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Review: Solubility And Bioavailability Enhancement Of Carvedilol Using Multicomponent Crystal Method

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Abstract

Carvedilol is included in the BCS class 2 classification, drugs that have low solubility and high permeability. Drugs with low solubility pose a major challenge for oral drugs in achieving the desired systemic circulation. Moreover, carvedilol is indicated for the treatment of cardiovascular disease and hypertension which requires a rapid pharmacological response. A way to increase drug solubility is by forming multicomponent crystals, including solvates, cocrystals, and salts. Cocrystal and salt formation methods are the most frequently used methods in the pharmaceutical field. The multicomponent crystal approach is a process of combining active drug ingredients with other compounds known as coformers which then interact through molecular bonds. Multicomponent crystals provide benefits to improve the physicochemical properties of drugs without affecting their pharmacological properties. In this review, we discuss the multicomponent crystal approach as an effort to increase the solubility and bioavailability of carvedilol. The main reference data used in this review are research journals published in the last 10 years (2012-2022) using the keywords carvedilol, multicomponent crystal, solubility, bioavailability, and using Google Scholar as a database. There is also a discussion on regulation of cocrystals, methods for forming multicomponent crystals, and characterization of multicomponent crystals. The multicomponent crystal approach has promising benefits in increasing the solubility and bioavailability of carvedilol in the body.

Keywords: Carvedilol, multicomponent crystal, solubility, bioavailability

1. Introduction

Carvedilol is a drug for the treatment of cardiovascular disease, that is mild to moderate congestive heart failure and hypertension. Carvedilol is taken orally in twice-daily doses for therapy in the immediate-release form or once-daily in controlled-release form. Dosage is individualized based on blood pressure and heart rate response, even when used in heart failure. The dosage range used was from 3.125 mg twice daily to 25 mg twice daily (1). Carvedilol is included in the BCS class 2 classification which has low solubility and high permeability (2). The oral

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bioavailability of carvedilol is 20%, because carvedilol has a first past effect metabolism in the liver with a short half-life (t½), which is about 6 hours. This causes the frequency of using oral carvedilol to become more frequent, so it is required to increase the use of oral doses which will certainly affect patient comfort and compliance in taking the drug (3,4).

To achieve the desired pharmacological response in systemic circulation using oral carvedilol, it is necessary to make efforts to increase the solubility and bioavailability of carvedilol by modifying the physico-chemical properties through a multicomponent crystal approach (5). Multicomponent crystals are classified into salts, cocrystals and solvates. In the pharmaceutical field, the formation of salts and cocrystals is the most commonly used method and is proven to increase the solubility of active pharmaceutical ingredients (6).

2. Method

The writing of article review begins with a literature search on Research Gate and Science Direct with the keywords "carvedilol", "multicomponent crystal", "solubility", and "bioavailability" published in various international journals and national. The literature obtained was then re-selected according to the inclusion criteria, they are articles and reviews with the last 10 years of publication (2012-2022), articles discussing the increase in solubility and dissolution rate of the drug carvedilol using the multicomponent crystal method approach, and also the characterization of multicomponent crystals. And the exclusion criteria are opinions and publications that are not in accordance with the topic of discussion.

Table 1. Methods performed for review

3. Result and Discussion

3.1 Carvedilol

β - blocker drug which is indicated for the treatment of cardiovascular disease, that is congestive heart failure and hypertension. Carvedilol's ability to lower blood pressure is the result of inhibition of β-adrenergic receptors and vasodilation which causes α -adrenergic inhibitory activity . Carvedilol has antioxidant activity because it is the only β-blocker class of drugs that has a carbazole group (3,7).

Based on the Biopharmaceutical Classification System (BCS), carvedilol is classified as BCS class II, it is drugs that have low solubility and high permeability. The solubility of carvedilol in water is known to be only 0.093 mg/mL. It has been reported that drug molecule solubility below 100 g/mL indicates limited absorption dissolution and may require increased dose to maintain effective therapeutic concentration (bioavailability). There are more than 70% of newly developed active pharmaceutical ingredients (API) and 40% of drugs that have been marketed belonging to BCS class II compounds, which is carvedilol. This can have an impact on the performance of drugs administered orally (8–10).

Figure 1. Carvedilol Moecular Structure (11)

3.2 Multicomponent Crystal

Multicomponent crystals are one of the crystal engineering techniques that have been proven to be able to improve physicochemical properties such as solubility, stability, and bioavailability of

drugs that are less soluble in water which are then applied in the concept of supramolecular synthone (12). Multicomponent crystals consist of two or more compounds that interact via molecular bonds (hydrogen bonds, electrostatics, van der Waals forces, π - π stacking, and other forms of non-covalent bonds) with each compound in the form of atoms, ions or molecules. Among these interactions, hydrogen bonding is the most important interaction in the formation of supramolecular compounds because it has high strength (6,13,14).

Figure 2. Hydrogen bonds in the formation of multicomponent crystals (15)

Generally, multicomponent crystals are classified into 3 main classes, these are solvates and their polymorphs, salts, cocrystals. However, based on the type of compound composition, multicomponent crystals are divided into 7 subclasses, among them are solvates, salts, cocrystals, solvate salts, solvate cocrystals, salt cocrystals, and solvate salt cocrystals (13,16). In applications in the pharmaceutical field, salt and cocrystal formation methods are potential methods and have been widely applied to increase the solubility of active drug ingredients (6).

Figure 3. Classification of Multicomponent Crystal (16)

The difference between cocrystal and salt lies in the transfer of protons. The formation of salts requires the transfer of protons from components of acidic compounds to components of basic compounds, which can also be predicted from the difference in the pKa of the two components of the compound, where the difference in pKa ≥ 3 will produce a salt form (17,18)

3.2.1 Solvates and hydrates

Solvates and hydrates are additional products from multicomponent crystalline solid molecules that are formed when the main molecule (API/excipient) is added to an additional molecule (water/hydrate) or another solvent (solvate) which is incorporated in a crystal lattice structure. Commonly known as the pseudo polymorphic form (19). Pseudo-polymorphism resulting in the formation of a crystalline solid addition with the solvent is often called pseudopolymorphism, whereas a group of solvates with different stoichiometry of the same solvent and compound is often called a "pseudo-polymorph". Solvates may form when pharmaceutical solids are processed or stored in solvents during periods of crystallization, reflux, wet granulation, or storage. Exposure to solvent vapors can also cause solvate formation (20).

3.2.2 Salt

Pharmaceutical salts are defined as components formed from active pharmaceutical ingredients (API) which can be ionized (can be anionic, cationic or switterion molecules) with counter ions to form neutral complexes. The counter ions used can be molecular, such as mesylate or acetate, or atomic, such as bromium or sodium. In addition to increasing solubility, other physicochemical properties that are affected by salt formation include flow properties, particle size, crystallinity, hygroscopicity, and melting point (18,21). Salt formation can produce a product that is more stable and easier to recrystallize, so that components with high purity can be obtained. Modification of compounds by forming salts has the advantage of producing compatibility with excipients, easy production, and safer use of API. However, because salt formation can only be carried out for ionized active pharmaceutical ingredients, its application is quite limited compared to cocrystal formation (17,18).

The formation of salts of pharmaceutical active ingredients with benzoic acid coformers has been produced one of them through desloratadine-benzoic acid, because it is known that benzoic acid is in anionic form. This means that a proton (H^+) is transferred via the carboxyl group of benzoic acid to the N atom of piperidine loratadine. The difference in the pKa values of the two components is quite large, which is greater than 3. Desloratadine-benzoic acid salt can increase its solubility in water by 51 times, and increase the dissolution rate by 10 times than pure desloratadine (22).

3.2.3 Cocrystal

Cocrystal is a crystalline phase formed from two or more neutral molecules (coformer compounds) bonded in a crystal lattice through non-covalent interactions in a certain stoichiometric ratio. Non-covalent interactions that occur in cocrystals are mainly hydrogen bonds, but can also occur through electrostatic interactions, van der Waals forces, and π - π stacking (18).

Similar to the formation of salts, cocrystals can improve the physicochemical properties of active pharmaceutical ingredients without affecting their pharmacological effects which include solubility, stability, bioavailability and mechanical properties. However, cocrystals have advantages that cannot be carried out by salt-making methods, that is cocrystals can be made on pharmaceutical active ingredients that have weak or no ionization capabilities (14,23). The drawback is in terms of procedures that require additional procedures in the process of synthesizing drug compounds (24). The term pharmaceutical cocrystal refers to cocrystals formed from pharmaceutical active ingredients with the appropriate coformer (18).

3.3 Co-crystal Regulation

Regulations on the formation of cocrystals and their formulations influence the development strategy and quality control. According to the FDA which was the first agency to provide guidance on the arrangement classification of pharmaceutical cocrystals, cocrystals are defined as "Solids which are crystalline materials consisting of two or more molecules in the same crystal lattice". Cocrystal is classified as a Drug Product Intermediate (DPI) which is expected to improve the physicochemical properties of a drug. According to the FDA, cocrystal is classified as a new polymorph form of the active ingredient so it is not considered a new API (16,25).

In 2015, the European Medicine Agency (EMA) published a reflection paper on the use of cocrystals from active ingredients in health products. EMA classifies co-crystals as novel active substances and defines them as “salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of a different active substance shall be considered to be the same active substance, unless their properties differ significantly with respect to with safety". However, dual-phase materials obtained by precipitation or physical mixing are not considered cocrystals by EMA (26). Parameter comparison based on FDA and EMA cocrystal regulatory status is shown in Table 2.

Table 2. Parameter comparison based on FDA and EMA regulatory status of cocrystal (25,26)

3.2 Methods for Forming Multicomponent Crystals

Common methods in the preparation of multicomponent crystals are divided into 2, that is the solution-based method and the solid-based method . The solution-based method requires high solvent to dissolve the multicomponent crystal constituents, and may affect the results of cocrystallization because it can change the intermolecular interactions of the active pharmaceutical ingredients and

the coformer. Meanwhile , the solid-based method does not require or requires little solvent in the formation of multicomponent crystals (27).

Figure 4. Multicomponent crystal formation method (27)

Figure 5. Illustration of the formation of a multicomponent crystal system (28)

3.4.1 Solution -based method

a. Solvent Evaporation

Solvent evaporation is the most commonly used method for the formation of multicomponent crystals. This method is carried out by dissolving a number of active drug substances and coformers in a common solvent. The solvent used must be able to completely dissolve the active drug substance and the coformer, because if there are substances that are not dissolved, components will be found that precipitate so that crystal formation fails. Ideally, solvent evaporation is carried out from three ratios, the ratio of active substances:coformer (1:1; 1:2; and 2:1) (27,29). Solvent evaporation has a simple and effective procedure for screening and laboratory scale (30).

b. Anti-solvent method

The anti-solvent method is an effective approach to control the quality, particle size and properties of cocrystals with a continuous cocrystallization process. The addition of anti-solvent will reduce the solubility of a solute and form crystals quickly. The choice of solvent combination in this method is a critical point where the resulting cocrystal must have low solubility with the use of a small amount of solvent. Examples of solvent:anti-solvent mixtures used to produce cocrystals are ethanol:water, ethanol:acetonitrile and ethanol:ethyl acetate (27,30).

c. Cooling crystallization

The cooling crystallization method is generally used for the formation of large-scale pure multicomponent crystals. This method is based on temperature variations and usually uses a reactor to mix the components and solvent. The reactor system is then heated to achieve dissolution of the two components, then saturation is achieved by lowering the temperature (27,30).

d. Reaction cocrystallization

The reaction cocrystallization method is used when there are 2 components having different solubility, in which reactants with nonstoichiometric concentrations are mixed to produce a saturated solution of cocrystals to form a cocrystal precipitate. In this method, the formation of cocrystals is controlled by the ability of the reactants to reduce the solubility of the cocrystals (30).

e. Slurry conversion

The slurry conversion method is a method for forming multicomponent crystals in which excess cocrystalline components are added to the solvent. Although this method is solution based, it does not require preparation of a clear (fully dissolved) initial solution (27,29).

3.4.2 Solid- based method (Solution based method)

a. Contact cocrystallization

The contact cocryztallization method is based on the interaction between the active pharmaceutical ingredients and the coformer spontaneously after the mixing process with the raw material . Higher humidity and temperature, as well as smaller raw material particle sizes can affect the formation of cocrystals with this method (27,31).

b. Neat grinding

Neat grinding or solid state grinding is carried out by mixing the cocrystal components stoichiometrically in the solid state and grinding them manually with a mortar pestle. This method is environmentally friendly and can avoid sulphate formation, but in terms of its efficacy it is considered less for the

formation of cocrystals in large quantities (30).

c. Liquid-assisted grinding

The liquid-assisted grinding method is accomplished by liquid-assisted grinding which involves adding a solvent, usually in very small amounts to a dry solid before grinding begins. The solvent acts as a catalytic to help form cocrystals (29). This method produces cocrystals with high crystallinity compared to neat grinding (27).

d. Melt crystallisation

Melt crystallization method is a technique for forming pharmaceutical cocrystals that does not require a solvent, but attention should be paid to the heat stability of the active pharmaceutical ingredients and the coformers used. High temperature and pressure are required to form a melt from the active ingredient and coformer using an extruder (30,32).

3.1 Coformer

Coformer is a cocrystal forming substance that functions to increase the solubility and bioavailability of active pharmaceutical ingredients. The selection of coformers for the formation of multi-component crystals is limited, only those defined and registered by the Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS) (33,34). The criteria that must be met in selecting a coformer are that it must be non-toxic, able to bind non-covalent with the active substance, can increase the solubility of the active substance in water, and be compatible with the active substance (35).

3.2 Solubility and Bioavailability

Solubility is one of the important parameters for achieving the desired drug concentration in the systemic circulation to achieve a pharmacological response. Drugs that have poor water solubility will be released inherently at a slow rate due to their limited solubility in the gastrointestinal tract, which causes a decrease in bioavailability in the body. Low bioavailability results in administration of higher doses in order to achieve therapeutic concentrations. The parameter that often determines the rate of drug absorption is the dissolution rate (3,36). This is in line with carvedilol which has a poor solubility in water, that is only 0.093 mg/mL and is practically insoluble in water (37), so it is linear with low bioavailability, which is only around 20% (3).

In general studies, several methods can be used to increase the solubility of BCS class II drugs such as Carvedilol using the multicomponent crystal method, solid dispersion, liquid-solid technique, emulsification, and nano-crystal methods. Here the several studies that proven can increase the solubility and dissolution rate of carvedilol significantly by various methods of multicomponent crystal approach using various coformers and solvents, the data of which is listed in table 3.

Table 3. Carvedilol solubility and bioavailability Enhancement using the Multicomponent Crystal Approach Method

The results of increasing the dissolution rate of multicomponent carvedilol crystals with pure carvedilol can be seen in the examples in Figures 6 and 7. In Figure 6, Fernandes et al., (2018), showed that pure carvedilol has a lower dissolution rate than the carvedilol-nicotinamide cocrystal. The dissolution rate of pure carvedilol at pH 1.2 was 18,35% at 60 minutes, while the dissolution rate of the carvedilol-nicotinamide cocrystal at the same pH and minutes increased significantly to 88%. The solubility of cocrystal carvedilol-nicotinamide (1:2) was also increased by 15 times. The solubility of pure carvedilol in 0.1 N HCl pH 1.2 was found to be 0.093

mg/mL, while the carvedilol-nicotinamide cocrystal showed a dynamic solubility of 1.41 mg/ml in 0.1 N HCl after 48 hours (39).

The use of pH medium is important in conducting dissolution tests to improve the dissolution rate of the drugs (44). Because in the ionized form, the solubility of carvedilol depends on the pH of the medium, where carvedilol, which is a weakly basic molecule, will be more soluble at increasingly acidic pH conditions (decreasing pH). The increase in carvedilol-nicotinamide solubility may also be due to cocrystal formation or due to the additive effect of carvedilol and nicotinamide as both have nitrogen in their parent ring which can be protonated at acidic pH.

Figure 6. Dissolution profile of pure CVD and CVD-nicotinamide multicomponent crystal at pH 1.2 (39)

In Figure 7, Zhang et al, (2021) proved that the dissolution rate of carvedilol multicomponent crystals was higher than pure carvedilol at an alkaline pH in water distilled medium. Pure carvedilol (S-CAR-XR), carvedilol-phosphate multicomponent crystal (P-S-CAR-XR), and carvedilol-hydrochloride multicomponent crystal (H-S-CAR-XR) have the same FBE (free base equivalent) of carvedilol, but the release of carvedilol with modification of the multicomponent crystal form was faster than free base in water distilled medium. These findings indicate that the release rate of pure carvedilol is limited by its low solubility in the intestinal environment (pH 5-7). The intestine is the main site of absorption of ost drugs, so the prolonged and effective release of pure carvedilol is difficult to achieve in vivo. The multicomponent carvedilol crystals have a higher rate of drug release compared to the free base, but the rate of release may still be limited by alkaline counterions in the intestinal environment.

Figure 7. Dissolution profile of pure CVD and CVD-phosphoric acid, CVD-sulfuric acid multicomponent crystal at water distilled medium (41)

3.7 Multicomponent Crystal Characterization

In the formation of multicomponent crystals, it is necessary to evaluate to ensure the quality of the drug being made. Evaluations carried out on cocrystals include FTIR spectroscopy, X-ray Diffraction (XRD), and Differential Scanning Calorimetry (DSC) (45).

3.7.1 Fourier Transform Infrared Spectrophotometer (FTIR)

FTIR is a characterization technique that can record the IR spectrum where there is a process of absorption of radiation that corresponds to the transition energy in the bond vibrating by the molecule being analyzed. The absorption process will occur when the IR frequency is the same as the vibrational frequency and quantitative information about the absorbed energy will be seen when the light is transmitted (46). Characterization using FTIR aims to confirm the interaction between the active ingredient and the coformer used. For example, seeing the presence of hydrogen bonds is characterized by a shift in group peaks, a decrease in peak intensity, and the

emergence of new peaks where these are the parameters that will be seen (47). FT-IR analysis is also used to differentiate salt formation compared to other multi-component crystals (cocrystals), as differentiated by the location of the protons between the acid and the base.

Hata et al., (2020), proved that in the formation of salt species, there is a typical carboxylate anion that has a carbonyl stretching band (a strong asymmetric band below 1600 cm^{-1}), and the appearance of a shoulder between 1505 cm−1 and 1610 cm^{-1} where it can be observed that ionized carboxyl groups are absent in the spectrum of the individual components. On the other hand, when the frequency of the carbonyl group in the carboxylic acid shifts to a higher energy (approximate frequency range 1700-1730 cm^{-1}), then cocrystalline species are formed. Figure 9 shows that examination of the FT-IR spectrum shows proton transfer from the salt form to the CVD, confirming the salt formation between CVD and DL-MA.

Figure 8. FTIR spectrum analysis of DL-Mandelic Acid, CVD, and CVD-DL Mandelate Acid (40)

3.7.2 X-Ray Diffractometer (XRD)

XRD is a method used to obtain structural information from its constituent components via a diftracogram (31). XRD analysis of multicomponent crystals aims to identify the formation of new crystalline phases where each crystalline phase of the compound has its own diffractogram characteristics so that XRD analysis can be used to differentiate the multicomponent crystalline products formed (38). Hiendrawan et al., (2016) proved that the result of CVD/MDA from the method of multicomponent crystals are forms I and II. The results of the PXRD analysis showed that form I was more stable than form II under ambient conditions. Then, the new CVD multicomponent crystal shows a PXRD pattern with different peak positions compared to CVD and coformer. Based on these results, it was explained that the new CVD multicomponent crystal has a different internal crystal structure compared to the initial components. And it is proved that during the desolvation process, the intermolecular interactions between the solvent and the CVD-coformer molecules are broken. The XRD analysis between CVD and CVD multicomponent crystal showed in figure 9.

Figure 9. XRD analysis of pure CVD and CVD multicomponent crystal (38)

3.7.3 Differential Scanning Calorimetry (DSC)

DSC is a thermal analysis procedure to measure how the physical properties of a compound sample change with temperature over time in the form of a thermogram (48). Through DSC, it can be seen whether or not the formation of multicomponent crystals is based on changes in the melting point which is usually at the melting point of the constituent components, that is the active ingredient and the coformer used. Mixtures that form multicomponent crystals will show endothermic and exothermic peaks, while mixtures that do not form multicomponent crystals will only show endothermic peaks (49).

Figure 10. DCS thermogram analysis a) pure CVD, b) HCT, c) multicomponent crystal CVD-HCT (50)

4. Conclusion

Modification of carvedilol through a crystalline multicomponent approach can be a promising option for increasing solubility and bioavailability in the body, especially when it is to be used for oral administration. Many coformers have been studied to form carvedilol multicomponent crystals, such as carboxylic acid groups, nicotinamide, and others. There are several methods for forming multicomponent crystals that can be selected according to

the criteria for active substances, coformers, both for small-scale synthesis methods in the laboratory and for large-scale production methods in industry.

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