzoic Acid pro analysis (Merck), hydrochloric acid (Merck), Isonicotinamide (Merck), potassium bromide (Merck), Carvedilol (CVD) (Kalbe), methanol (Merck), and Saccharin (Sigma Aldrich).

Screening coformers by *in silico*

A literature search was employed on a list of coformers that had never been used in Carvedilol. The 2D structure of Carvedilol and coformers candidate was obtained through the PubChem Database in .sdf format and converted into .pdb format using Discovery Studio Visualizer BIOVIA. Then, ligand preparation was carried out using the AutoDockTools program, and the ligands were docked using PyRX software. The interaction and bond energy between Carvedilol and each coformer were observed (Siswandi et al. 2015).

Preparations of multicomponent crystal

The preparation of multicomponent crystals was carried out using the solvent evaporation method. Pure Carvedilol and coformers with stoichiometric ratios of 1:1, 1:2, and 2:1 were dissolved in methanol. The mixture was stirred until completely dissolved at room temperature. Then, the solvent was evaporated by allowing the solution to stand at room temperature until cocrystals were formed. The formed crystals are collected in vials for further analysis (Rajurkar et al. 2015).

Saturated solubility test

The measurement of the solubility of Carvedilol was carried out using the shake flask method. Pure Carvedilol

and multicomponent crystal equal to 10 mg in excess were dissolved using 10 mL distilled water and stirred for 24 hours at 25 °C using an agitator at 120 rpm. Then, the sample solution was filtered using Whatman paper No. 42 and analyzed using a verified UV spectrophotometer (Specord 200 – 222U203) (Yuvaraja and Khanam 2014). Sample absorbance in saturated solubility tests was observed using the zero-crossing spectrophotometry method. Samples are measured at their coformers' zero-crossing wavelength, so that only the absorbance of Carvedilol as an active ingredient are obtained. The acquired sample absorbance is entered into a standard curve equation to find the carvedilol concentration contained in each mg/L unit.

Dissolution test

The dissolution test was carried out using USP apparatus II (Sotax AG CH-4008 BASEL) using 0.1 M HCl pH 1.45 (900 mL) at a speed of 50 rpm at 37 °C. The test sample (pure Carvedilol and crystalline multicomponent) was weighed as much as 12.5 mg, or the equivalent amount of the crystalline multicomponent, and was compressed to form a tablet. The test tablet was put into the media, and 10 ml of the sample solution was taken at certain time intervals of 5, 10, 15, 20, 25, and 30 minutes and refilled with the same amount using the new medium. The samples were then analyzed using a UV spectrophotometer using derivative spectrophotometry with the same procedure as the saturation solubility test only for the solvent using dissolution medium (Specord 200 – 222U203) (Tapas et al. 2012; Prado et al. 2014).

Fourier transform infrared (FTIR)

FTIR spectrum readings on pure Carvedilol samples, coformers, physical mixtures, and Carvedilol multicomponent crystals were performed separately using an FTIR spectrophotometer (Shimadzu IRPRESTGE-21). A total of 2 mg of sample was mixed with 248 mg of KBr and compressed to form a pellet using a hydraulic pump. The reading of the FTIR spectrum is seen in the range of 4000–400 cm^{-1} at a resolution of 4 cm^{-1} (Eesam et al. 2020).

Powder x-ray diffraction (PXRD)

The diffractogram PXRD pattern of multicomponent crystal Carvedilol, pure Carvedilol, and the physical mixture was observed using an x-ray diffractometer (Bruker AXS) with copper radiation Kα (wavelength = 1.54060), voltage 40 kV, and current 20 mA. A total of 100–200 mg of sample was put into a sample holder, an aluminum plate, and scanned in the range of 5–60° (2θ) at a speed of 0.02°/second (Eesam et al. 2020).

Differential scanning calorimetry (DSC)

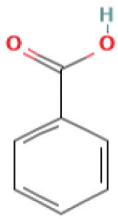
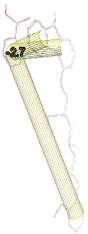
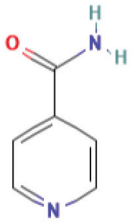
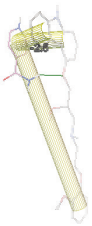
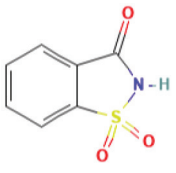
Multicomponent crystal phase transitions of Carvedilol, pure Carvedilol, and physical mixtures were analyzed using the DSC method (Shimadzu). About 2 mg of the sample was put into an aluminum container for DSC samples and heated over a temperature range of 25–180 °C at a rate of 10 °C/minute under a nitrogen atmosphere (50 ml/min). The resulting thermograms will be observed and compared to obtain a different profile between pure Carvedilol, physical mixture, and Carvedilol multicomponent crystal (Fernandes et al. 2019; Thenge et al. 2020).

Result and discussion

Screening of coformers by *in silico*

Table 1 displays the results of the coformers' *in silico* screening. Only Carvedilol created hydrogen bonds with Isonicotinamide out of the three coformers, and those bonds had a bond energy of -2.5 kcal/mol. The ether group in the carbazole-4-yloxy fragment serves as the acceptor for the hydrogen bond, and the H atom on the amine group in the isonicotinamide structure serves as the donor. Due to its formation in many functional groups, the synthon is a heterosynthon. The aromatic ring of the isonicotinamide structure interacts with carvedilol through a π-π stacking interaction in addition to hydrogen bonding.

Table 1. Results of screening coformer of drugs and coformers.

Coformers	2D structure of coformer	Interaction	Binding energy
Benzoic Acid		 π-π stacking	-2.7 kkal/mol
Isonicotinamide		 1 hydrogen bonding dan π-π stacking	-2.5 kkal/mol
Saccharin		 π-π stacking	-3.5 kkal/mol

Carvedilol with Benzoic Acid and Saccharin only formed π-π stacking interactions with strengths of -2.7 kcal/mol and -3.5 kcal/mol, respectively. This interaction is formed due to an aromatic ring in the structure of Benzoic Acid, Saccharin, and Carvedilol. Based on the bonds formed, it is estimated that Carvedilol-isocotinamide multicomponent crystals will be more easily formed.

There are two types of multicomponent crystals that can be formed: salts and cocrystals. The difference in pKa (pKa) between the active ingredient and Carvedilol is one way to predict the type of multicomponent crystal formed. The pKa value indicates the ability of an acidic compound to donate protons. A pKa value greater than 4 indicates proton transfer, so it is possible that the multicomponent crystal formed is salt (Childs et al. 2008). pKa values close to acids are said to form cocrystals, while those that form bases are said to form salts (Berry and Steed 2017).

It is predicted that Carvedilol-Benzoic Acid and Carvedilol-Saccharin multicomponent crystals will form salts because pKa > 4, but Carvedilol-Isonicotinamide crystals will create cocrystals based on the pKa values of coformers and Carvedilol in Table 2. Benzoic acid, isonicotinamide, and saccharin will be used in this study as coformers based on the coformers that were screened.

Table 2. pKa and ΔpKa value of Carvedilol and coformers.

Compound	pKa	ΔpKa
Carvedilol	8,77	-
Benzoic Acid	4,19	4,58
Isonicotinamide	10,61	1,84
Saccharin	1,31	7,46

Preparations of multicomponent crystal

The preparation of multicomponent crystals in this study was carried out on each candidate coformers, which are Benzoic Acid, Isonicotinamide, and Saccharin. The method used is the solvent evaporation method using methanol as a solvent with three different mol ratios between Carvedilol and each coformer, which are 1:1, 1:2, and 2:1 (9 variations).

According to the results of the multicomponent crystal preparations, it was found that CVD: Benzoic Acid and CVD: Isonikotinamide multicomponent crystals with ratios of 1:1, 1:2, and 2:1 produced dry, non-sticky solids, whereas CVD: Saccharin with a ratio of 1: 1 is a little sticky. CVD: Saccharin created a solid, multicomponent crystal with a mol ratio of 1:2 and 2:1 that was wet and extremely sticky, preventing it from moving on to the next test stage. Therefore, only seven different kinds of multicomponent crystals were examined for saturated solubility in this study. A multicomponent crystal is, by definition, a dry solid formed at room temperature by the combination of two or more distinct components. Creating multicomponent Carvedilol crystals has produced the results shown in Table 3.

Table 3. The appearance of multicomponent crystal Carvedilol.

Saturated solubility test

A saturated solubility test was performed on seven different multicomponent crystal variations with aquades as the media for 24 hours. According to the results of the solubility test, pure Carvedilol has a saturation solubility of 2.460 mg/L. Carvedilol crystals of CVD: Benzoic Acid occurred in a 1:2 ratio of 140 mg/L (56.91 times) in the multicomponent crystals solubility test, followed by CVD: Benzoic Acid (2:1) at 115 mg/L (47.75 times), and CVD: Benzoic Acid (1:1) at 56.67 mg/L. (23.03 times). The highest solubility test results in CVD: Isonicotinamide, like CVD: Benzoic Acid, occurred at a 1:2 mol ratio of 101.5 mg/L (41.26 times), followed by CVD: Isonicotinamide 1:1, which was 59,083 mg/L (24.02 times), and CVD: Isonicotinamide (2:1), which is 25.75 mg/L. (10.47 times). The findings of the saturated solubility test for CVD showed that saccharin 1:1 crystals were 70 mg/L and that there was a 26.5-fold improvement in solubility.

Even though it was known that Benzoic Acid had the lowest solubility in water when compared to Isonicotinamide and Saccharin, multicomponent crystals between Carvedilol and Benzoic Acid produced the greatest results. Theoretically, it is believed that the solubility of the coformer will influence the solubility level of the active ingredient to the extent that the employment of a more hydrophilic coformer will result in the production of more multicomponent crystals (Sanphui et al. 2013). Hiendrawan et al. (2016) disagreed with this assertion, claiming that there is no connection between salt-forming and carvedilol salt. Fig. 1 shows the results of the saturated solubility test.

The saturation solubility of the multicomponent crystal Carvedilol was found to be superior to that of the pure Carvedilol. The production of salt between Carvedilol and

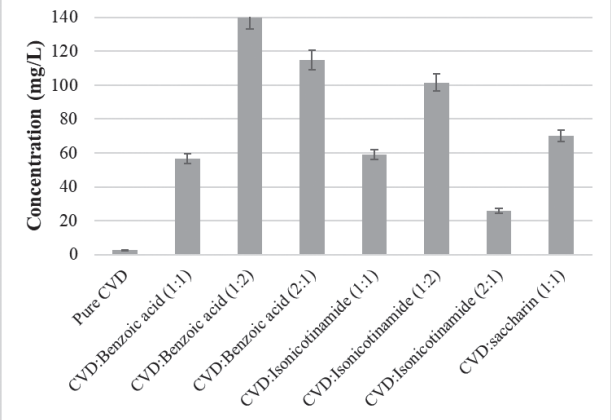


Figure 1. Graph of pure Carvedilol and Carvedilol multicomponent crystal saturated solubility test results.

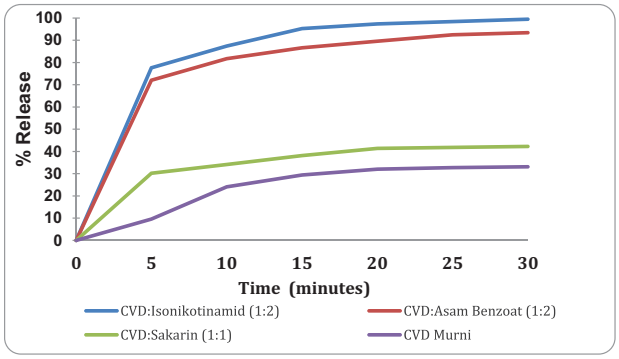


Figure 2. Graph of pure Carvedilol and Carvedilol mulricomponen crystal dissolution test results.

the coformer as a result of the proton transfer from the coformer to Carvedilol (formation of salt) or the development of hydrogen bonds are two potential causes of the rise in solubility (formation of cocrystal) (Alatas et al. 2019).

The multicomponent crystal with a ratio of 1:2 exhibits the best solubility when the mol ratios of each coformer are compared to 1:1 and 2:1. This is because the solubility capacity of the active pharmaceutical ingredient or medicine will likewise rise with a greater mol ratio of the coformer (Li and Matzger 2016). Additionally, the quantity of coformers used in the 1:2 ratio was higher than in other studies and served as a strong water molecule attractant. Carvedilol would be more likely to interact with water if it were to do so (Sopyan 2018). The number of contacts established around the active ingredient in a multicomponent crystal affects the active ingredient's solubility, with the number of interactions increasing the solubility of the active ingredient. Coformers can thereby improve the active ingredient's solubility profile by decreasing interactions around it (Rajput et al. 2013).

Dissolution test

The dissolution test was carried out on multicomponent crystal samples at the ratio that showed the best increase in solubility of each coformer, which are CVD: Benzoic Acid (1:2), CVD: Isonicotinamide (1:2), and CVD: Saccharin (1:1) in HCl pH medium. 1.45. The results of the dissolution profile of each sample were compared with the dissolution profile of pure Carvedilol. Like the solubility test, the absorbance of each sample is read at a predetermined zero-crossing wavelength.

The dissolution test results of Carvedilol and multicomponent crystals can be seen in Fig. 2.

According to Fig. 2, the dissolution profile of pure CVD started to seem steady at minute 20 and dissociated by 33.115% by minute 30. Saccharin (1:1) displayed the lowest disintegration rate of all the multi-component crystals at 30 minutes, at 42.26%. Contrary to CVD: Saccharin (1:1), CVD: Benzoic Acid (1:2) and CVD: Isonicotinamide (1:2) showed high results, with respective dissolving rates of 93.42% and 99.48% at the 30th minute. This suggests that the maximum rate of solubility is shown by CVD: isonicotinamide (1:2). The potential for hydrogen bonding and π-π stacking, which would increase the polarity of Carvedilol, could explain the high dissolution rate of CVD: isonicotinamide (1:2).

According to the dissolution findings, CVD:Isonicotinamide (1:2) had the highest rate of dissolution. The solubility test showed that CVD: Benzoic Acid showed the largest rise (1:2). This is possible because different mediums are employed in these two tests. In the solubility test, water was employed, but the dissolution test used HCl pH 1.45 as the dissolving media. Isonicotinamide is a weak base medication whose solubility is affected by pH; in acidic environments, it will be more soluble. Carvedilol will also dissolve more readily in acidic environments. Because the two constituent components are weak base compounds with improved solubility in acidic environments, the multicomponent crystal CVD:Isonicotinamide (1:2) has a better dissolving rate (Beattie et al. 2013).

Fourier transform infrared (FTIR)

Multicomponent crystal formation is verified by FTIR analysis. By comparing variations in the vibrational frequency of particular functional groups of multicomponent crystals to their constituent components, it can be used to help identify the different types of multicomponent crystals that have been created (Hiendrawan et al. 2016). A physical mixture of CVD: Isonicotinamide (1:2), multicomponent crystals of CVD: Isonicotinamide, pure Carvedilol, and pure Isonicotinamide were the four materials used in this study for FTIR analysis (1:2).

Based on the results of FTIR analysis (Fig. 3 and Table 4), Carvedilol has two N-H groups stretching at 3342 cm^{-1} for the secondary heterocyclic amine group and 3305 cm^{-1} for the aliphatic amine Carvedilol. This is to research conducted by Prado et al. (2018), where the peak of the secondary heterocyclic group is at 3344 cm^{-1} and aliphatic amines at 3305 cm^{-1}. Similarly, Tapas et al. (2012) results showed N-H stretching at 3343 cm^{-1}. In addition, the C=C group (aromatic ring) was found at the peak of 1592 cm^{-1} (1592), C-O at 1214 cm^{-1} (1214) and 1257 cm^{-1} (1255), and C-H stretching at 2923 cm^{-1} (2923) (Tapas et al. 2012; Eesam et al. 2020).

Table 4. IR spectrum of pure Carvedilol and multicomponent crystal CVD: Isonicotinamide (1:2).

Functional group	CVD (cm^{-1})	Isonicotiamide (cm^{-1})	Physical mixture of CVD: Isonicotinamide (1:2) (cm^{-1})	Multicomponent crystal of CVD: Isonicotinamide (1:2) (cm^{-1})
C-H stretch	2923	-	-	-
N-H stretch	3342 and 3305	-	3500–3000	3345
C-O	1214 and 1257	-	1254	1215 and 1257
C=C	1592		1593	1592
NH_2 group	-	3368 and 3185	-	3186
C=O	-	1665	-	1682

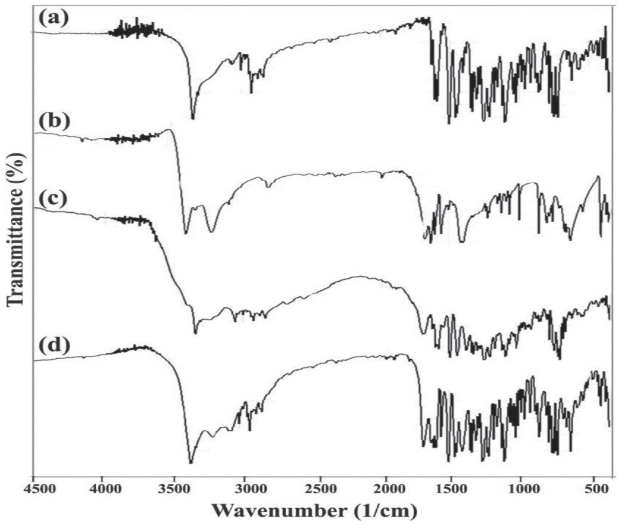


Figure 3. FTIR spectrum overlay pure Carvedilol (**a**), Isonicotinamide (**b**), physical mixture CVD:Isonicotinamide (1:2) (**c**), and multicomponen crystal CVD:Isonicotinamide (1:2) (**d**).

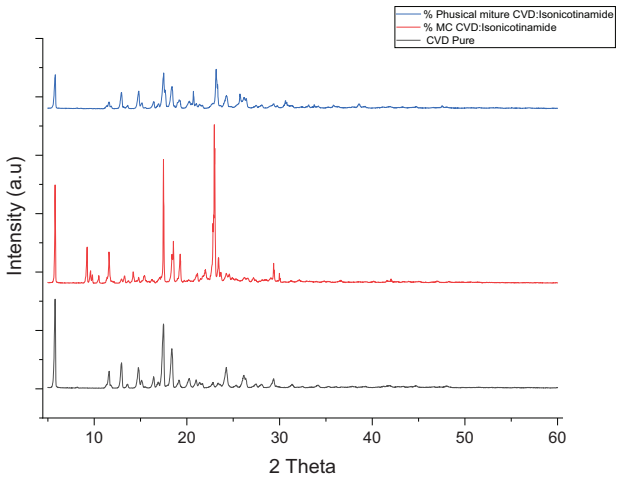


Figure 4. Diffractogram overlay of pure carvedilol (black), multicomponent crystal CVD: isocinotinamide (1:2) (Red), and physical mixture CVD:Isonicotinamide (Blue).

The results of the FTIR analysis of pure Isonicotinamide showed peaks at 3368 cm^{-1} and 3185 cm^{-1} belonging to the NH_2 group, which is in line with research by Alatas et al. (2019), namely 3368 cm^{-1} and 3186 cm^{-1} and Wisudyaningsih et al. (2019), namely 3371 cm^{-1} and 3186 cm^{-1}. In addition, a C=O group was also found at 1665 cm^{-1} (1668 cm^{-1}).

The two basic components, namely carvedilol and isonicotinamide, displayed a pattern that was remarkably comparable in multicomponent crystals of CVD: isonicotinamide (1:2). According to *in silico* coformer screening, carvedilol and isonicotinamide establish hydrogen bonds on the ether group of carvedilol and one of the H atoms in the NH_2 group of isonicotinamide. The peak of the NH_2 group changed to 3186 cm^{-1} in the spectrum, whereas the C-O group in the multicomponent crystal shifted to 1215 cm^{-1}. Additionally, a shift was seen in some groups, particularly C=O at 1682 cm^{-1} and C=C at 1592 cm^{-1}, both of which had decreasing intensities. In the CVD: Isonicotinamide multicomponent crystal, the existence of a shift in peak denotes an interaction between carvedilol and isonicotinamide (1:2). According to an *in silico* prediction, there are hydrophobic and hydrogen bonds between the drugs carvedilol and isonicotinamide (Fernandes et al. 2019).

Powder X-Ray Diffraction (PXRD)

PXRD analysis of multicomponent crystals seeks to pinpoint the occurrence of a novel crystalline phase, with each compound's crystalline phases having unique diffractogram properties. PXRD analysis can identify the created product (multicomponent crystals) (Hiendrawan et al. 2016). Comparing the location and intensity of the lines on the diffractogram of pure Carvedilol, a physical mixture of CVD: Isonicotinamide (1:2), and multicomponent crystal CVD: Isonicotinamide allowed researchers to determine the emergence of a new crystalline phase (1:2). Fig. 4 shows a diffractogram of pure Carvedilol, a physical mixture, and a multicomponent crystal.

The diffractogram of Carvedilol showed the presence of 2θ characteristics, namely 5.8, 11.64, 12.97, 14.75, 17.49, 18.37, 24.25, and 29.35. this is similar to the Carvedilol diffractogram tested in the study by Prado et al. (2014). In this study, the degree of crystallinity of Carvedilol was 90.70%. The results of the CVD: Isonicotinamide (1:2) multicomponent crystal diffractogram showed high and sharp peaks, so it was concluded that crystalline forms were formed. Overall, the diffractogram pattern is similar to the physical mixed diffractogram pattern, except that there are new peaks at 2θ = 9.24, 9.75, 22.96, and 29.96. Several multicomponent crystal peaks, specifically those at 2θ = 12.97, 14.75, and 24.25, experienced a drop in intensity. Additionally, the degree of crystallinity of CVD: Isonicotinamide (1:2) multicomponent crystals dropped by 83.6% as compared to pure carvedilol. Carvedilol's solubility may be impacted by a decline in crystallinity, and the appearance of a new peak denotes the creation of a new solid phase (Sathisaran and Dalvi 2018).

Differential scanning calorimetry (DSC)

Thermodynamic properties of multicomponent crystals are examined using differential scanning calorimetry (DSC), also known as thermal analysis, to spot any exothermic and endothermic changes in the solid phase combination. By contrasting the thermogram of Carvedilol, the physical mixture of CVD: Isonicotinamide (1:2), and the multicomponent crystal of CVD: Isonicotinamide, it was possible to identify the emergence of a new solid phase based on the melting point shift (1:2). Fig. 5 displays the thermogram obtained from the DSC study.

Carvedilol's DSC analysis revealed three endothermic peaks: one at 111.76 °C with a heat of melting of -60.69 J/g; one for the physical mixture CVD: Isonicotinamide (1:2) at 102.89 °C with a heat of melting of -43.04 J/g; and one for the multicomponent crystal of CVD: Isonicotinamide (1:2) at 103.92 °C with a The melting point of the CVD: Isonicotinamide (1:2) multicomponent crystal is lower than that of pure carvedilol. The multicomponent crystal of CVD contains one endothermic peak, which denotes the development of a new solid phase called isonicotinamide (1:2). A rise in the solubility of multicomponent crystals is also explained by a decrease in the heat of melting. (Sopyan 2018; Fernandes et al. 2019; Dutt et al. 2021).

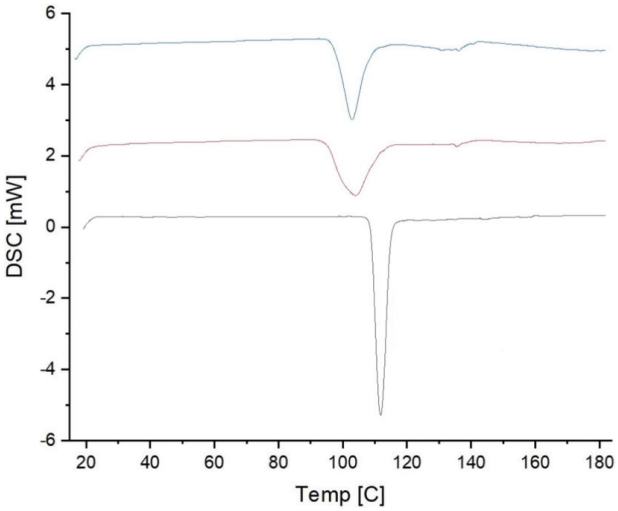


Figure 5. Thermogram overlay of physical mixture CVD: Isonicotinamide (1:2) (blue), multicomponent crystal CVD: Isonicotinamide (1:2) (red), and pure Carvedilol (black).

Conclusion

Based on *in silico* coformer screening, Benzoic Acid, Isonicotinamide, and Saccharin can be used for the formation of multicomponent CVD, because there is an interaction between CVD and each coformer, namely the interaction of π-π stacking in CVD with Benzoic Acid and Saccharin, as well as hydrogen bonding and π-π buildup in CVD with Isonicotinamide. The solubility and dissolution rate of CVD can be increased through a multicomponent crystal approach with the coformer, where the best coformer in increasing solubility is CVD:Benzoic Acid (1:2) which is 56.92 times, and the highest dissolution occurs in CVD:Isonicotinamide (1:2) which is 99.484%. CVD:Isonicotinamide (1:2) multicomponent crystals experience a shift in the IR spectrum, which can be caused by interactions in the form of hydrogen bonds between constituents. Moreover, the thermogram shows the change in melting point, and the diffractogram pattern shows the formation of a new solid phase. This change in physicochemical properties can increase the solubility of CVD.

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