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REVIEW ARTICLE

CARVEDILOL SOLUBILITY ENHANCEMENT BY INCLUSION COMPLEXATION AND SOLID DISPERSION: REVIEW**Abdelmoumin Zoghbi, Bo Wang***

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ABSTRACT:

Carvedilol is an antihypertensive drug characterized by its low aqueous solubility, a major obstacle in drug formulation development to improve its bioavailability. To overcome problem of poor aqueous solubility of Carvedilol, various approaches have been investigated including physical and chemical modifications of the drug. Most of these investigations focused on modifying the drug structure from crystalline insoluble form to amorphous soluble form, reducing drug particle size to provide high surface area subjected to solvent, enhancing porosity degree, and improving wettability. A wide variety of polymers was used in order to achieve these goals. Carvedilol inclusion complex with Cyclodextrin (CD) and derivatives, solid dispersion with water-soluble carriers such as Polyvinylpyrrolidone K-30 (PVP K-30), Gelucire 50/13, porous silica (Sylysia 350), and Soluprus® (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) were previously investigated using different preparation methods such as Solvent evaporation method, fusion method, kneading method, and spray drying method. Analytical tests were conducted to characterize these preparations. FTIR, SEM, DSC, XRD are among the most commonly used. The present paper summarizes different drug-carrier combinations used for solubility, dissolution rate and/or bioavailability enhancement of Carvedilol, with emphases on the preparation methods of Carvedilol inclusion complex and solid dispersions, and different tests used for their characterization.

Keywords: Carvedilol, solubility enhancement, inclusion complex, solid dispersion, bioavailability.

1. INTRODUCTION:

Carvedilol is an effective nonselective alpha-1 and beta blocker discovered by Fritz Wiedemann^[1]. It is an antihypertensive drug indicated for the treatment of mild to severe congestive heart failure (CHF), angina pectoris, cardiac arrhythmias and myocardial infarction^[2]. Water solubility of Carvedilol is a fundamental property that affects the drug absorption after oral administration. Moreover, its dissolution and gastrointestinal permeability are the parameters that control its

bioavailability^[3]. The most frequent causes of low oral bioavailability is attributed to poor solubility and low permeability^[4]. Carvedilol is categorized as class II drug with low solubility and reasonable membrane permeability.

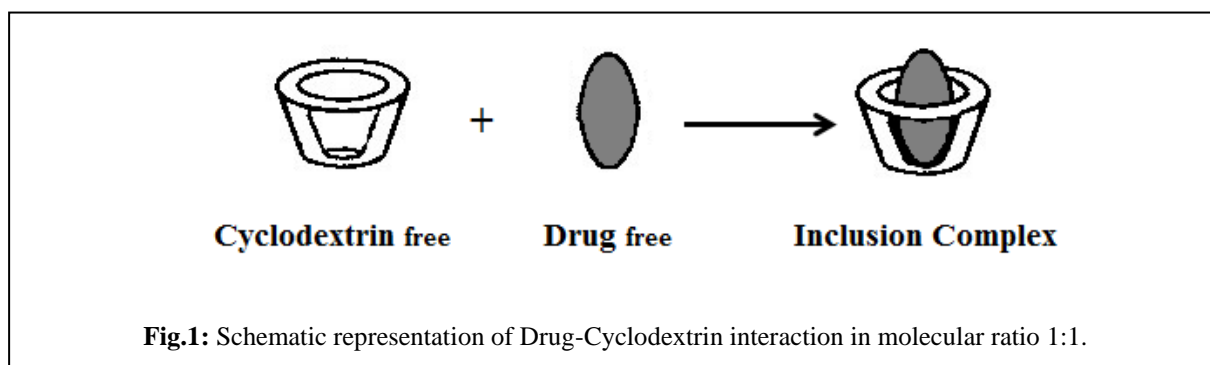
Cyclodextrins are cyclic (α -1,4)-linked oligosaccharides of α -D-glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface^[5]. Drug solubility enhancement using Cyclodextrin and

derivatives is generally proceed through formation of inclusion complexes. Cyclodextrins serve as host and form compound with different drug molecules^[6, 7] (**Fig.1**). Each drug molecule is enclosed by a Cyclodextrin molecule. Cyclodextrins have been widely used to enhance the aqueous solubility and dissolution rate of poorly water-soluble drugs^[8, 9]. β -Cyclodextrin and its derivatives (2-hydroxypropyl- β -cyclodextrin HP- β -CD, sulfobutyl ether- β -cyclodextrin SB- β -CD) are the most commonly used in the inclusion complex^[10-13].

Solid dispersion is another approach for drug solubility and dissolution enhancement. The concept of solid dispersion was proposed by Sekiguchi and Obi^[14]. Solid dispersion, also called solid solution^[15], is widely and successfully applied for the solubility, dissolution rate, and by consequence bioavailability enhancement of

poorly water-soluble drugs^[16]. It consists of a hydrophobic drug dissolved in a hydrophilic matrix, which can be amorphous (clusters) or crystalline particles^[17, 18]. Solid Dispersions have the advantage of uniformity distribution of the drug into carrier. It results in particles with amorphous structure^[19-21], reduced particle size, higher porosity degree, and improved wettability^[15, 22, 23]. The dispersion of drug into the carrier is rate limiting. Therefore, the formation of solid solution is restricted to relatively low concentration of the drug^[24, 25].

In order to improve the dissolution characteristics of carvedilol and enhance its aqueous solubility, several investigations have been established such as complexation with β -Cyclodextrin^[26-28] and solid dispersion with different water-soluble carriers.



2. SATURATION SOLUBILITY:

The solubility of a drug is the maximum quantity of drug that can dissolve in certain volume of a specific solvent at chosen conditions of temperature and pH. It might be stated in units of concentration, molarity, mole fraction, mole ratio, and other units^[29]. In general, solubility is defined as an equilibrium thermodynamic parameter, at which the chemical potential of the solute in the solid phase is the same as that in the liquid (solution) phase^[30]. Saturation solubility of a drug is used to determine the maximum amount of the drug dissolved in a specific solvent. It is a preliminary step in any solubility enhancement research particularly for poorly water-soluble drugs. It can strongly depend on the presence of other species in the solvent.

In general, Solubility measurement is performed according to method reported by Higuchi and Connors^[31]

where an excess amount of the drug is dissolved in a specific volume of the dissolution medium of a chosen pH. The dissolution medium can be pure water or a solution of different concentrations of the water-soluble carriers. This study is carried out for 24 – 72 hours using temperature controller orbital shaker.

Saturation solubility of Carvedilol is pH-dependent because of the ionization and the basic nature of Carvedilol^[32]. Carvedilol remains in a unionized form within solutions of high pH. However, it has an appreciable solubility in acidic pH^[33]. Some surfactants might affect Carvedilol solubility. Chakraborty et al.^[33] investigated the effect of different classes of surfactants (anionic-sodium dodecyl sulfate SDS and sodium taurocholate STC, cationic-cetyltrimethylammonium bromide CTAB and non-ionic-Tween 80) on the solubility of Carvedilol in different pH. Each of the surfactants showed a remarkable enhancement in the solubility of

Carvedilol in both acidic and basic pH^[33].

Solutions containing water-soluble polymers used in the solubility study also have a great effect in the solubility, and the enhancement is polymer concentration-dependent. The presence of β -Cyclodextrin (β CD) or derivate

(hydroxypropyl-beta-Cyclodextrin HP- β CD) showed an improvement in the solubility of Carvedilol^[32, 34, 35](**fig.2**). Cyclodextrins profile exhibits A_N -type isotherm^[36]. Therefore, the solubility of the drug molecule increases linearly with Cyclodextrin concentration up to certain extent and further its deviates negatively^[32].

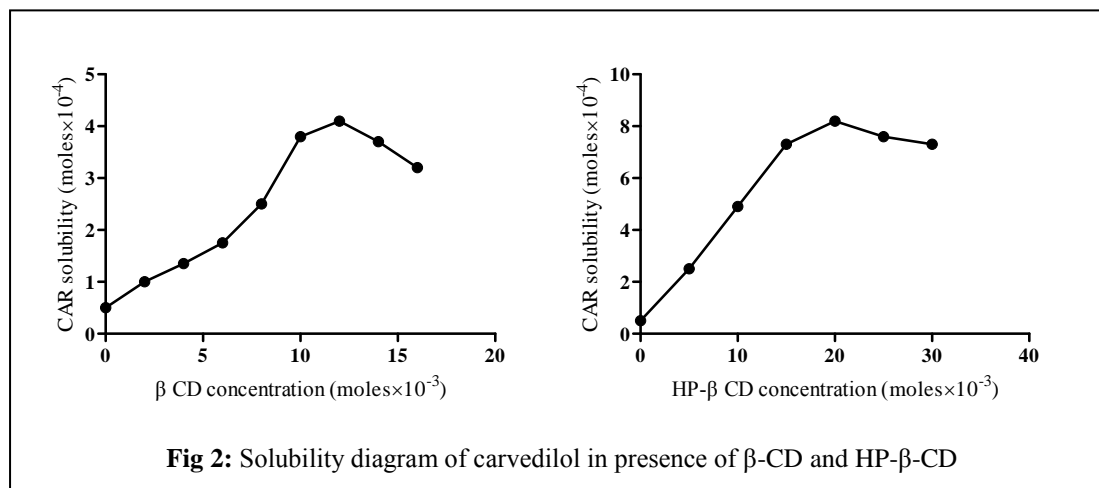


Fig 2: Solubility diagram of carvedilol in presence of β -CD and HP- β -CD

Other investigations used different polymers (PVP K-30^[32, 37], Poloxamer 407^[32], HPMC^[38], Gelucire^[39], some Eudragits^[38], PEG 4000, porous silica^[40], Soluplus^{®[41]}) alone or in combination also showed a solubility enhancement of the drug. After plotting Carvedilol solubility versus carrier concentration, the apparent complexation constant (K_c) of the solid dispersions can be calculated using the equation:

$$K_c = \frac{\text{Slope}}{S_0(1 - \text{Slope})}$$

Where S_0 is the intrinsic solubility of the drug in absence of Carrier.

3. CARVEDILOL SOLUBILITY ENHANCEMENT TECHNIQUES:

3.1. Carvedilol-Cyclodextrin inclusion complexation:

Several recent investigations showed that the inclusion complex is effective in the solubility and dissolution rate enhancement of Carvedilol. β -Cyclodextrin can reduce the interfacial tension between the solid particles of pure drug^[42] because of its surfactant-like property. This improvement is guest/host ratio-dependent. The molar ratio of 1:3 (Carvedilol: β Cyclodextrin) showed a high

and rapid dissolution rate in acidic media pH 1.2^[43]. Preparation method of the inclusion complex as well can affect the dissolution rate. A variety of methods used to prepare Carvedilol-Cyclodextrin inclusion complexes:

3.1.1. Solvent evaporation method:

Solvent evaporation method is the most commonly used method when the experiment concerns complexation of two compounds. The method was evaluated by Tachibana and Nakamura^[44] when they dissolved both drug and carrier in a common solvent to have a clear solution, then the solvent was evaporated under vacuum to have the complex in solid form. In the case of Carvedilol- β Cyclodextrin inclusion complex, this method is less effective comparing to other methods.

3.1.2. Kneading method:

Mostly used in industry when a big quantity of the complex is needed. An aqueous Cyclodextrin paste is prepared, using mortar and pestle in laboratory or kneading machine in large scale, by adding a small volume of solvent, which can be pure water or mixed with methanol. A specific amount of the drug is added to the paste while keeping vigorous stirring for 1 – 4 hours. Complex formation is indicating by the increasing viscosity of the mixture. The paste is then dried under

vacuum at temperature 40 – 60°C [42, 43, 45], and ground to obtain the complex powder.

3.1.3. Freeze-drying method:

This method is an alternative to solvent evaporation method. The drug and carrier molecules are mixed in a common solvent [46]. It involves an amorphous form of the complex with high interaction between Carvedilol and Cyclodextrin. It consists of freezing the solution containing the complex then allows the frozen solvent to sublimate by reducing the surrounding pressure. The freeze speed has an effect on the product form. It was found that slow freezing provided crystalline products, while rapid freezing provided amorphous inclusion complexes [47].

3.1.4. Coprecipitation method:

Coprecipitation is a phenomenon where a solute that would normally remain dissolved in a solution precipitates out on a carrier that forces it to bind together, rather than remaining dispersed [48]. Carvedilol was dissolved in methanol, the solution was then added dropwise into Cyclodextrin solution with continuous vigorous stirring. Crystals of a Cyclodextrin are formed and Carvedilol finds holes in the crystal matrix to occupy. The precipitate explains the inclusion complex formation. The remaining solvent were removed by desiccation under vacuum [42] or rotary evaporator [49].

3.2. Carvedilol solid dispersion:

Solid dispersion is one of several methods to increase solubility and dissolution rate of Carvedilol. For this purpose, different methods and carriers are utilized:

3.2.1. Solvent evaporation method:

Organic solvents are used to dissolve both the carrier and the drug. There is no thermal destruction of the drug because low temperature is required to evaporate organic solvent under vacuum [50]. Carvedilol solid dispersion using solvent evaporation method is recommended with wide variety of carriers such as: PVP K-30 [37, 51], Tartaric Acid and Poloxamer 407 [32], Gelucire 50/13 [39], porous silica [52], and Soluprus® [53].

3.2.1.1. Carvedilol-PVP solid dispersion:

Carvedilol and PVP were taken in the weight ratio 1:1, 1:3 and 1:5. Generally, the solvent used is methanol. When a

clear solution was formed, the solvent evaporated under vacuum at temperature about 50°C. The resultant solid mass was crashed, desiccated and finally evaluated using *in-vitro* dissolution tester. Different dissolution media can be used (acidic pH 1.2, PBS of different pH and pure water). Dissolution rates of Carvedilol-PVP solid dispersion at different ratios in simulated gastric fluid are summarized in (table 1) [37]. PVP improves Carvedilol wettability and, because of its high glass transition temperature (T_g), prevents Carvedilol recrystallization through nucleation [54].

3.2.1.2. Carvedilol-Gelucire 50/13 solid dispersion:

An appropriate amount of Gelucire was added to Carvedilol solution in a mixture of acetone and dichloromethane taken in 1:1 ratio [39]. The solvent was then evaporated under vacuum using rotary evaporator at 40°C. *In-vitro* dissolution test results of the obtained solid dispersion in pure distilled water are showed in (table 1) [39]. The results showed a significantly higher dissolution profiles comparing to the pure drug due to the amorphous structure and improved wettability of Carvedilol in solid dispersion.

3.2.1.3. Carvedilol-porous silica solid dispersion:

Solid dispersion consists of Carvedilol loading into the porous silica. Solvent evaporation under vacuum and adsorption from acetone solution were the methods used [40]. Porous Silica was suspended in a specific amount of carvedilol solutions in acetone (1%, 2%, and 4%, w/v). The solvent was evaporated in a vacuum evaporator at 50°C to ensure an effective pore-filling procedure [52]. Dissolution experiments was conducted in phosphate buffer (pH 6.8) and the results are shown in (table 1) [40]. As hypothesized by Monkhouse and Lach [55], the rapid drug release in phosphate buffer can be explained by the rapid desorption of Carvedilol from silica in presence of water.

3.2.1.4. Carvedilol-Soluprus solid dispersion :

Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) is designed for solid solutions because of its amphiphilic properties. It can be classified in the fourth generation of solid dispersion members because it serves as a matrix polymer for solid solutions and an active solubilizer through micelle formation in water [56]. Solid dispersion was prepared by

adding a solution of Carvedilol in methanol onto the copolymer, triturated with a pestle, and then kept to dry in desiccators over anhydrous calcium chloride^[57]. *In-vitro* dissolution test was carried out using distilled water. The rapid dissolution of Carvedilol from the solid dispersion may be attributed to its molecular and colloidal dispersion in the hydrophilic carrier matrix. As the soluble carrier dissolves, Carvedilol, in the form of very fine particles, is exposed to dissolution medium and the consequent increase in the surface area results in the improved dissolution^[58].

3.2.2. Fusion method:

This method cannot be processed in the case of thermolabile drugs. The carrier is heated at temperature just above its melting point, and then the drug is dissolved in the melted matrix with constant stirring for a specific time to homogeneously disperse the drug into the matrix^[59]. The mixture is cooled at room temperature or using ice-bath. Carvedilol solid dispersion with Poloxamer 188 (PLX188) were conducted using fusion method^[60]. Dissolution test were performed using distilled water as

medium and the results are shown in (table 1)^[60]. The increased dissolution rate of Carvedilol in solid dispersion can be explained by the amorphous state of the drug. The polymer might acts by tension lowering effect of polymer to the medium and, by consequence, improved wettability of Carvedilol.

3.2.3. Spray drying method:

Solid dispersion by spray drying method improves the dissolution property of a drug by combining a poorly soluble drug and a hydrophilic carrier^[35]. This method was found to be effective in the preparation of Carvedilol-HPMC solid dispersion^[61]. Carvedilol and HPMC, at different ratios were dissolved in a co-solvent of methylene chloride and methanol with the volume ratio 1:1. The suspension was prepared as solid dispersion using spray dryer under the condition showed in (table 2)^[61]. *In-vitro* dissolution test showed a sustained release of Carvedilol during 120mn of dissolution period. These results might be explained by the fact that HPMC was swelled by water and slowly released Carvedilol^[62].

Table 1: Dissolution study of different Carvedilol solid dispersions in different mediums

Medium	Carrier	Drug:carrier ratio (w:w)	Preparation method	Dissolution rate at 10mn	Dissolution rate at 120mn	t _{50%} (mn)
Pure water	PLX188 ^[60]	1:0	Fusion method	1.93%	17%	>120
		1:1		46.25%	76.60%	<20
		1:3		54.5%	86.186%	<10
		1:5		59.75%	93.214%	<10
	Gelucire ^[39]	1:0	Solvent evaporation method	1.93%	17%	>120
		1:1		26.58±0.27%	61%	51.8±1.03
		1:3		37.66±1.10%	72%	41.33±0.57
		1:5		49.015±0.27%	88%	15.76±0.25
		1:7		57.78±0.57%	99%	12.13±0.11
		1:9		67.56±0.73%	100%	10.06±0.11
PBS pH 6.8	Porous silica ^[40]	1:0	Solvent evaporation method	5.33±0.33%	23%	>120
		1:1		59.30±2.00%	90.6%	<20
		1:3		64.00±0.27%	100%	<10
		1:5		78.01±1.33%	100%	<10
Simulated gastric fluid pH 1.2	PVP K-30 ^[37]	1:0	Solvent evaporation method	2.6%	6.5%	>120
		1:1		45%	75%	<120
		1:3		50%	82%	<100
		1:5		60%	90%	<10

Table 2: ^[61].Parameters of spray drying.

Parameter	Setting
Inlet temperature	130°C
Outlet temperature	75±5°C
Atomizing	10×10 kPa
Row rate	0.45 m ³ /mn
Pump speed	3.0 mL/mn

4. COMPLEX AND SOLID DISPERSIONS CHARACTERIZATION

The pure drug, inclusion Complexes and solid dispersions can be characterized by several analytic methods:

- *Fourier Transform InfraRed spectroscopy (FTIR)*^[63] identifies chemical bonds in a molecule by producing an infrared absorption spectrum. Thus, it is effective for detecting functional groups in a compound by their different vibrational modes.
- *Scanning Electron Microscopy (SEM)* provides

information about the sample's surface topography and identifies the morphology of the particles.

- *Powder X-ray Diffractometry (XRD)* is used for the structural characterization of materials ^[64] and determines the crystal structure of powders.
- Thermal analysis: *Differential Thermal Analysis (DTA)* and *Differential Scanning Colorimetry (DSC)* are alternative techniques used to measure the crystalline phase transition temperature and energy.

5. CONCLUSION

Carvedilol aqueous solubility has been successfully improved by different combination methods. Both inclusion complex and solid dispersion can form stable complexes between Carvedilol and carriers. The interaction between them might be slightly influenced by preparation method. However, increasing carrier content in the complex can rise the drug solubility. The crystalline form of the drug is converted to amorphous metastable state. The new morphological form of Carvedilol is confirmed by different characterization tests.

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