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Research Article

Solubility enhancement of carvedilol by multicomponent crystal approach using glycine and arginine as coformers

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Abstract

A Carvedilol is a member of BCS class II, it has a low solubility and bioavailability. This work intends to increase the solubility of carvedilol using a multicomponent crystal method. Based on in silico investigations showed that carvedilol-arginine formed one hydrogen bond and carvedilol-glycine formed two hydrogen bonds. Compared to the solubility of pure carvedilol, CVD: GLY multicomponent crystal ratios of 1:1, 1:2, and 2:1 resulted in increases in solubility of 1.9 times, 2.6 times, and 2.5 times respectively. The solubility of the multicomponent crystals in the CVD:ARG however, did not increase. The best dissolution profile was provided by multicomponent crystal CVD: GLY (1:2), with a % dissolution of 86.03% in HCl medium pH 1.45 and 29.5% in phosphate buffer medium pH 6.8. The results of characterization included FTIR, DSC, PXRD, and SEM evaluation of CVD: GLY multicomponent crystal (1:2) indicated the formation of a new solid crystalin phase. CVD: GLY multicomponent crystal (1:2) showing the best solubility and dissolution profile as compared to pure carvedilol.

Keywords

Solubility, carvedilol, multicomponent crystal, glycine, arginine

Introduction

Oral administration is the most common and feasible drug delivery route. A medicine must dissolve in the digestive fluids before it can be taken orally and be absorbed into the blood and reach its target. Solubility is a significant factor in successfully achieving medication concentrations in the systemic circulation and producing the desired therapeutic effect (Loftsson and Brewster 2010; Savjani et al. 2012).

Carvedilol is a non-selective β-adrenergic inhibitor indicated in the management of coronary artery disease, heart failure, and hypertension. Based on the Biopharmaceutical Classification System (BCS), carvedilol is included in BCS class II. Carvedilol's low solubility is one of the main causes associated with carvedilol's low systemic bioavailability (25–35%) in the oral route of carvedilol. Carvedilol solubility in water was found to be very low at <1 μg/ml above pH 9.0, 23 μg/ml at pH 7, and 100 μg/ml at pH 5 (Eesam et al. 2020; Jhaveri et al. 2020).

Several approaches have been used to tackle the problem of carvedilol's low solubility, including modification of the drug's physical and chemical properties. These include changing the solid form into an amorphous form, increase wettability and porosity, and minimizing the particle size to enhance the effective surface area (Fernandes

et al. 2018). Several techniques have been done as the effort to enhance the solubility of carvedilol including micronization (Chatterjee and Pal 2010), solid dispersions (Sharma and Jain 2010), dendrimers (Zheng et al. 2013), cyclodextrin complexes (Wen et al. 2004), and nanotechnology (Janakiraman et al. 2017). However, these techniques are still ineffective at solving the problem of carvedilol solubility, so other techniques are needed to enhance carvedilol solubility, including the multicomponent crystal techniques. Multicomponent crystals are a crystal engineering technique, in which a solid phase is formed when more than one molecule of a different substance crystallizes together in a single crystal lattice with a specific stoichiometric ratio (Putra and Uekusa 2020).

The advantage of the multicomponent crystal technique is that the medicine is in a stable crystal form and the formulation does not need excipients or other ingredients. The primary benefit of the multicomponent crystal technique is that it enables the active pharmaceutical components' physicochemical qualities to be improved without impacting their pharmacological properties (Kumar and Nanda 2018).

In this investigation, coformers of the amino acids arginine and glycine are employed. Amino acids are structurally promising coformers because of their functional groups' capacity to establish hydrogen bonds and their zwitterion group's capacity to boost stability through the support of strong contacts. Additionally, amino acid group coformers are recognized as generally safe (GRAS), demonstrating that amino acids are safe and have minimal toxicity. (Liu et al. 2016). According to Kang et al.'s research, arginine is used as a coformer in the febuxostat cocrystal and has the ability to boost the solubility and dissolution rate of the drug by up to 75 times (Kang et al. 2017). According to Shete et al.'s research, using glycine as a coformer in itraconazole cocrystals can increase the drug's solubility by up to three times when compared to pure itraconazole (Shete et al. 2015).

Materials and methods

Materials

Arginine (Merck), aquadest, hydrochloric acid (Merck), potassium bromide (Merck), potassium phosphate (Merck), carvedilol (Kalbe), glycine (Merck), methanol p.a. (Merck).

In silico study

ChemDraw 15.0 was used to create the 2D structures of carvedilol and its coformers (glycine and arginine). The optimization of the 3D shape structure was carried out using Chem3D Ultra 15.0 and the MM2 (Molecular Mechanic-2 Minimization) energy minimization process was carried out. In the AutoDock Tools 1.5.6 program, hydrogen atoms and charge are added and saved in pdbqt format. The PyRx program (Vina) was used to determine the binding affinity of the arginine coformer with carvedilol. The interactions formed were observed using the AutoDock Tools 1.5.6 application. The parameters observed were tp predict the bond distance, interaction energy, and type of interaction between the coformer and carvedilol (hydrogen bonds, van der Waals bonds, and π-π bonds) (Siswandi et al. 2015; Sopyan et al. 2017).

Multicomponent crystal preparation

Carvedilol multicomponent crystals with mole ratios of 1:1, 1:2, and 2:1 was prepared using the solvent evaporation method. Carvedilol was dissolved in methanol and coformer (arginine, glycine) was dissolved in distilled water. Solvent selection was based on the solubility profile of the constituent ingredient. The mixture was then stirred until fully dissolved. At room temperature, the solvent was allowed to slowly evaporate in an evaporating dish for 24 hours (Rajurkar 2015).

Evaluation of multicomponent crystal

Saturated solubility test

Samples of pure carvedilol, multicomponent crystals CVD: ARG and multicomponent crystals CVD: GLY equivalent to 10 mg pure carvedilol were dissolved in 10 mL of distilled water. The samples were stirred at room temperature for 24 hours using a shaker at 120 rpm. The sample was then filtered through Whatman filter paper (No. 42), and a UV-Vis spectrophotometer at 285 nm was performed to measure the amount of drug that had been dissolved (Thenge et al. 2020).

Dissolution test

The HCl medium pH 1.45 and the phosphate buffer medium pH 6.8 were used as the dissolution media for the dissolution test. The dissolution test was conducted in 900 mL of dissolution medium at 50 rpm while maintaining a 37 ± 0.5 °C temperature. Dissolution testing used the paddle method. The test samples, namely pure carvedilol and multicomponent carvedilol crystals, were weighed in the equivalent of 25 mg. The sample is then put into the dissolution medium. Samples were taken as much as 10 mL at intervals of 5, 10, 15, 20, 30, 45, and 60 minutes. To maintain sink conditions, the volume of the dissolution media was kept at 900 mL by replacing it every time a sample was taken with new media. the samples were analyzed with a UV-Vis spectrophotometer at a 285 nm wavelength (Prado et al. 2014; Eesam et al. 2020).

Characterization of multicomponent crystal

Fourier transform infrared (FTIR)

The individual FTIR spectra of pure carvedilol, pure coformer, physical mixture, and carvedilol multicomponent

crystals were obtained using FTIR. A total of 1 mg of sample was added to 60 mg of potassium bromide (KBr) and compacted to create pellets. The spectrum was scanned in the range of 4000–400 cm^{-1} with a spectral resolution of 4 cm^{-1} (Eesam et al. 2020).

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was used for analyzing thermal properties of pure carvedilol, pure coformer, physical mixture, and multicomponent carvedilol crystals. Approximately 3 mg sample was heated until 350 °C in an aluminum container at a heat rate of 10 °C/min under a nitrogen atmosphere (50 ml/min) (Thenge et al. 2020).

Powder X-ray diffraction (PXRD)

The diffractogram patterns of pure carvedilol, pure coformer, physical mixture, and carvedilol multicomponent crystals were obtained using an X-ray powder diffractometer operating at an electric voltage of 40 kV, a current of 40 mA, using Cu-Kα radiation (λ = 1.5418). A total of 100–200 mg of sample is placed in the sample holder, and the sample is scanned in the range 5 – 60° (2θ), at a step size of 0.0167° and a step time of 0,5 seconds (Eesam et al. 2020).

Results and discussion

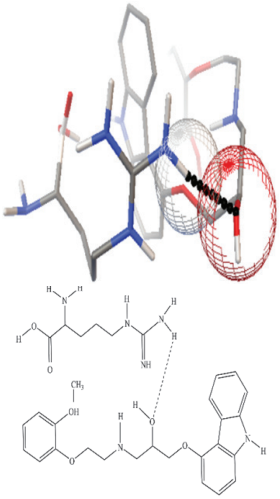
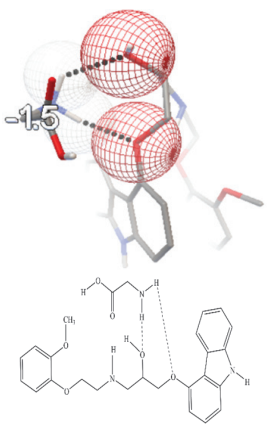
In silico study

Through in silico study, it is possible to observe the interaction of carvedilol with the coformer, such as the type of interaction formed (Table 1), the bond distance, and the energy of hydrogen interaction between carvedilol and the coformer. Table 1 displays the results of carvedilol and coformer interaction through in silico study.

Based on the in silico results, CVD:ARG forms one hydrogen bond with an energy of -6.224 kcal/mol and a hydrogen bond distance of 1.939 Å. The oxygen atom of the carvedilol hydroxyl group acts as a hydrogen acceptor and the amine group of arginine as a hydrogen donor to form a hydrogen bond.

Meanwhile, CVD:GLY forms 2 hydrogen bonds. The first hydrogen bond is formed between the amine group of glycine as a hydrogen donor and the oxygen atom on the hydroxyl group in the carvedilol aliphatic chain as a hydrogen acceptor. The hydrogen bond energy formed is -1.412 kcal/mol and the hydrogen bond distance is 2.241 Å. The oxygen atom in the ether group of carvedilol, acting as a hydrogen acceptor, and the amine group of glycine, acting as a hydrogen donor, form the second hydrogen bond.

Table 1. Results of carvedilol and coformer interaction.

Compound	Complex structure	Interaction	Hydrogen binding energy (kkal/mol)	Hydrogen bonding distance (Å)
CVD: ARG		1 hydrogen bond	-6,224	1,939
CVD: GLY		2 hydrogen bonds	-1,412 -5,042	2,241; 2,045

The hydrogen bond distance is 2.045 Å, and the hydrogen bond energy formed is -5.042 kcal/mol. The interactions that occur in CVD:ARG and CVD:GLY are classified as heterosynthone supramolecules because the groups that interact in forming hydrogen bonds are different. Based on the structure of carvedilol and coformer, there are functional groups that can act as proton donor and proton acceptors. So that when carvedilol is mixed with a coformer that also has a proton acceptor or donor, hydrogen bonds are likely to form between carvedilol and coformer. Hydrogen bonds are non-covalent interactions that form between hydrogen atoms attached to electronegative atoms such as oxygen or nitrogen atoms. Hydrogen bonds are becoming a critical factor in the multicomponent crystal approach. Hydrogen bonding interactions help stabilize most of the multicomponent crystal structures reported in the Cambridge Structural Database (CSD). In multicomponent crystal systems, hydrogen bonds can form supramolecular synthons and stabilize molecular structures even though they are weak individually (Sathisaran and Dalvi 2018).

A straightforward method to forecast the type formation of multicomponent crystals is to contrast the pKa values of the various components of the multicomponent crystal as in Table 2. The difference in the pKa values of the components of the multicomponent crystal provides an estimate of proton transfer, which suggests the formation of salts or cocrystals. Proton transfer does not occur when the active substance's and the coformer's pKa (ΔpKa) differences are close to acidity (the difference in values is smaller), which is expected to lead to the formation of cocrystals. Proton transfer is anticipated to cause salt formation if the difference in pKa (ΔpKa) is greater than 4. (Berry and Steed 2017).

Table 2. Difference in pKa between carvedilol and conformer.

Compound	pKa	ΔpKa
Carvedilol (CVD)	7,80	-
Arginine (Arg)	12,5	4,7
Glycine (Gly)	9,6	1,8

In the multicomponent CVD:ARG crystal, it is estimated that salt formation will occur because the ΔpKa value > 4. Meanwhile, in the multicomponent crystal CVD:GLY, it is estimated that cocrystals are formed because the ΔpKa value <2.

Evaluation of multicomponent crystal

Saturated solubility test

Fig. 1 displays the results of the saturation solubility test. The saturated solubility of carvedilol in distilled water is 1.88 ± 0.03 ppm. Based on the test results, the saturated solubility test value of CVD:ARG multicomponent crystals ratio of 1:1 was 1.778 ± 0.086 ppm, CVD:ARG ratio of 1:2 was 1.832 ± 0.023 ppm, and a CVD:ARG ratio of 2:1 was 1.81 ± 0.0066 ppm. According to the test results, the solubility of CVD:ARG multicomponent crystals did not increase over pure carvedilol.

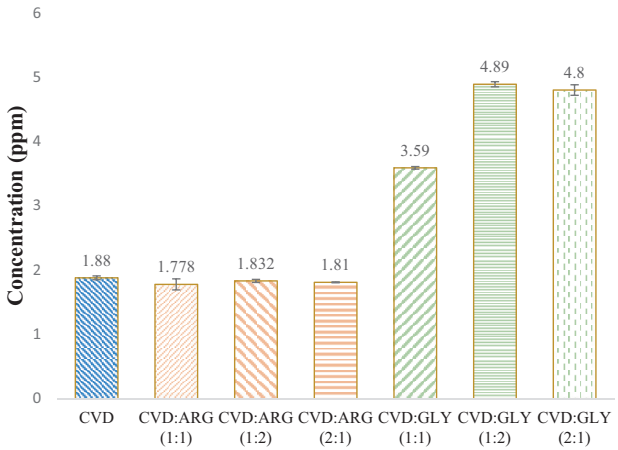


Figure 1. Saturated solubility comparison of pure carvedilol and carvedilol in multicomponent crystals with various molar comparation.

The multicomponent crystals of CVD: GLY showed increased solubility compared to pure carvedilol in the solubility test results (Fig. 1). The highest increase in solubility was observed in the multicomponent crystal CVD:GLY ratio of 1:2 with a saturation solubility value of 4.89 ± 0.04 ppm (2.6 times increase), followed by the multicomponent crystal CVD:GLY ratio of 2:1 with a value saturated solubility was 4.80 ± 0.04 ppm (2.5 fold), and multicomponent crystal CVD:GLY ratio 1:1 with a saturation solubility value of 3.59 ± 0.02 ppm (1.9 times increase). The most soluble multicomponent crystals have a ratio of 1:2 because there are more coformers serving as attractors of water molecules, increasing the likelihood that carvedilol will come into contact with water molecules.

A one-way ANOVA statistical test and a follow-up test using Tukey's post hoc test were used to ascertain whether there was any significant difference between pure carvedilol and carvedilol multicomponent crystals. The findings for the crystal multicomponent CVD showed that there was no discernible difference between ARG and pure carvedilol ($p > 0.05$). In the meantime, as the value ($p < 0.05$) shows, there was a substantial difference between each adjustment in the mole ratio of the CVD: GLY multicomponent crystal and the solubility of pure carvedilol.

Dissolution test

Dissolution tests were carried out on crystal multicomponent samples with coformers which showed an increase in solubility, namely CVD:GLY 1:1, 1:2, and 2:1 mole ratio compared to pure carvedilol. According to the USP Pharmacopeia standards, the dissolution medium for carvedilol is hydrochloric acid with a pH of 1.45. The dissolution test was conducted in HCl medium pH 1.45 and phosphate buffer medium pH 6.8 to determine the dissolution profile of CVD:GLY multicomponent crystals in acidic and intestinal mediums that represent the pH of the digestive tract and to observe the trend of multicomponent crystal dissolution profiles.

Figs 2, 3 show the results of the dissolution test. Pure carvedilol dissolved up to 78% in 60 minutes in HCl

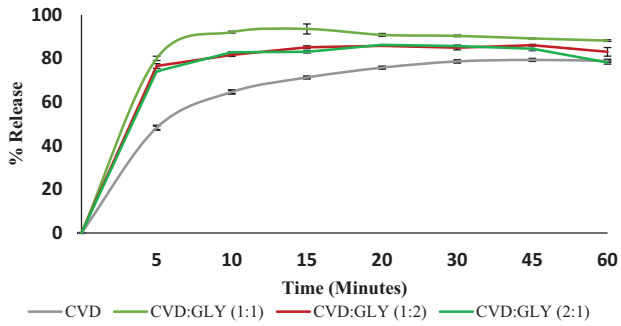


Figure 2. Dissolution test in medium HCl pH 1.45 results.

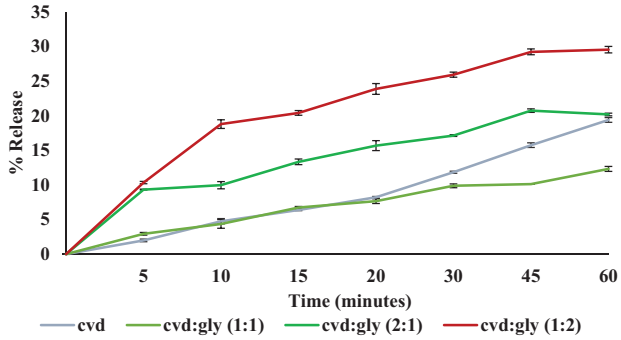


Figure 3. Dissolution test in medium phosphate buffer pH 6,8 results.

dissolution media pH 1.45 and dissolved up to 19.39% in 60 minutes in phosphate buffer medium pH 6.8.

CVD:GLY crystal multicomponent (1:2) gave the best % dissolution increase in phosphate buffer medium pH 6.8. Meanwhile, in the dissolution test of HCl medium pH 1.45, the best % increase in dissolution occurred in the crystal multicomponent CVD:GLY (1:1), followed by a ratio of 1:2 and 2:1. However, the crystal multicomponent CVD:GLY (1:1) showed a lower % dissolution than pure carvedilol in phosphate buffer medium pH 6.8. Thus, the multicomponent crystal CVD:GLY (1:2) was chosen to proceed to the next evaluation, because the multicomponent crystal CVD:GLY (1:2) showed a significant increase in % dissolution in both dissolution media, namely in HCl dissolution medium pH 1.45 and phosphate buffer medium pH 6.8. In phosphate buffer medium pH 6.8, % dissolution in 60 minutes reached 29.5%. Whereas in HCl medium pH 1.45% dissolution reached 86.03% in 60 minutes.

Statistical tests were conducted on the dissolution test results of pure carvedilol and CVD:GLY multicomponent crystals using the one-way ANOVA test, followed by the Tuckey HSD post-hoc test with IBM SPSS Statistics 25 software, at a confidence level of 95%. Based on the results of the Tuckey HSD post-hoc test which aimed to identify groups with significant differences, it was observed that all ratio variations of the CVD:GLY multicomponent crystals exhibited significant differences compared to pure carvedilol under acidic conditions (pH 1.45). Meanwhile, in the dissolution test conducted in phosphate buffer medium at pH 6.8, the results indicated that only the CVD:GLY multicomponent crystal with a 1:2 ratio showed a significant difference when compared to pure carvedilol.

Based on the dissolution test results in HCl medium (pH 1.45) and phosphate buffer pH 6.8, it can be concluded that carvedilol and CVD: GLY multicomponent crystal had a higher % dissolution in HCl medium pH 1.45. Carvedilol is a weak base drug so it will dissolve more easily in an acidic environment. Meanwhile, glycine is a group of amino acids composed of two chemical groups, namely the amine group ($-NH_2$) which is basic and the carboxyl group (-COOH) which is acidic. The existence of these two groups causes amino acids to react with both acids and bases.

Characterization of multicomponent crystal

Fourier transform infrared (FTIR) result

The formation of multicomponent crystals can be showed by indication of peak shifts, changes in peak intensity, or the emergence of new peaks in the infrared spectrum. Fig. 4 indicated the FTIR spectra of pure carvedilol, pure glycine, CVD: GLY (1:2) multicomponent crystal, and CVD: GLY (1:2) physical mixture (Fig. 4).

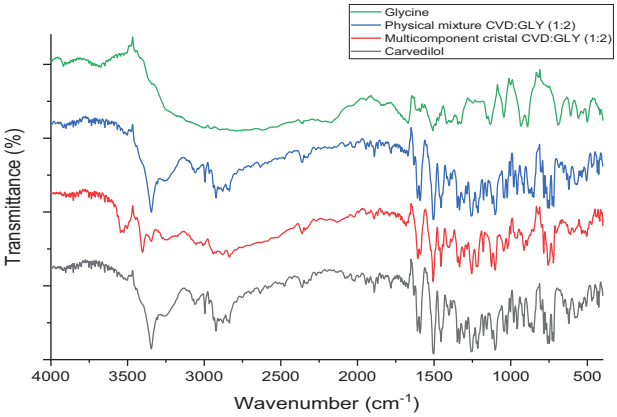


Figure 4. FTIR spectrum result.

Table 3. Analysis of functional group FTIR spectra of pure carvedilol, crystal multicomponent CVD:GLY (1:2), and physical mixture of CVD:GLY (1:2).

Functional group	Carvedilol (cm^{-1})	Glycine (cm^{-1})	CVD:GLY (1:2) multicomponent crystal (cm^{-1})	CVD:GLY (1:2) physical mixture (cm^{-1})
N-H	3344,57	3350	3402,43	3344,57
C-H	3061,03; 2922,16	3159	3061,03; 2922,16	3061,03; 2922,16
C-O	1255,65 and 1215,15	–	1255,65 and 1217,08	1255,65 and 1215,15
C=C	1591,27	–	1591,27	1591,27
C-N	1332,81	1138,21	1332,81	1332,81

The peak at 3344 cm^{-1} in the FTIR spectra of pure carvedilol indicated the N-H stretching group. In addition to the N-H peak, at the peak of 3248–3400 cm^{-1} a broadening of the peak was observed indicating an O-H vibration that appears simultaneously with N-H (Table 3).

In addition, the C=C group was discovered at the peak of 1591.27 cm^{-1}, C-N at 1332.81 cm^{-1}, C-O at 1255.65 cm^{-1} and 1217.08 cm^{-1}, and C-H stretching at 2922.16 and 3061 cm^{-1} (Tapas et al. 2012; Eesam et al. 2020).

According to the physical mixture of CVD: GLY (1:2) FTIR spectrum results, there is no peak shift or difference with the FTIR spectrum of pure carvedilol, this showed that in the physical mixture of CVD: GLY (1:2), there was only physical interaction and no hydrogen interaction. Meanwhile, the peak wave number of the N-H group in the CVD: GLY (1:2) multicomponent crystal shifted from 3344.57 cm^{-1} to 3402.43 cm^{-1}. Additionally, at the C-O group's peak, the peak wave number also shifted from 1215.15 cm^{-1} to 1217.08 cm^{-1}. The shift in wavenumber suggests that carvedilol and glycine functional groups have formed hydrogen bonds (Doloking et al. 2021). According to the in silico study that was carried out, carvedilol and the glycine coformer form hydrogen bonds to the oxygen atom in the carvedilol ether group acting as a hydrogen acceptor and a hydrogen atom in the glycine structure's amine group acting as a hydrogen donor.

Differential scanning calorimetry (DSC) result

The thermal characteristics of multicomponent crystals were analyzed using DSC measurements. Fig. 5 displays DSC thermograms of pure carvedilol, glycine, CVD: GLY (1:2) multicomponent crystal, and CVD: GLY (1:2) physical mixture.

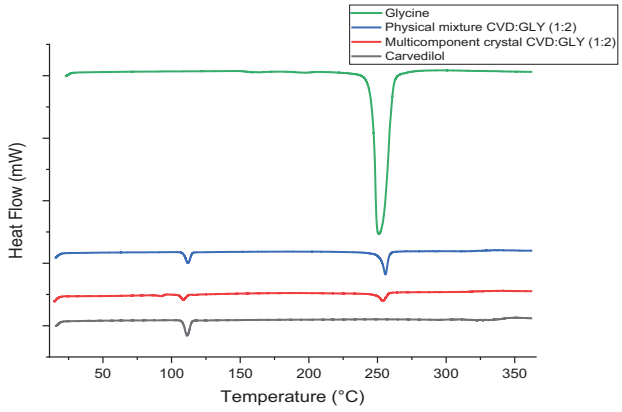


Figure 5. DSC thermogram result.

The pure carvedilol DSC thermogram's results revealed an endothermic peak indicating the drug's melting point at 111.35 °C and an enthalpy value of -23.66 J/g. Pure glycine's DSC thermogram revealed an endothermic peak with a melting point of 251.05 °C. On the DSC thermogram of the physical mixture CVD: GLY (1:2) two endothermic peaks can be observed, where the first endothermic peak had a similar peak to that of pure carvedilol at 111.92 °C which is close to the melting point of pure carvedilol. The second endothermic peak is shown at 255.76 °C which is also similar to the melting point of the pure glycine coformer. Thus, it can be said that there is no interaction between carvedilol and glycine molecules in the physical mixture CVD: GLY (1:2).

Two endothermic peaks could be seen on the CVD: GLY (1:2) multicomponent crystal's thermogram. The first endothermic peak appeared at a temperature before the melting point of pure carvedilol, which is at 108.54 °C with a lower enthalpy than pure carvedilol, which is -7.61 J/g. The decrease in melting point and enthalpy explains the increase in solubility that occurs in the CVD: GLY (1:2) multicomponent crystal. Based on research, most cases of multicomponent crystals show lower melting points than drugs and coformers (Saganowska and Wesolowski 2018). The second endothermic peak occurred at 253.96 °C. The appearance of the second endothermic peak indicated a transformation occurring in the multicomponent crystal. Additionally, an interaction between carvedilol and the glycine coformer changed the crystal lattice's shape forming a relatively new crystal pattern, as demonstrated by the diffractogram pattern, which contributed to the shift in the melting point of the CVD:GLY (1:2) multicomponent crystal (Musfikah et al. 2015).

Powder X-ray diffraction (PXRD) result

Fig. 6 showing the diffractograms for pure carvedilol, pure glycine, a CVD:GLY (1:2) multicomponent crystal, and a CVD:GLY (1:2) physical mixture. The characteristics of 2θ observed in the diffractogram of pure carvedilol were 5.8°, 11.61°, 12.97°, 13.60°, 14.75°, 15.11, 16.44°, 17.49°, 18, 37°, 19.21°, 20.21°, 21.05° 21.62°, ,22.8°, 23.4°, 24.25°, 26.15°, 26.33°, 27, 44°, 28.08°, 29.37°, 31.37° and 34.16°. Meanwhile, the peak characteristics of the pure glycine diffractogram were seen at 2θ = 14.83°, 19.02°, 21.81°, 25.33°, 29.88°, 35.88°, 39.05°, 41.61°, 44.4°, 45.56°. Based on the diffractogram pattern showing sharp and tall peaks, pure carvedilol and pure glycine have crystalline solids with % crystallinity of 90.7% and 95.7%, respectively.

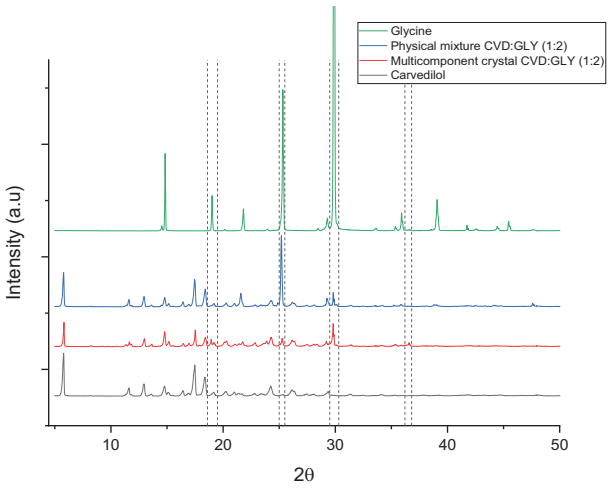


Figure 6. PXRD diffractogram result.

With additional peaks at 18.94°, 25.25°, and 29.8°, the diffractogram of the CVD: GLY physical mixture (1:2) resembled the pattern of carvedilol. There was no change in peak intensity or percentage crystallinity in the physical mixture diffractogram as compared to pure carvedilol.

Peak features of the CVD-GLY (1:2) multicomponent crystal diffractogram, on the other hand, revealed novel peaks at 18.94°, 25.25°, 29.8°, and 36.57°, but otherwise had a pattern similar to that of pure carvedilol. When compared to pure carvedilol, the percentage of crystallinity in the CVD: GLY (1:2) multicomponent crystal dropped to 84.4%. The peak intensity of the multicomponent crystal CVD: GLY (1:2) was relatively lower than pure carvedilol and pure glycine. In general, new peak formation and a decrease in crystallinity are indications that multicomponent crystals are forming a new solid crystalline phase. The physicochemical characteristics of multicomponent crystals, such as solubility and dissolution, will be impacted by the change in crystal phase. (Sathisaran and Dalvi 2018). This explains why the solubility and dissolution profile of the CVD: GLY (1:2) multicomponent crystal increased.

Conclusion

Carvedilol interacted with each coformer, generating two hydrogen bonds with the glycine coformer and one hydrogen bond with the arginine coformer, according to in silico research. Among the other comparisons, CVD:GLY (1:2) indicated the best saturated solubility and dissolution profile. The saturated solubility test yielded a 2.6-fold increase for the CVD:GLY (1:2) multicomponent crystal; the percentage of dissolution reached 86.03% in HCl medium pH 1.45 and 29.5% in phosphate buffer medium pH 6.8. The characterization results of multicomponent crystal CVD:GLY (1:2) included FTIR spectrum shifts which indicated hydrogen interaction between carvedilol and the glycine coformer, the thermogram pattern from the DSC results showed a decrease in melting point and enthalpy, and based on the PXRD diffractogram there is a new peak and a decrease in % crystallinity in CVD:GLY (1:2) multicomponent crystal, which indicates the formation of new solid phase.

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