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Review: Methods for Enhancing Solubility of Carvedilol

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Abstract

The oral route of administration is the most frequently used route of drug administration and is generally the most convenient for patients. For an oral drug to be effective, a therapeutic concentration in the blood must be achieved. Solubility in water and permeability of active pharmaceutical ingredients are often used as the main conditions for rapid and complete absorption and high bioavailability. Carvedilol is beta blockers that works as an antihypertensive drug and included in biopharmaceutical classification system (BCS) class II with high permeability but low solubility. Due to this, the goal of this review is to go through a few different methods for increasing solubility of carvedilol. Review article was done by searching the literature first, then the data extraction process was carried out. Key words were arranged consisting of "carvedilol ", "increasing solubility", and "dissolution" in the search column of the Science Direct database for last 10 years. dissolution, and bioavailability. Various solubility enhancement techniques have been applied to carvedilol, including co-crystallization, liquidsolid technique, cyclodextrin inclusion complex, nanoparticles, hydrotrophy, nanosuspension, solid dispersion, nanoemulsion, and dendrimers. These techniques have been shown to increase the solubility and dissolution rate of carvedilol thereby increasing its bioavailability.

Keywords: carvedilol, solubility enhancement, BCS class II

1. Introduction

The oral route of administration is the most frequently used route of drug administration and is generally the most convenient for patients. For an oral drug to be effective, a therapeutic concentration in the blood must be achieved. This concentration is largely dependent on its bioavailability, which is strongly influenced by the rate and extent of absorption [1]. More than 70% of the active pharmaceutical ingredients (API) in the formulation development are highly hydrophobic and poorly soluble in water. Solubility in water and permeability of API are often used as the main conditions for rapid and complete absorption and high bioavailability [1,2].

Cardiovascular disease is said to be the leading cause of death in the world where there are reportedly at least 17.9 million people dying from it [3].) Beta blockers are known to have the ability to cope with some cardiovascular diseases such as stable angina, heart failure, arrhythmia, myocardial infraction, and also hypertension. Carvedilol represents one of the nonselective beta blockers that works by blocking adrenergic receptors --1, β-1, and --2.

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Broadly speaking, carvedilol has been used to treat long-term hypertension [3].

Compared to other beta blockers that works as an antihypertensive drugs such as atenolol and metoprolol, Carvedilol is known to have better benefits against increased glucose, lipid metabolism, and lipid peroxidase in patients with diabetes and hypertension. However, carvedilol is included in BCS class II with high permeability but low solubility (around <1 µg/ml at pH and 0, 23 µg/ml di pH 7, also around 100 µg/ml at pH in room temperature, this condition led to slight formulation development of carvedilol [4]. Low solubility results in low carvedilol bioavailability (approximately 25% due to hepatic first pass metabolism) and therefore, repeated oral administration is required and it may reduce patient compliance with drug intake [3, 5, 6].

The low bioavailability of a drug becomes a common obstacle in drug development because in order to achieve optimal therapeutic effects, a drug needs to have high oral bioavailability. Low bioavailability can be caused by several things such as experiencing high first pass metabolism and poor water solubility. Carvedilol has low solubility and thus low bioavailability. In addition, carvedilol has a half time of about 6-8 hours. Therefore, low solubility with small bioavailability becomes a major challenge in the development of carvedilol formulations. There are several techniques performed to address the problem of poor solubility of carvedilol including physical and chemical modifications of the drug, such as increasing particle size, increasing porosity and wettability, and changing shape from crystal to amorph. Furthermore, there are methods used to improve the solubility of carvedilol which are nanosuspension, nanoemulsion**,** dendrimers**,** solid dispersion**,** hydrotropy**,** cocrystallization, liquidsolid technique, cyclodextrin complexation, and nanoparticle. arr[1,7–12].

2. METHOD

The writing of this review article was done by searching the literature first, then the data extraction process was carried out. Key words were arranged consisting of "carvedilol ", "increasing solubility", and "dissolution" in the search column of the Science Direct database. The literature was selected according to the inclusion criteria, namely literature that discusses the drug colon delivery system, evaluations carried out, polymers used, various approaches taken, and articles with a maximum year of publication in the last 10 years. The exclusion criteria are articles that are not in accordance with the topic of discussion and which cannot be fully accessed**.**

The selection of articles is presented in the flowchart image below

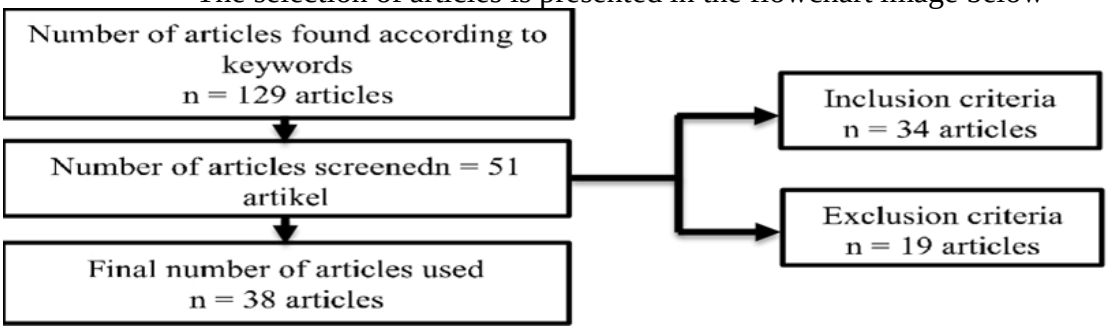


Figure 1: Flow chart or selection of articles

TECHNIQUES TO INCREASE SOLUBILITY OF CARVEDILOL

The method of developing the solubility enhancement of carvedilol which will be discussed in this review is as shown in the flow chart below :

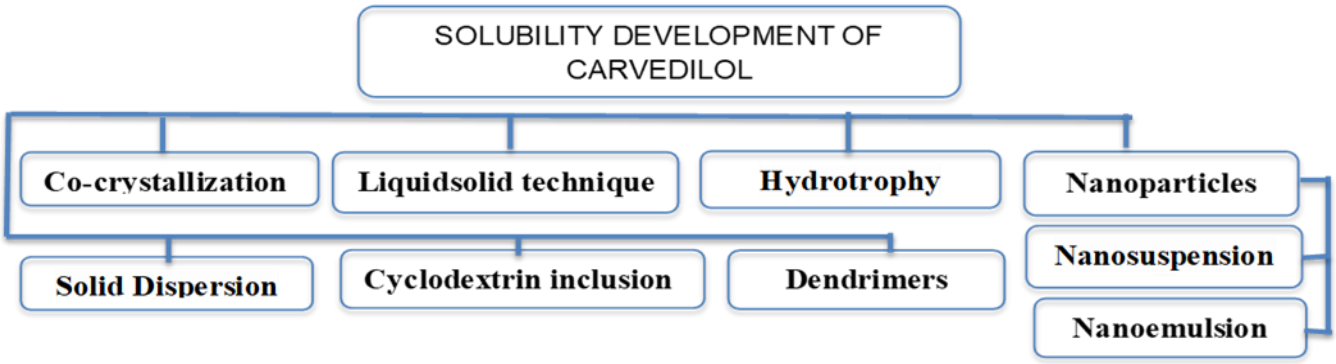


Figure 2. Solubility development methods of carvedilol

2.1 Co-crystallization

Cocrystallization is a technique of crystal engineering through the application of the concept of supramolecules in the pharmaceutical industry. In a chemical supramolecular compound, a supramolecular compound is defined as a compound arranged on two or more components which are mutually bonded or interacted through hydrogen bonds, electrostatic bonds, van der Waals force, pi-pi stacking, as well as other forms of non-covalent bonds. Of all the types of bonds that occur, hydrogen bonds are the most important interaction due to their considerable strength levels [13].

In the formation of a cocrystal, function group which can form a supramolecular synthon bond i.e., a supramolecular heterosynthon and a supramolecular homosynthon are required. Supramolecular heterosynthons are a type of interaction that occurs in two or more different compounds but has the same functional group. Homosynthon supramolecular is an interaction between the same functional group [14].

Cocrystallization methods are already frequently used to improve the solubility of BCS class II drugs such as nifedipine (Reetu *et al*., 2019), glimepiride [15], Atorvastatin calcium [16], phenofibrate [17], and Carvedilol [5,8]. In the cocrystallization technique, it is necessary to add another compound or known as a coformer to form a crystal lattice with carvedilol. There are several coformers reported to have been used in increased carvedilol solubility through cocrystallization namely hydtocholorothiazide [5], nicotinamide [18], fumarate acid, succinic acid, and oxalic acid [8].

Broadly speaking, the multicomponent crystal can be formed using two methods namely solution-based method and solid-based method. Solution-based method comprises 5 methods i.e., solvent evaporation (solvent evaporation), antisolvent method, cooling crystallization, reaction cocrystallization, and slurry conversion. Whereas, the solid-based method comprises contact cocrystallization, neat grinding, liquid-assisted grinding, and mell crystallization [19]. Each technique will be described bellow in brief.

a. Solvent evaporation
   This method represents a simple method by dissolving an active substance and a coformer in a solvent until it dissolves perfectly. Then, the solution is evaporated until the solvent evaporates and a crystal is formed. The selection of solvents on this method is critical because when neither the pharmaceutically active material nor the crystal forming component is very soluble, some components will precipitate which causes the failure of the formation of the cocrystal [20].
b. Antisolvent method
   A method carried out by adding antisolvent so that there is a retardation of the cocrystal until it reaches a saturated passing state and deposition occurs [21].
c. Cooling crystallization

This method involves a cooling process against the mixed solution of the active pharmaceutical ingredient with the coformer [20].

d. Slurry conversion
This method constitutes the formation of a cocrystal by adding an excess cocrystal component to the solvent used. In the method, each component is to be slowly dissolved which forms a complex that causes the formation of a cocrystal [20].

e. Solid-state grinding
Formation of the cocrystal through grinding using a machine such as ball milling (Liquid assisted grinding) or manually (neat grinding) [20].

f. Melt crystallization
This method utilizes high temperature and pressure so that melt is formed on the active pharmaceutical ingridient and coformer [22].

This method has been shown to improve the solubility of carvedilolin several reseraches. One of them was reported in a study conducted by Thenge *et al*, 2020 that cocrystal formation of carvedilol using solvent evaporation with several different coformers such as fumarate acid, oxalic acid, and succinic acid can enchance the solubility and the rate of dissolution significantly compared to pure carvedilol. The results of the characterization of SEM, FT-IR, DSC, and XRD also supported the statement and confirmed that new solid-phase formation occurred. The graph of the increase in solubility and dissolution rate as well as the characterization results can be seen in Figure. 1, Figure. 2, Figure. 3, Figure. 4, Figure. 5, and Figure. 6 respectively.

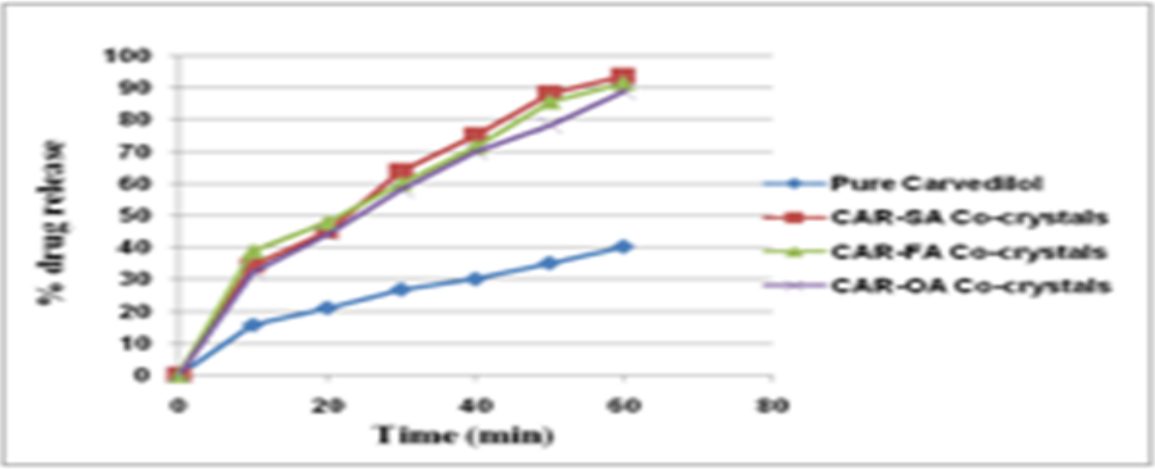


Figure 3: Dissolution profile of pure carvedilol dan Co-crystals

S. No.	Formulation code	Saturation solubility in distilled water (µg/ml)	Increase in solubility
1	Pure Carvedilol	0.376±0.06	--
2	CAR-SA Co-crystals	2.225±0.35	Six fold
3	CAR-FA Co-crystals	1.880±0.20	Five fold
4	CAR-OA Co-crystals	1.128±0.23	Three fold

Standard deviation (n=3)

Figure. 4: Solubility studies of pure carvedilol and Co-crystals

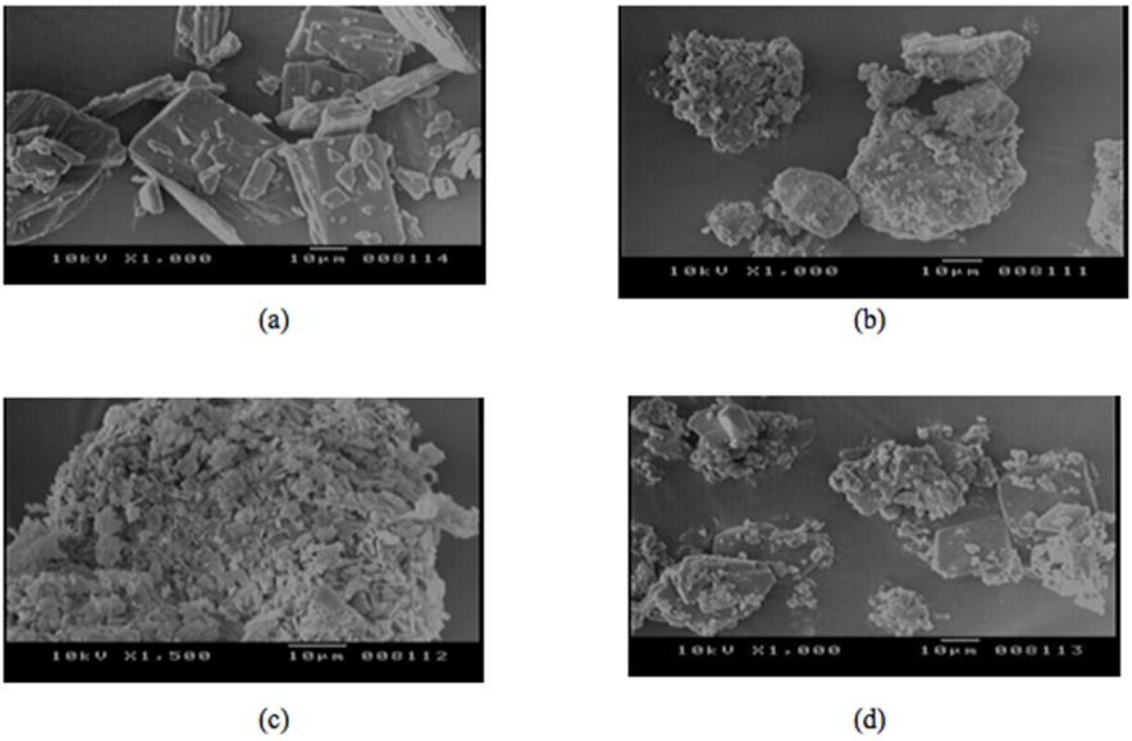


Figure. 5: SEM of pure carvedilol (a), CAR-SA Co-crystal (b), CAR-FA Co-crystal (c), and CAR-OA Co-crystal (d)

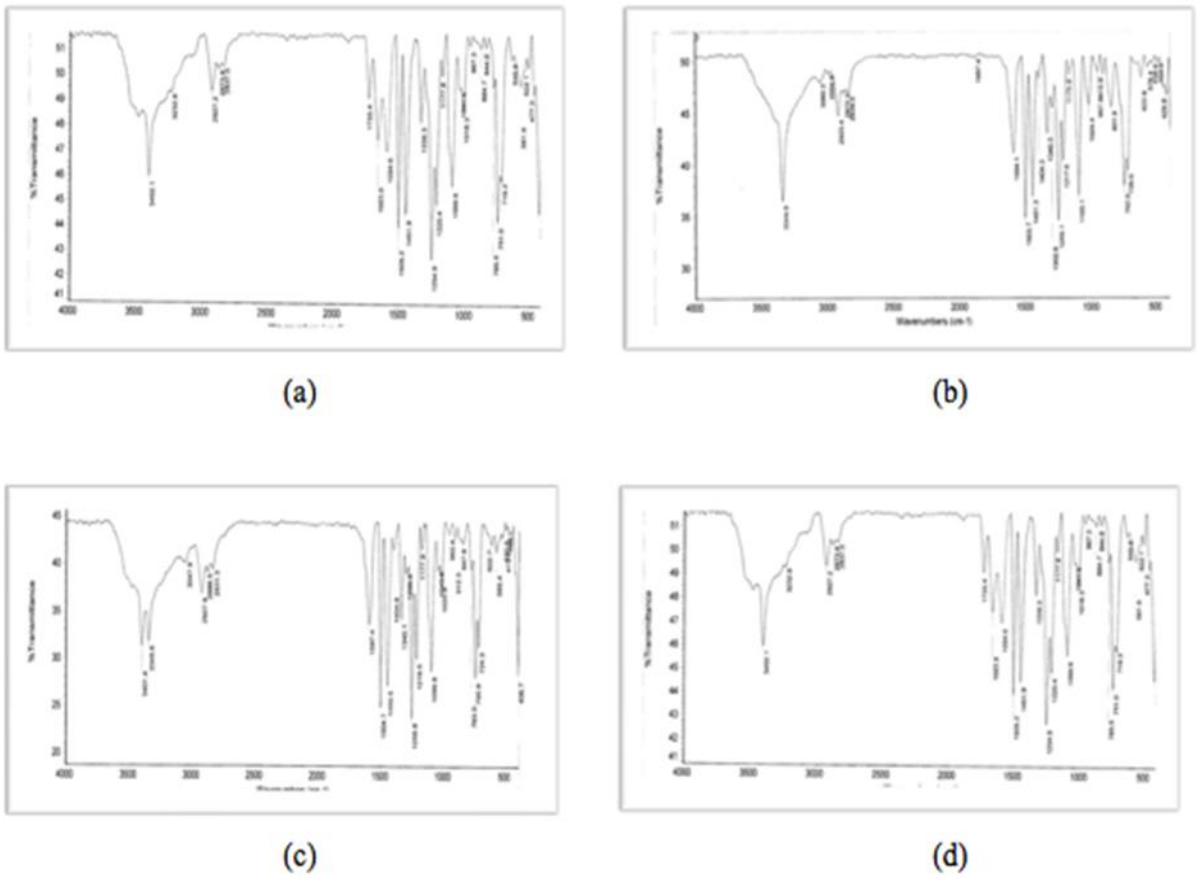


Figure. 6: FT-IR spectra of pure carvedilol (a), CAR-SA Co-crystal (b), CAR-FA Co-crystal (c), and CAR-OA Co-crystal (d)

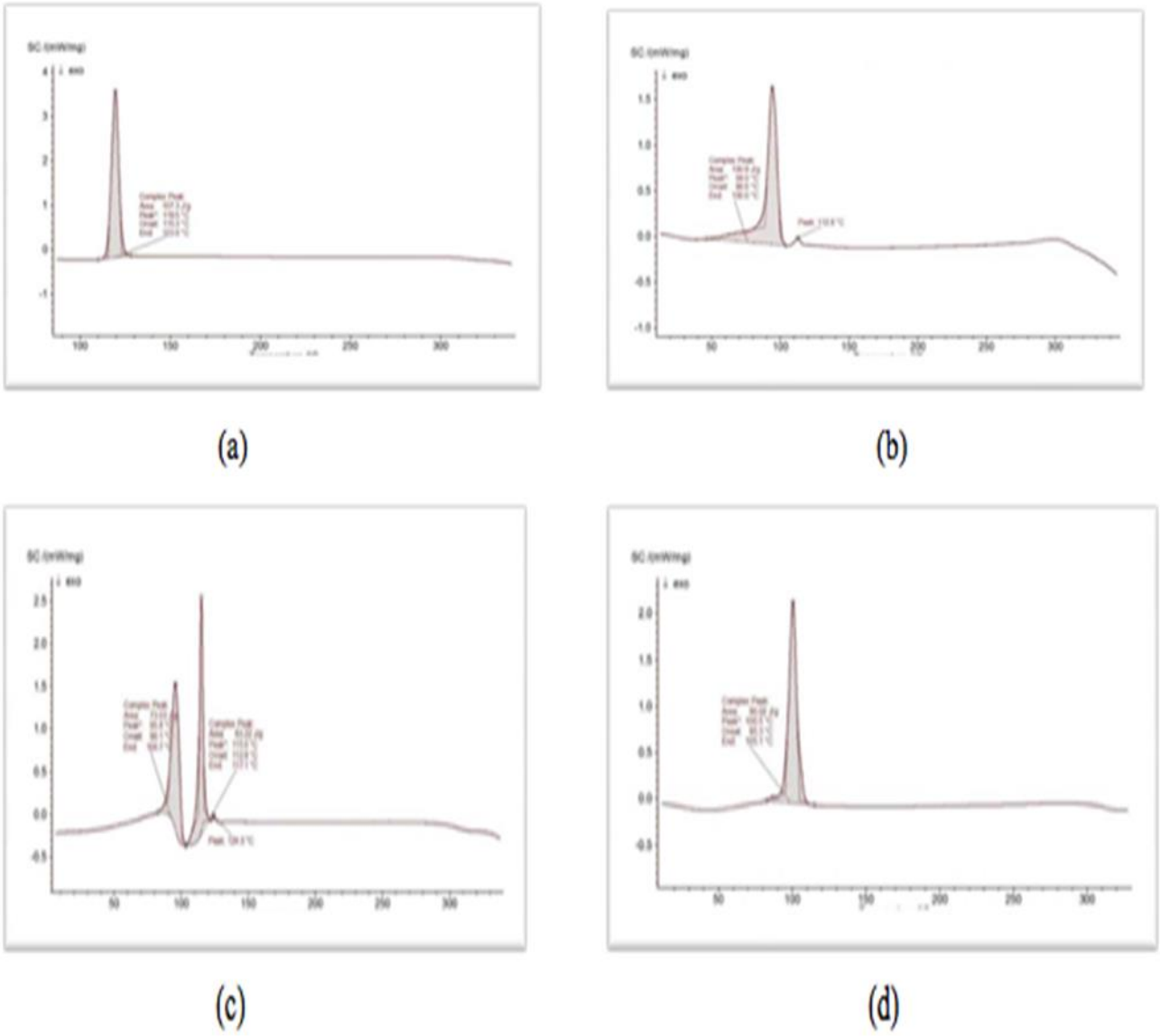
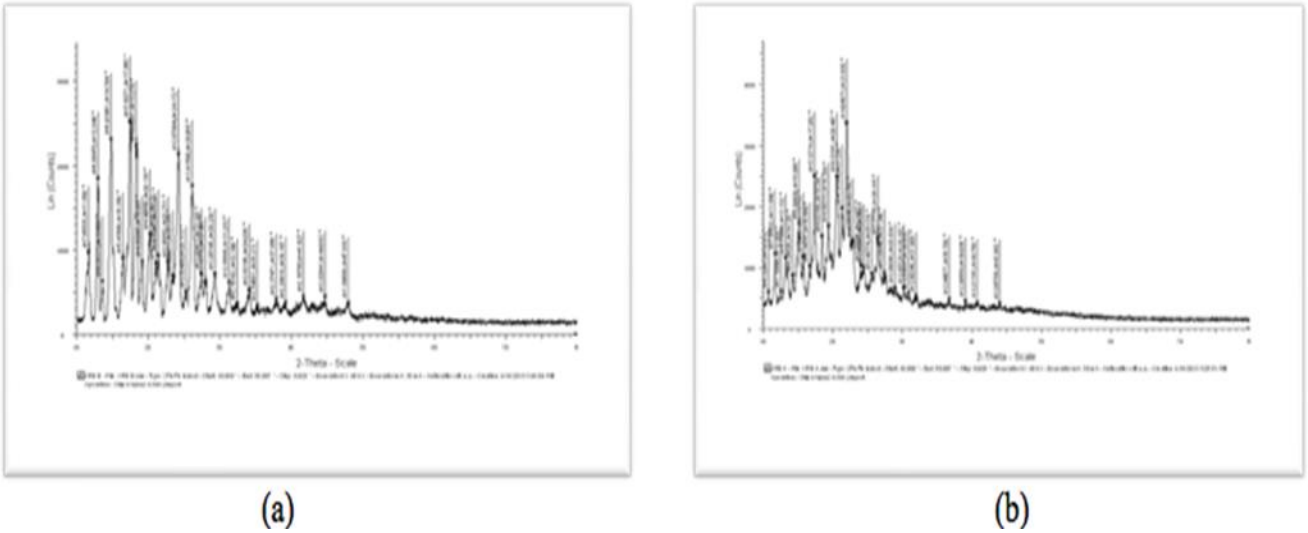
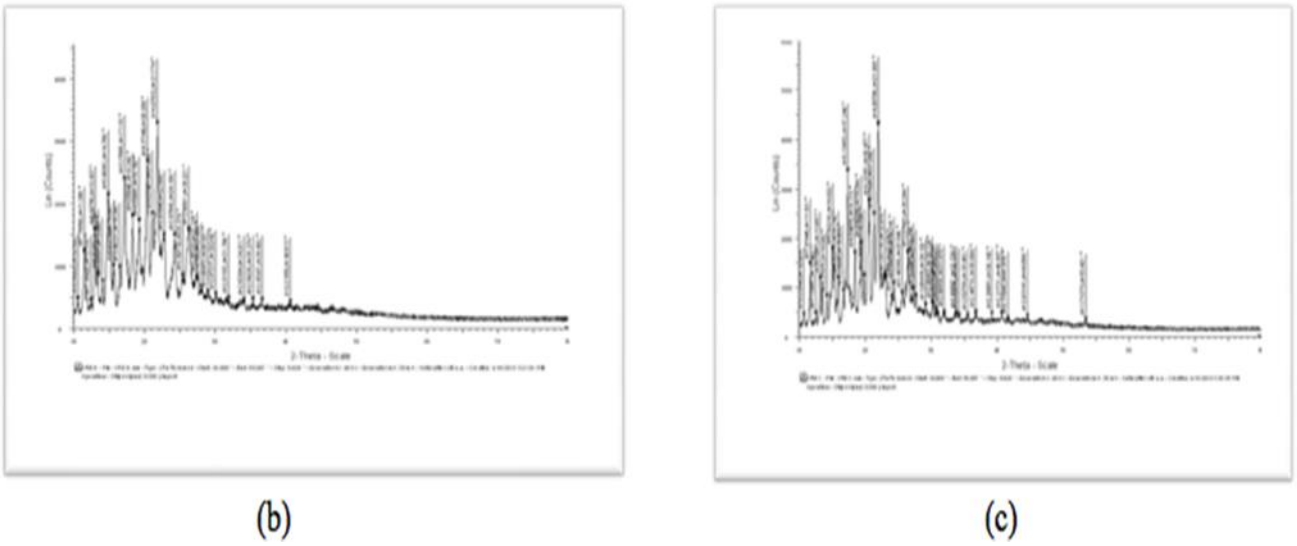


Figure. 7: DSC Thermogram of pure carvedilol (a), CAR-SA Co-crystal (b), CAR-FA Co-crystal (c), and CAR-OA Co-crystal (d)





(b) (c)

Figure.8: XRD spectra of pure carvedilol (a), CAR-SA Co-crystal (b), CAR-FA Co-crystal (c), and CAR-OA Co-crystal (d)

2.2 Liquidsolid technique

The technique comprises changing liquid lipophilic drugs or suspension or water-insoluble drug solutions in non-volatile solvents into dry, nonadherent, powder-ready compressible through mixing with carrier agent or coating agent. As for the concept of this technique, when a drug soluble in a carrier solution is incorporated into a carrier having pore or textured fiber as cellulose then absorption and adsorption will occur (Bhavsar and Anand, 2017)

The following are the preparations performed on this technique:

a. Liquid formulation: Obtaining the liquid medicine (drug dispersion in a non-volatile solvent) and then added with a carrier material, a disintegrating/coating agent so that a liquid system is formed

b. Pelletization process: Performed by addition granulating agent into the liquid-solid system and then carried out the excretion-spheronization stage and put into fluid bed drying so that pellets are produced for further analysis (Bhavsar and Anand, 2017)

In a study conducted by Bhavsar and Anand, 2017. the pellet formulation concsits of carvedilol, crosspovidone (coating agent and disintegrating agent), PEG 400 as a nonvolatile solvent, copovidone (wetting agent), and microcrystalline cellulose/avicle (carrier material). Through this study, it was proved that through the technique of liquidsolid with PEG400 as a non-volatile solvent can improve the solubility and dissolution rate of carvedilol. The drug release profile in Figure. 7 showed that pellets of the liquid system had a higher dissolution percentage (96.51%) compared to market carvedilol drugs (79,36%).

This might happened because in the pellet of the liquid system, the drug is already in the form of a solution in PEG400 and at the same time, it is carried by the microcrystalline cellulose, thus increasing the dissolution rate due to the increasing of wettability and surface avaibility against the dissolution medium.

SEM results on Figure. 8 indicates that the particle in pellet exhibits the shape of a sphere with a smooth surface and the formation of several agglomerates.

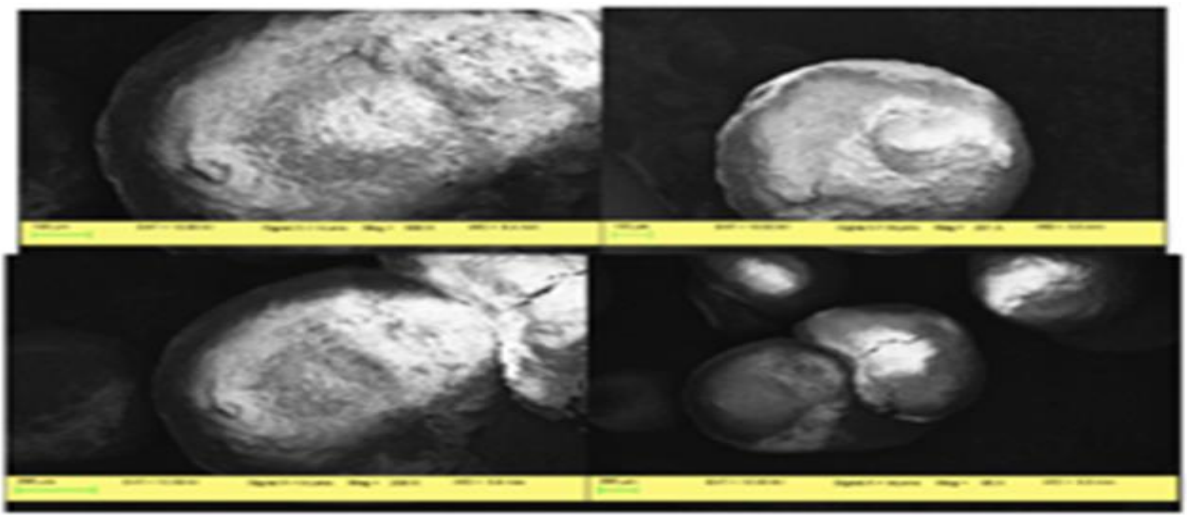
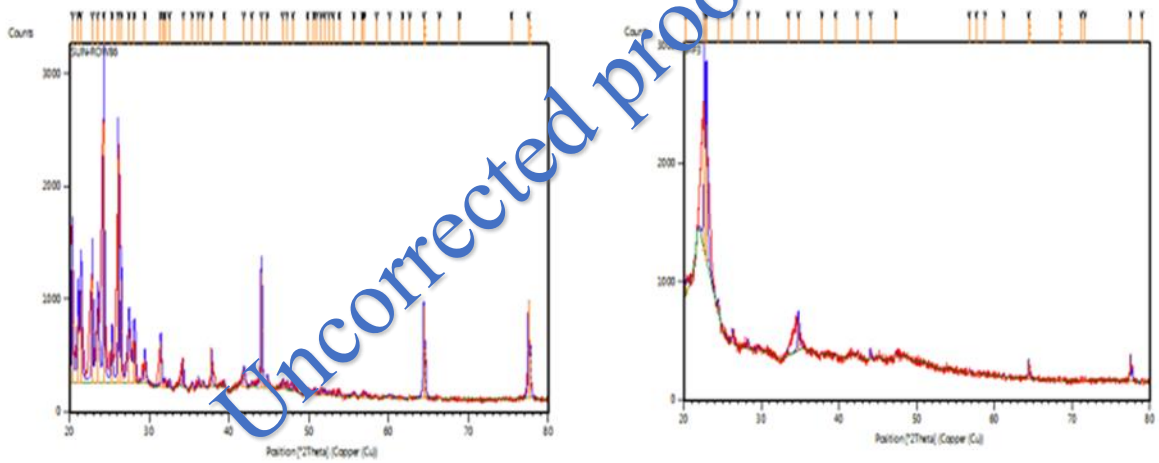


Figure 9: SEM of liquidsolid pellets

XRDP results (Figure.9) indicate that there are several missing peaks or a decrease in peak intensity in the liquid pellets of carvedilol compared to pure carvedilol. Therefore, it is concluded that the carvedilol liquid pellet has an amorphous shape.



(a) (b)

Figure. 10: Difractogram of pure carvedilol (a) and liquidsolid pellets (b)

2.3 Cyclodextrin inclusion complex

Cyclodextrin is a cyclic (1-1,4)-oligosaccharide of cider d-D-glucopyranose, which is relatively hydrophobic at its center and has the hydrophilic outer surface. sik-cyclodextrin is used to denote the solubility of the drug by formation of an inclusion complex [9]. ---cyclodextrin and its derivatives (2-hydroxypropyl- ---cyclodextrin or HP hp-CD and sulfobutyl ether- cyclodextrin or SBcd-CD) constitute are the most commonly used compounds in inclusion complications [23](Wang *et al*., 2011; Xu *et al*., 2014; Wang *et al*., 2014).

This method is known to have several benefits such as improved solubility, bioavailability, stability, and preventing incompatibility. Formation of cyclodextrin complexes can be performed by several methods such as spray drying, kneading, grinding, solvent

evaporation, co-precipitation, microwave irradiation, and freeze drying [24]. Each technique will be described bellow.

a. Spray drying

This method is also known as atomization which will form dry powder from liquid with the help of hot gas.

b. Freeze drying

This approach creates porous amorphous powders with a high degree of drug-cyclodextrin interaction. The drug and cyclodextrin are added to the solvent and then freeze-dried in this technique. At the start of the freezing process, the solvent system will be removed, and drying will occur when the pressure is reduced. This technique is frequently used as a substitute for solvent evaporation.

c. Kneading

A method is performed by forming a cyclodextrin paste through the addition of water or hydroalcoholic solution and then followed by the addition of a pharmaceutical active ingredient which is then kneaded. The kneaded products will be sieved to obtain fine powder (Ünlüsayin *et al*., 2015).

d. Grinding

The active ingredients of the drug and cyclodextrin will go through a grinding process to obtain a fine mixed powder. The product will be stored in a container at room temperature.

e. Co-precipitation

This method is performed by adding the drug to the cyclodextrin solution slowly accompanied by continuous magnetic agitation. The complex will precipitate, then be filtered and dried at room temperature.

f. Microwave irradiation

Because it saves time, this technology is most commonly utilized in industrial environments. The drug and cyclodextrin will be dissolved in a solution of water and an organic solvent, then microwaved at 60 degrees Celsius to react. The remaining solvent mixture will be added once the reaction is finished to remove uncomplexed drugs and cyclodextrin, and the sediment will be filtered and dried.

g. Solvent evaporation

This method represents a simple method by dissolving active substances and cyclodextrin in a solvent until it is perfectly soluble. Then, the solution is evaporated until the solvent evaporates and a complex is formed [20].

Research by Zoghbi *et al*., 2017 showed a significant increase in solubility by approximately 22 to 70-fold in inclusion complexes using hydroxypropyl---cyclodextrin (HPcdCD) with solid dispersion using two carriers: polyoxamer 188 (PLX) and Polyvinylpyrrolidone K-30 (PVASI) preparation (PVASI) [9].

2.4 Nanoparticles

Nanotechnology drug delivery system is one of the drug administration system that is considered effective, especially for lipophilic drugs. Nanoparticles are a drug delivery system that is considered to increase the oral bioavailability of carvedilol [25]. Micronization of drug crystals by various mechanisms to a lower size can increase drug dissolution. According to the Noyes-Whitney

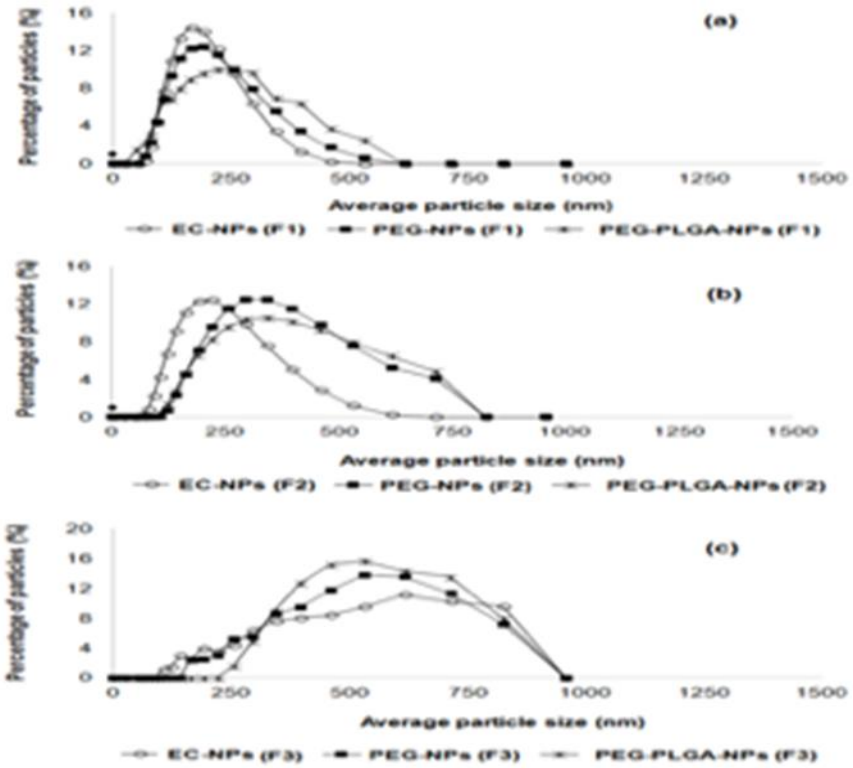
equation, the dissolution rate increases with an increase in the specific surface area. According to the Ostwald-Freundlich equation, solubility increases with decreasing particle size. The preparation of nanoparticles can be carried out as follows:

a. Ionic gelation
b. Polymerization of monomers seperti emulsion, microemulsion, dan miniemulsion
c. Dispersion of performed polymer

The methods included in this preparation are evaporation solvent, diffusion solvent, salting out, nanoprecipitation, supercritical fluid technology, and dialysis [18,25,26].

Research by Sharma *et al*., 2019, showed that carvedilol-chitosan nanoparticles with sodium tripolyphosphate as a cross-linking agent using ionic gelatin methods can increase in vivo bioavailability compared to market drugs. Carvedilol-chitosan nanoparticles are characterized for particle size, morphology, zeta potential, FTIR, encapsulation efficiency, In vitro drug release studies, pharmacokinetic studies, gastric mucosa irritation tests, drug entrapment efficiency tests, and stability tests. The zeta potential of the carvedilol-chitosan nanoparticles shows +32 mV 2 2 mV which showed physical stability and mucoadhesive where the higher the value then the stability will also increase and it's prevents aggregation of the particles [26].

In addition, studies by Khan *et al*., 2016 also showed an increase in the solubility and dissolution rate in carvedilol preparation nanoparticles using poly lacetic co glycolic acid (PLGA), polyethylene glycol 8000 (PEG 8000), and ethyl cellulose in differential ratio (1:1, 1:2.5). Carvedilol nanoparticles are characterized for particle size, entrapment efficiency, zeta potential, polydispersity index, and percent drug loading. Based on research results, it showed that increasing particle size will increase polymer concentration also where the highest is on carvedilol-PLGA-PEG (Figure. 10).



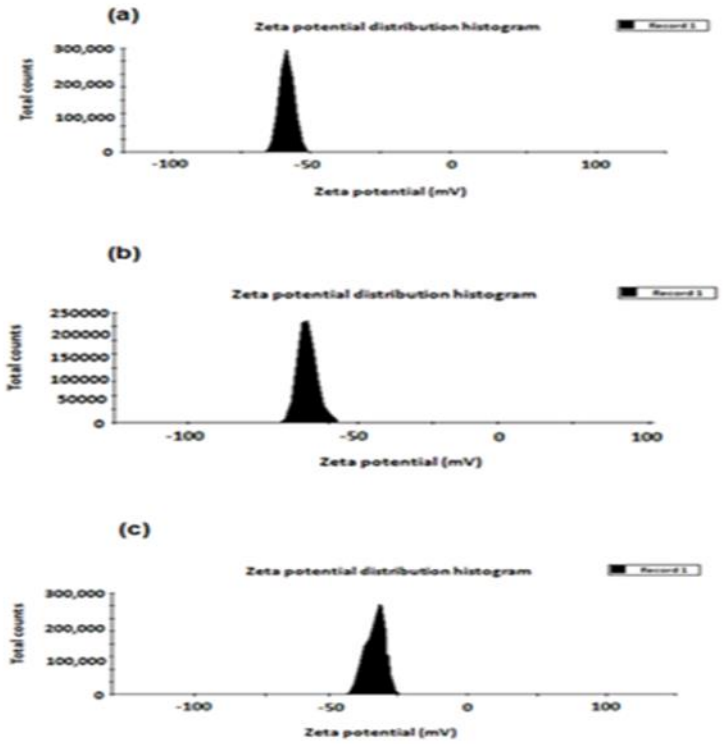


Figure.11: Particle size (a) and zeta potensial of nanoparticles (b)

Carvedilol-PLGA-PEG showed the highest potential zeta yield so it was concluded that there was an increase in colloidal stability. The results of the in vitro dissolution test in Figure.11 showed maximum drug release of 95% in 24 hours on nanoparticles using ethyl cellulose, 85% for PEG nanoparticles, and 65% for PLGA-PEG nanoparticles [10].

2.5 Hydrotrophy

Hydrotropy is a technique that was first introduced by Neubeurg (1916) in which a large amount of the second solute is dissolved into the first solute so that it will increase the solubility of the first solute [26]. In this technique, a hydrotrope, which is an ionic organic salt of various types of organic acids such as urea and sodium acetate, is used. Hydrotrope has two sides in its structure, namely an anion group that plays a role in increasing solubility in water and an aromatic ring group. The mechanism of action of hydrotrope is to involve the interaction between lipophilic drugs and hydrotropic agents such as nicotinamide, urea, and sodium alginate [18,27].

Chikhle *et al*., 2016 conducted a study to increase solubility using this technique to increase the solubility of carvedilol in which the hydrotropic dispersion method used sodium benzoate, nicotinamide, and sodium citrate in a ratio of 20:15:5 dissolved in water. The results of this study showed that the dissolution rate of the hydrotropic solid dispersion product of carvedilol (99%) was increased compared to market carvedilol.

2.6 Nanosuspension

Nanosuspension is a method in which a dispersion solution containing a pharmaceutical active ingredient or drug is stabilized with a surfactant or polymer. There are several methods used to form nanosuspensions, namely high-pressure homogenization, melt emulsification where the drug is dispersed in an aqueous solution and stabilizer then goes through a heating and cooling process, emulsion diffusion method where the drug is dispersed in an organic solvent and homogenized to form an emulsion, and media milling [28].

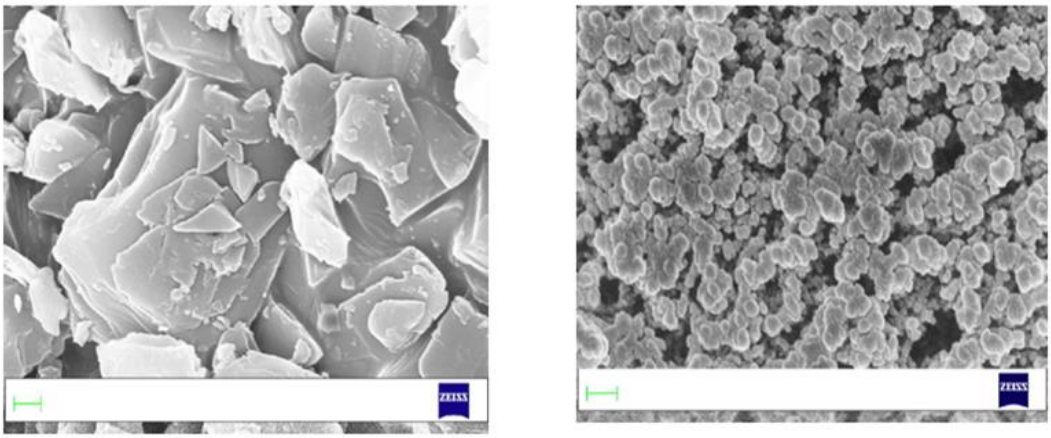


Figure. 12: SEM micrographs of pure carvedilol (a) and nanosuspensions (b)

Carvedilol nanosuspension studies were conducted on four formulations where the carvedilol nanosuspension showed the highest dissolution profile of 90% for 60 minutes compared to pure carvedylol which was 40% at pH 1 [28].

Studies on intestinal absorption performed in situ in wister rats and in vivo in beagle dogs showed an increase in carvedilol nanosuspension compared to pure carvedilol. This study concluded that the formation of carvedilol nanosuspension may improve the profile of dissolution and oral absorption.

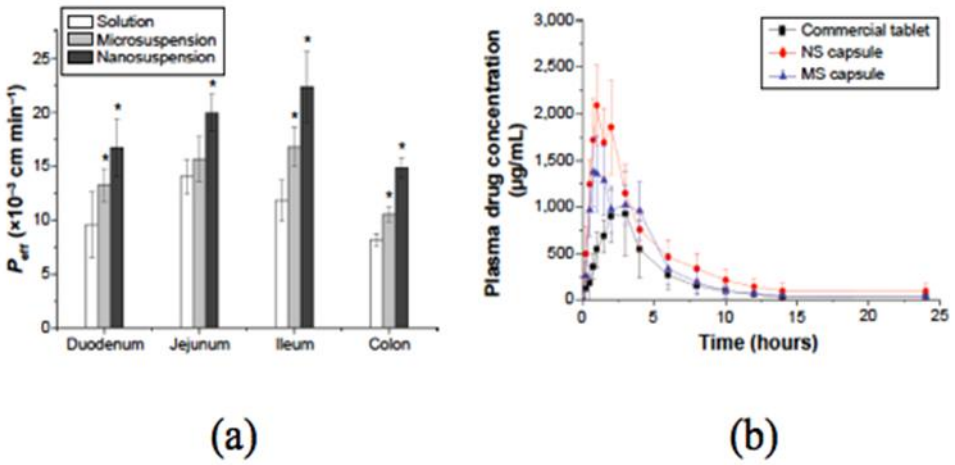


Figure. 13: In situ absorption (a) and Pharmacokinetics study (b)

2.7 Solid Dispersion

Solid dispersions can be defined as solid products in which the hydrophobic drug is dispersed in a hydrophilic matrix, either in an amorphous, and/or molecularly microcrystalline form. The hydrophilic matrix, also known as the carrier, affects the characteristics of the solid dispersion formulation. Solid dispersion techniques have been widely used to increase the solubility of drugs that are poorly soluble in water so as to increase the dissolution rate, absorption and therapeutic efficacy of drugs in oral dosage forms. In this technique, the drug is completely dispersed in a hydrophilic carrier by various methods [29,30].

The following are some of the advantages of solid dispersion techniques:

a. In solid dispersion, the particle size of the drug is reduced to a smaller size thereby increasing the surface area which can increase the solubility and dissolution rate of the drug.

b. The form of the drug is changed from a crystalline form to an amorphous form which has a higher energy level so that it is more soluble.
c. The wettability of the drug particles is increased by the dissolved carrier so that it will increase the solubility of the drug.
d. Solid dispersion can increase the porosity of drug particles depending on the nature of the carrier so as to increase the drug release ability.
e. The interaction between the drug and the carrier can reduce aggregation and agglomeration as well as the release of drug particles in a saturated state so as to produce rapid absorption and can increase drug bioavailability.

However, in addition to the advantages of solid dispersion, there are also some disadvantages of solid dispersion techniques:

a. Physical instability.
b. Solid dispersions showed a change in crystallinity and decreased dissolution rate with the length of storage time.
c. Thermodynamic instability so that the solid dispersion is sensitive to humidity and temperature during storage which can cause phase separation and crystallization.
d. The instability of the solid dispersion during storage time can have an impact on drug quality and treatment effectiveness [31,32].

Solid dispersions can be prepared by various methods, including:

a. Melting/fusion method
This method involves directly heating a drug and a hydrophilic carrier until they melt at a temperature slightly over their eutectic temperature, resulting in a physical combination. The melt is then cooled and rapidly solidified in an ice bath while being stirred. The resulting solid mass is crushed and sieved (Pankaj and Prakash, 2013; R. Sharma *et al*., 2013).
b. Solvent evaporation method
The solvent evaporation method is a typical method for producing solid dispersions in the pharmaceutical industry, in which the drug and carrier are dissolved in a volatile solvent. The solvent was then evaporated while being constantly agitated. After that, the solid dispersion was crushed and sieved (Pankaj and Prakash, 2013; R. Sharma *et al*., 2013).
c. Melt evaporation
This method is a combination of melting and solvent evaporation methods. The principle of this method is that the drug is dissolved in a suitable solvent and then introduced into the carrier melt. The mixture is then evaporated to dryness [31,32].
d. Melt agglomeration process
In this method the binder acts as a carrier. There are two ways of making solid dispersions, the first is by spraying the drug dispersion on the melted binder. The second method is that the drug, binder and other excipients are heated above the melting temperature of the binder used to form agglomerates [31,33].
e. Hot-melt extrusion method
The HME method is carried out by a combination of smelting and extruder methods, in which a homogeneous mixture of drugs, polymers, and plasticizers is melted and then extruded. The shape of the product can be controlled in the extruder so that it does not require milling in the final step [32].
f. Freeze-drying
In this method the drug and carrier are dissolved in a common solvent then the solution is frozen and sublimated in liquid nitrogen to form a lyophilized molecular dispersion [34].
g. Electrospinning method
This method is a combination of solid dispersion and nanotechnology. In this method, solid fibers are produced from a stream of polymer liquid or melt delivered through a millimeter-scale nozzle [32,33].

h. Co-precipitation
In this method, the carrier is dissolved in a solvent then the drug is introduced into the solution with stirring to form a homogeneous mixture. Then, water is added dropwise to the homogeneous mixture to induce precipitation. The precipitate formed is then filtered and dried [32].

i. Supercritical fluid technology
The drug and carrier are dissolved in a supercritical solvent (e.g., CO2) and sprayed through a nozzle into a lower-pressure expansion vessel. The fast expansion causes the drug and solute carrier to nucleate quickly, resulting in the creation of solid dispersion particles with the required size distribution in a short amount of time [32].

j. Spray-drying method
To prepare the feed solution, the drug is dissolved in a suitable solvent and the carrier is dissolved in water. The two solutions are then blended together using sonication or another suitable process until the solution is transparent. The feed solution is sprayed into fine droplets in a drying chamber using a high-pressure nozzle during the procedure. Droplets of drying fluid (hot gas) are generated, forming nano or micro-sized particles [32,33].

k. Kneading method
The carrier is dispersed in water or an organic solvent and processed into a paste in this procedure. Then it's mixed with the drug and kneaded until it is completely homogenous. The uniform mixture is next dried and, if necessary, sifted [32,33].

l. Co-grinding method
In this procedure, the drug powder and carrier are precisely weighed and then blended for a period of time at a specific speed in a blender. The slurry is then put into the grinding chamber of a vibrating ball mill (Pankaj and Prakash, 2013).

This solid dispersion technique has been widely used in an effort to increase the solubility of a drug, especially carvedilol. For example, a study conducted by Yuvaraja and Jasmina (2014) showed an increase in water solubility up to 353 times in the ionized solid dispersion of carvedilol: HP□CD: tartaric acid (1:3:0.75) when compared to pure carvedilol. The increase in solubility also occurred in other solid dispersions with CD, PVP K-30, HP□CD, PLX-407, and tartaric acid as carriers at various mass ratios. In addition to the increase in solubility in water, this study also showed an increase in the solubility of carvedilol in various pH variations, namely at pH 1.2, 6.8, and 7.4, which can be seen in Figure. 15.

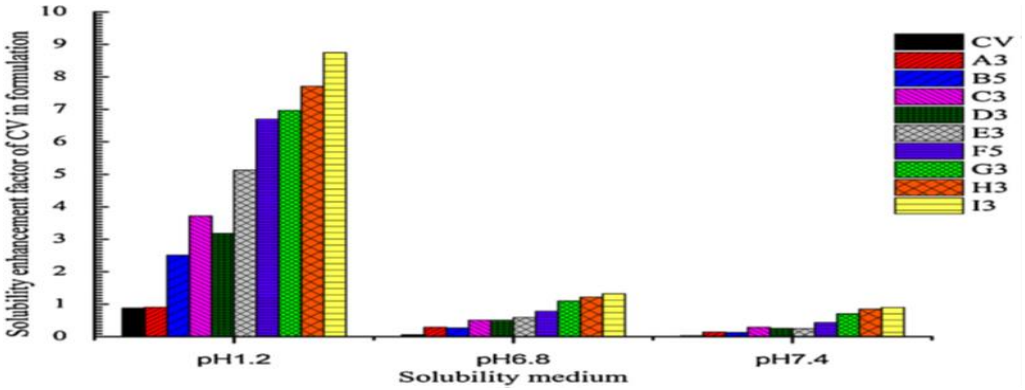


Figure. 14: Solubility enhancement factor of carvedilol in formulation at different pH [33]

An increase in the dissolution rate at various pH variations was also observed (Figure. 16). In this study, evaluations were also carried out in the form of FTIR, XRD, DSC and SEM tests. The FTIR spectrum (Figure. 17) showed a significantly different intensity and band shape in the solid dispersion when compared to pure carvedilol and the physical mixture, these

results allow physical interaction (physical association) between carvedilol and cyclodextrin. Diffractograms of solid dispersions CV:HP□CD:TA:PVP K-30 (1:3:0.75:0.03) and CV: HP□CD:TA (1:3:0.75) (Figure. 18) showed that carvedilol is no longer present as a crystalline substance, and drug molecules are molecularly scattered in carrier domains, with solid complexes existing in an amorphous state, as indicated by a halo with an amorphous appearance. It suggested the establishment of a CV-HP□CD inclusion complex.

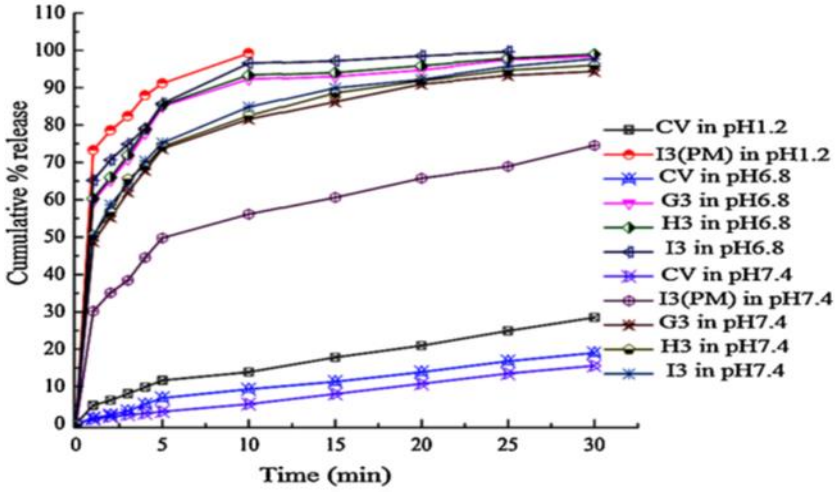


Figure. 15: Carvedilol dissolution in various pH mediums from various formulations [33]

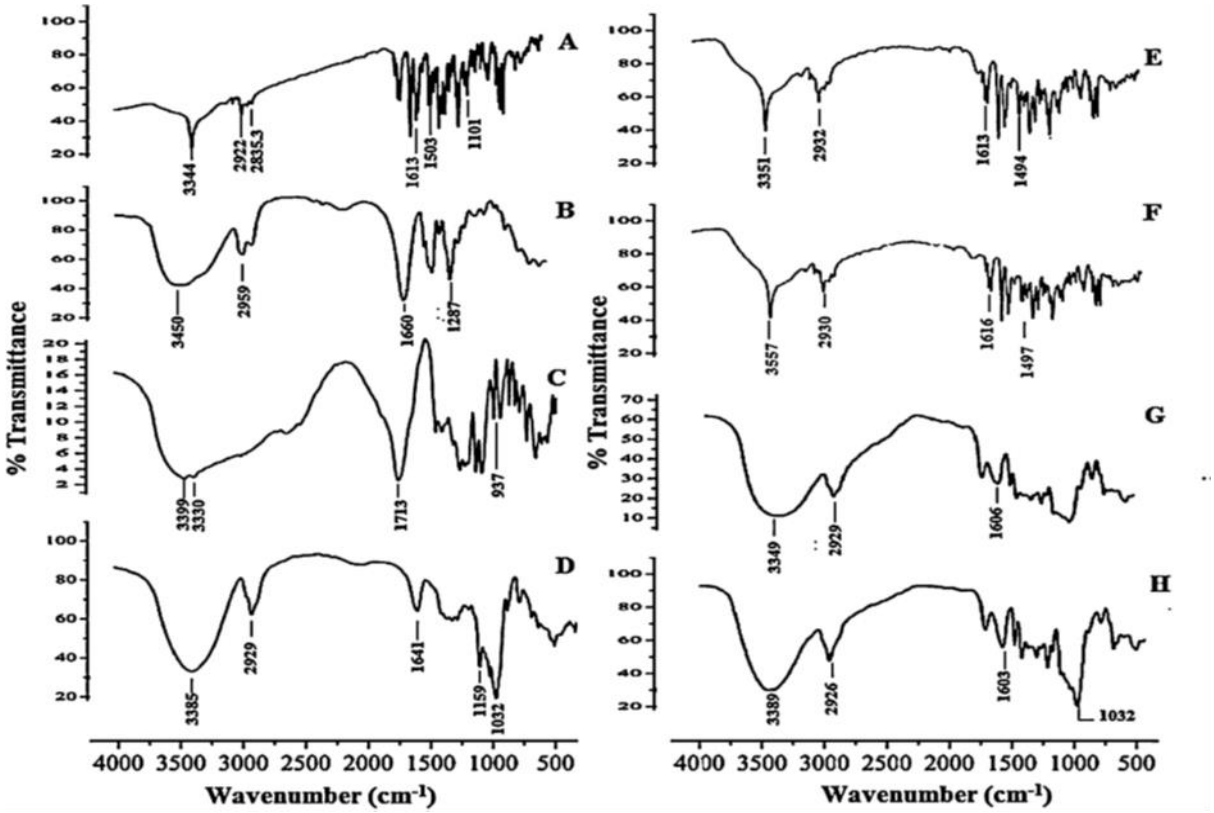


Figure. 16: FTIR spectrum of carvedilol (A), PVP K-30 (B), tartaric acid (C), HP□CD (D), physical mixture of CV:HP□CD:TA:PVP K-30 (E), physical mixture of ionized CV: HP□CD:TA (F), solid

dispersion of CV:HP□CD:TA:PVP K-30 (G), and solid dispersion of ionized CV: HP□CD:TA (H) [33]

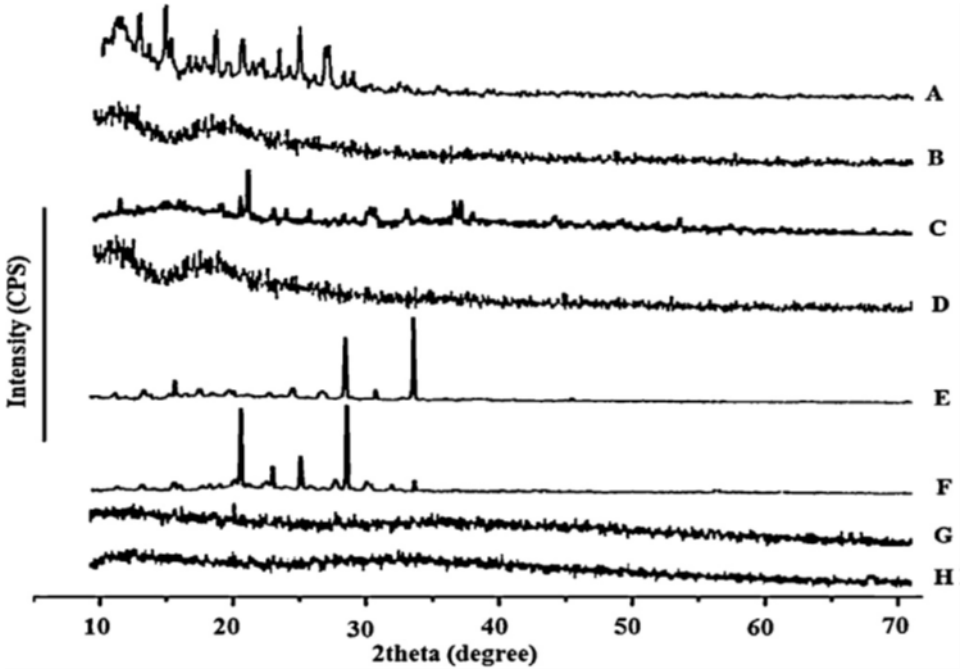


Figure. 17: XRD of carvedilol (A), PVP K-30 (B), tartaric acid (C), HP□CD (D), physical mixture of CV:HP□CD:TA:PVP K-30 (E), physical mixture of ionized CV: HP□CD:TA (F), solid dispersion of CV:HP□CD:TA:PVP K-30 (G), and solid dispersion of ionized CV: HP□CD:TA (H) [34]

The removal of the endothermic peak of carvedilol corresponding to its melting point was seen in thermograms of solid dispersion systems (Figure. 17). It could be because of its perfect homogenous dispersion within the carrier and amorphization caused by overcoming crystal lattice energy, followed by hydrogen bond binding within the amorphous carrier HP□CD. This fact showed that an amorphous inclusion complex had formed. The amorphization of the drug, as indicated by FTIR, XRD, and DSC tests, is an indicator of its amorphization and creation of an amorphous inclusion complex between carvedilol and carriers, resulting in an increase in the drug's solubility. Thus, the change of the drug's crystalline state to an amorphous state may be responsible for the improved solubility of poorly soluble carvedilol. The SEM results of the solid dispersion (Figure. 18) appear as a uniform mass and homogeneously mixed with a wrinkled surface. This may be due to the homogeneous dispersion of the drug in the carrier.

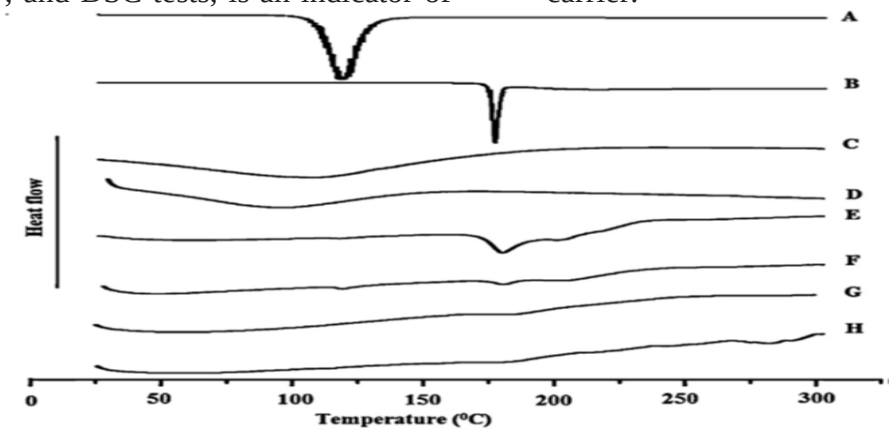


Figure. 18: DSC of carvedilol (A), PVP K-30 (B), tartaric acid (C), HP□CD (D), physical mixture of

CV:HP□CD:TA:PVP K-30 (E), physical mixture of ionized CV: HP□CD:TA (F), solid dispersion of CV:HP□CD:TA:PVP K-30 (G), and solid dispersion of ionized CV: HP□CD:TA (H) [34]

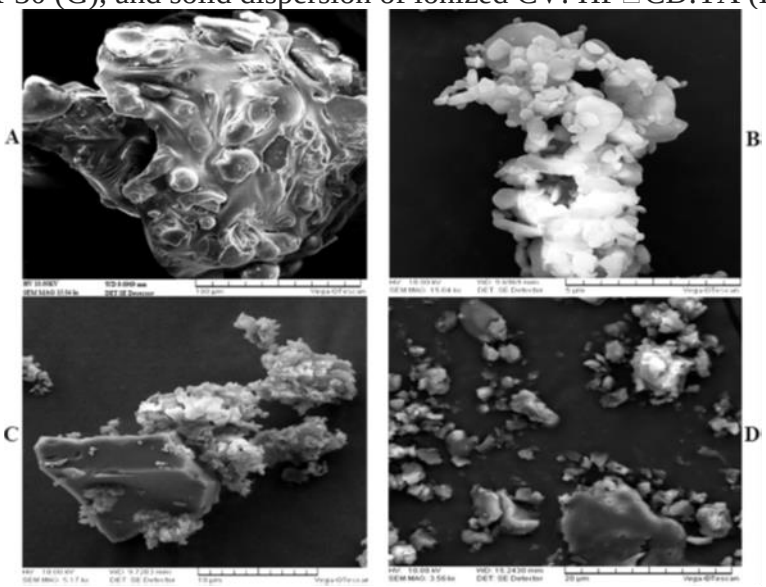


Figure. 19: SEM of HP□CD:TA (A), carvedilol (B), physical mixture of ionized CV: HP□CD:TA (C), solid dispersion of ionized CV: HP□CD:TA (D) [34]

2.8 Nanoemulsion

The name 'Nanoemulsions' refers to emulsions with internal phase droplets ranging in size from 50 to 1000 nanometers[1]. Nanoemulsions are nanodispersed systems that can be a safe choice for the creation of new pharmaceutical and cosmetic formulations due to their relatively high physical stability and acceptable aesthetic appeal. They are made up of an oil phase, an aqueous phase, a surfactant, and a cosurfactant in the proper proportions. The particles can exist in two forms: water in oil and oil in water, with the core of the particle being either water or oil. Low interfacial tension is accomplished by adding a co-surfactant to nanoemulsions, resulting in the spontaneous production of a thermodynamically stable nanoemulsion. Nanoemulsions, with their high kinetic stability, low viscosity, and transparency/translucency, are ideal for a variety of industrial applications, including drug administration [35].

Chidi *et al*., 2017 used an aqueous phase titration method to make carvedilol nanoemulsion. The solubility of carvedilol in various oils (capryol 90, isopropyl myristate, oleic acid, olive oil, sunflower oil, clove oil, linseed oil) was used to choose the oil with the highest solubility, while percentage transparency and ease of emulsification were used to choose the surfactant (tween 20 and tween 80) and cosurfactant (transcutol P, propylene glycol, PEG 400, and glycerol). After extensive testing, clove oil, tween 20, and PEG 400 were chosen as the oil, surfactant, and cosurfactant, respectively. The research was conducted with various formulation of the S_{mix} ratio as can be seen in table 1. Characterization which includes centrifugation test, freezing-thawing test, heating-cooling test, particle size and zeta potential (ZP) measurement, poly dispersity index (PDI) assay, determination of pH, refractive index, viscosity, drug content, in vitro drug release studies, kinetic models and drug release mechanism, and statistical analysis were carried out on nanoparticles. The carvedilol nanoemulsion formulation of batch NEC4 (S_{mix} Ratio 1:3) was proven to be the best formulation based on several in-vitro release studies (Figure. 20). Low particle size, low viscosity, and high percentage transmittance were all found in the optimized formulation. The present investigation clearly demonstrated the utility of nanoemulsion in improving carvedilol solubility, dissolving rate, and, as a result, oral bioavailability.

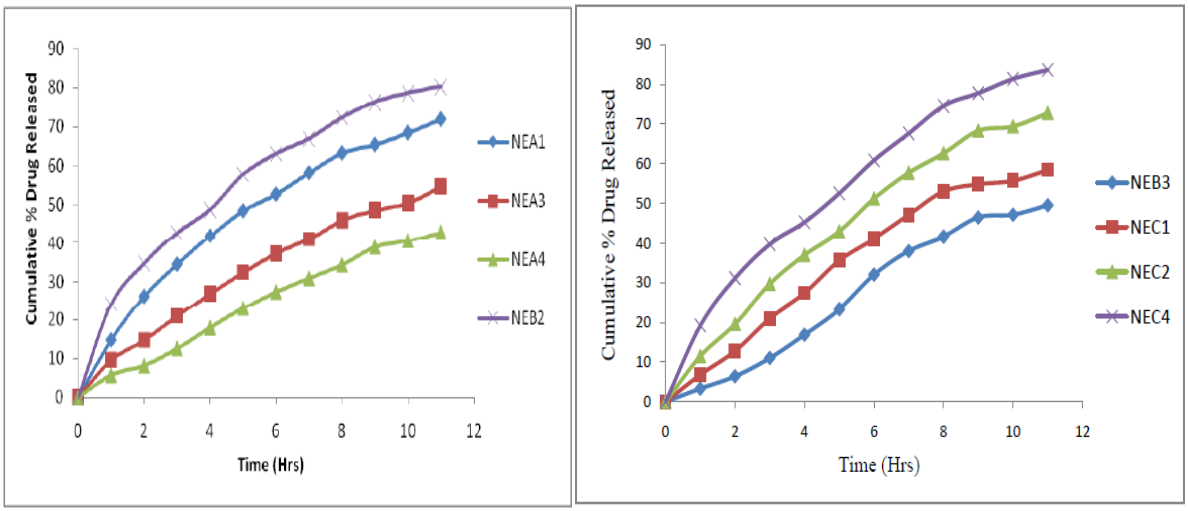


Figure 20. In vitro dissolution profiles of carvedilol nanoemulsion formulations [35]

2.9 Dendrimers

Dendrimers first introduced by Vogtle in 1978, are an unique and efficient nanotechnology platform for drug delivery. Dendrimers range in size between 1 and 100 nm with three distinct domains: (i) a core, which is centrally located containing atoms or molecules with at least two identical chemical functions; (ii) branches, which are repeating units in a geometric series leading to radially concentric layers known as "generations"; and (iii) a terminal functional group, on the surface which determines the nature of the dendrimer. Dendrimers are highly branched, well-organized nanoscopic macromolecules (typically 5000-500,000 g/mol), have a low polydispersity index and have shown an important role in the emerging field of nanomedicine. Dendrimers have garnered a lot of attention in biological applications due to their high water solubility, biocompatibility, polyvalence, and precise molecular weight. Because of these properties, it's a great medication delivery and targeting vehicle. Solubility is influenced by dendrimer concentration, pH, generation size, core, terminal functionality, and temperature. Different types of dendrimers are available based on different polymers such as polyamidoamine (PAMAM), polyamines, polyamides (polypeptides), poly(aryl ethers), polyesters, carbohydrates, and DNA [36–38].

In a study conducted by Zheng *et al* (2013) effectively synthesized carvedilol PAMAM-multiwalled carbon nanotubes using the divergent growth technique for dendrimer assembly. Carvedilol was incorporated into the dendrimer using three ways: fusion, incipient wetness impregnation, and solvent approaches. The dissolving results revealed that the samples created using the fusion approach disintegrated faster than those created using the incipient wetness impregnation method. Additionally, the items made with the solvent technique had the slowest drug release. However, all of the samples created with PAMAM-MWNTs significantly increased the solubility of carvedilol. From the molecular form, the physicochemical characterization revealed the distribution of carvedilol inside and outside the PAMAM-MWNTs. On poorly water-soluble medicines, the new drug delivery system may provide a potential advantage in terms of improved dissolution and drug-loading capacity.

3. CONCLUSION

The low bioavailability of a drug becomes a common obstacle in drug development because in order to achieve optimal therapeutic effects, a drug needs to have high oral bioavailability. Carvedilol has low solubility and thus low bioavailability. Various solubility enhancement techniques have been applied to carvedilol,

including co-crystallization, liquidsolid technique, cyclodextrin inclusion complex, nanoparticles, hydrotrophy, nanosuspension, solid dispersion, nanoemulsion, and dendrimers. These techniques have been shown to increase the solubility and dissolution rate of carvedilol thereby increasing its bioavailability.

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