

## Preparation and Characterization of Carvedilol Solid Dispersion by Kneading Method

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### Abstract:

Solid dispersion using hydrophilic carrier is one of the approaches that has a potential to increase solubility, dissolution rate and consequently the oral bioavailability of poorly-water soluble drugs. In this study,

class II drug "Carvedilol" (CVD) was used because of its poor solubility, it serves as a model drug that contributes to irregular dissolution and limited bioavailability. CVD: PVP K30 solid dispersion formulations SD1, SD2 and SD3 were prepared by kneading method at different weight ratios ,1:1; 1:2 and 1:4 respectively and evaluated for drug content, solubility and dissolution rate. Kneading method enhances the stability of drugs and suitable for processing thermolabile substances. The optimum solid dispersion ratio was characterized also for drug-carrier interaction by FTIR spectroscopy, and crystallinity by SEM and PXRD and compared with physical mixture and pure drug powder.

The results showed that the solubility of carvedilol increased by increasing the proportion of PVP K30 used in the dispersion of the drug. On the other hand, dissolution study revealed a significant enhancement in the dissolution rate of the drug using solid dispersion compared to pure drug and physical mixture. X-ray diffraction of the solid dispersion suggest that the drug's transformation from crystalline to amorphous form may be responsible for the observed improvement in dissolving rate. The carvedilol solid dispersion improved the solubility and dissolution, which depend on the carrier concentration ratio. The dissolution of drugs increased with an increase in carrier content. The studies of PXRD, SEM, and FTIR revealed the amorphous nature of the drug in solid dispersion. The solid dispersion by kneading approach using PVP K30 as a carrier is a potential method for improving CVD's solubility and dissolution rate.

**Keywords** Solid dispersion · Carvedilol (CVD) · Hydrophilic carrier · Solubility · Bioavailability

تحضير وتقييم حمل دواء الكارفيديلول بحامل محب للماء بتقنية العجن  
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### الخلاصة:

يعد التشنت الصلب باستخدام مادة حاملة محبة للماء أحد الأساليب التي لديها القدرة على زيادة قابلية الذوبان ومعدل الذوبان وبالتالي التوافر البيولوجي عن طريق الفم للأدوية قليلة الذوبان في الماء. في هذه الدراسة، تم استخدام عقار "كارفيديلول" من المجموعة الثانية طبقاً لتصنيف علم الصيدلانيات بسبب ضعف قابليته للذوبان، وهو كدواء ذو ذوبانية غير منتظمة بالإضافة إلى التوافر البيولوجي المحدود. تم تحضير تركيبات التشنت الصلب من كارفيديلول PVP K30 وهي SD1 و SD2 و SD3 بطريقة العجن بنسب وزنية مختلفة، ١:١؛ ٢:١ و ٤:١ على التوالي وتقييم محتوى الدواء وقابلية الذوبان ومعدل الذوبان. تعمل طريقة العجن على تعزيز ثبات الأدوية وهي مناسبة لمعالجة المواد القابلة للتحلل بالحرارة.

تم تمييز نسبة التشتت الصلب المثلى أيضًا التفاعل مع حامل الدواء بواسطة التحليل الطيفي FTIR ، والتبلور بواسطة SEM و PXRD ومقارنتها مع الخليط الفيزيائي ومسحوق الدواء النقي. أظهرت النتائج أن قابلية ذوبان الكارفيديلول تزداد بزيادة نسبة المستخدمة في تشتت الدواء. من ناحية PVP K30 أظهرت النتائج أن قابلية ذوبان الكارفيديلول تزداد بزيادة نسبة أخرى ، أظهرت دراسة الذوبان تحسنا معنويًا في معدل انحلال الدواء باستخدام المشتت الصلب مقارنة بالعقار النقي والخليط الفيزيائي. يشير حيود الأشعة السينية للتشتت الصلب إلى أن تحول الدواء من الشكل البلوري إلى الشكل غير المتبلور قد يكون مسؤولاً عن التحسن الملحوظ في معدل الذوبان. في الختام ، أدى تشتت الكارفيديلول الصلب إلى تحسين القابلية للذوبان والذوبان ، وهو ما يعتمد على نسبة تركيز المادة الحاملة. يزداد انحلال الأدوية مع زيادة محتوى الناقل. الطبيعة غير المتبلورة للعقار في التشتت الصلب. يعد التشتت الصلب عن FTIR و SEM و PXRD كشفت دراسات كحامل طريقة محتملة لتحسين قابلية ذوبان الكارفيديلول ومعدل الذوبان PVP K30 طريق أسلوب العجن باستخدام

**الكلمات المفتاحية:** التشتت الصلب، كارفيديلول، حامل محب للماء، الذوبانية، التوافر البايولوجي

## Introduction:

Carvedilol (CVD) is a nonselective beta-blocker of the third generation with alpha-1-adrenergic blocking properties, antioxidant, and calcium antagonist characteristics(1). Carvedilol blocks dual beta1- and beta 2-adrenergic receptors, which improves myocardial function and reduces (or reverses) adverse cardiac remodeling in heart failure(2). CVD exists at room temperature as a crystal (3). It is a dispersed crystalline powder composed of rod-shaped particles and various solid-state configurations (three polymorphic forms I–III)(4). Polymorphism is the capability of a single chemical component to exist in multiple crystal-line phases with different molecular configurations(5, 6). This drug is a weak basic, and according to the biopharmaceutical classification system (BCS), CVD is classified as a class II medicine, which means it has low water solubility and high permeability, hence, the low aqueous solubility is one of the most important factors contributing to the low systemic bioavailability (25-35%) displayed by CVD administered orally (7). The dissolution of BCS class II drugs is often pH-dependent, which may affect drug release rate(8). The oral absorption of carvedilol was estimated to be 45.9% using GastroPlus™ simulation(9).

The production of solid dispersion in a suitable carrier is the most promising strategy for promoting dissolution. It has been observed that the integration of medication into solid carriers increases drug

solubility, resulting in enhanced bioavailability (10). The solid dispersion method allows for the near-molecular reduction of particle size. As the hydrophilic carrier dissolves, the poorly soluble medication is exposed as extremely small particles to the dissolving medium for rapid dissolution and absorption.(11, 12). As carrier materials for solid dispersions, hydrophilic carriers have been extensively studied. Polyvinylpyrrolidone (PVP) is one of the most studied hydrophilic polymeric carriers. (13-15). The goal of this study was to enhance the carvedilol solid dispersions solubility and dissolution, and subsequently, the bioavailability, in comparison to a pure drug and physical mixture, by using the kneading technique.

## 1. MATERIALS AND METHODS

CVD was provided by Awamedica pharmaceutical company, Erbil, Iraq, as a gift sample and PVP K30 purchased from Thomas baker, India. All other chemicals and reagents used were of analytical grade.

### 1.1. Preparation of carvedilol/polyvinyl pyrrolidone solid dispersions and physical mixture formulations

CVD's solid dispersion was created by kneading CVD with polyvinyl pyrrolidone (PVP) K30 at various drug-to-carrier ratios as shown Table 1. Carvedilol and PVP K30 were weighed based on their respective ratios. These were kneaded in a few drops of methanol for 30 minutes to form a paste,

then oven-dried at 40°C for 24 hours. This dry substance was passed through a 0.36 mm sieve and stored for 48 hours in desiccator at 25°C. The optimal ratio of

medication to polymer was compared to a physical combination with the same weight ratio of drug to carrier and pure carvedilol.

**Table 1: The prepared solid dispersions and physical mixtures formulations of carvedilol: PVP K30 ratios and their characters.**

Number	CVD: PVP K30 w/w ratios	Type	Character
1	1:1	Solid dispersion	SD1
2	1:2	Solid dispersion	SD2
3	1:4	Solid dispersion	SD3
4	1:1	Physical mixture	PM1
5	1;2	Physical mixture	PM2
6	1:4	Physical mixture	PM3

## 1.2. Characterization of physical mixture and solid dispersions of carvedilol

### 1.2.1. Drug content of physical mixture and solid dispersions

The drug content homogeneity of carvedilol solid dispersions and physical mixture formulas previously illustrated in Table 1 were examined. This was done by adding 10 mg of each formula to 100 ml of HCl (pH 1.2) and stirring for 30 minutes at 100 rpm using a magnetic stirrer(16). The solution was filtered through a 0.45 µm filter syringe, diluted appropriately using HCl (pH 1.2), and spectrophotometrically evaluated for CVD concentration(17).

### 1.2.2. Determination of saturated solubility of pure carvedilol and carvedilol dispersed in PVP K30:

An excess amount of CVD, CVD solid dispersions, and CVD physical mixtures were added separately to 10 mL of HCl (pH. 1.2) buffer until the turbidity of the solution, to estimate the saturation solubility of the pure drug and formulations of solid dispersions and physical mixtures. The liquid was stirred for 24 hours at 37°C using a magnetic stirrer at 100 rpm, and then

the supernatant was filtered through a 0.45 µm filter syringe. Finally, the serial dilution was prepared appropriately and analyzed with a UV spectrophotometer at 242 nm for carvedilol. The experiment was carried out three times (18, 19).

### 1.2.3. In vitro dissolution study:

For the *in-vitro* dissolution analysis, The USP type II dissolution test (paddle type) equipment was used (Cosmo Lab, India). Separately, 25 mg of pure carvedilol, SD1, SD2, SD3, and PM3 were placed in dissolution vessels for 120 minutes, after that 5 ml of samples were taken and the same volume of HCl (pH 1.2) was added at the appropriate time intervals (5, 15, 30, 45, 60, 90, and 120 minutes) to maintain a steady sink condition (20). The samples were then filtered by filter syringe 0.45µm and spectrophotometrically examined for the amount of carvedilol released each time interval. For each run test, the procedure was executed three times to compute the standard deviation and mean (21).

### 1.2.4. Fourier transforms infrared spectroscopy (FT-IR)

Samples of CVD, PVP, an optimal SD formula and its physical mixture were

combined separately with dry potassium bromide and compacted into a disc using a hydraulic press. The FTIR spectra of the disc was examined by FTIR spectroscopy (Shimadzu 8300, Japan) within the range ( $4000-400\text{cm}^{-1}$ ) (22) .

### 1.2.5. Scanning electron microscopy (SEM)

In this study, scanning electron microscope (SEM Tescan Vega 111Czech) was used to visualize the drug and PVPK30 particles and to explore the effect of solid dispersion and physical mixing on the properties of drug crystal and size. Prior to analysis, each sample was attached to an aluminum foil using double-sided adhesive tape and made electrically conductive with a thin layer of gold (approximately 20 nm) in a vacuum(23). The surface of the sample was raster-scanned with a high-intensity electron beam, generally between 0.5 kV and 40 kV, to create an image. Samples were scanned at 500 x(24).

### 1.2.6. Powder x-ray diffraction (PXRD)

The range of crystallinity for pure drug, physical mixture, and optimal solid dispersion formula was established using a Cu radiation-equipped PXRD system (Shimadzu, Japan) ( $\lambda=1.54060 \text{ \AA}$ ) and a

voltage of (40 Kv) and a current of (30 mA). Samples were analyzed in the range ( $5-80^\circ$ ) with a step size of ( $0.05^\circ$ ) at a scanning speed of ( $5^\circ/\text{min}$ ) and an axis number of (2 $\theta$ ) (24).

## 2. Result and discussion

### 2.1. Drug content and saturated solubility of carvedilol, physical mixture formulations, and solid dispersion formulations

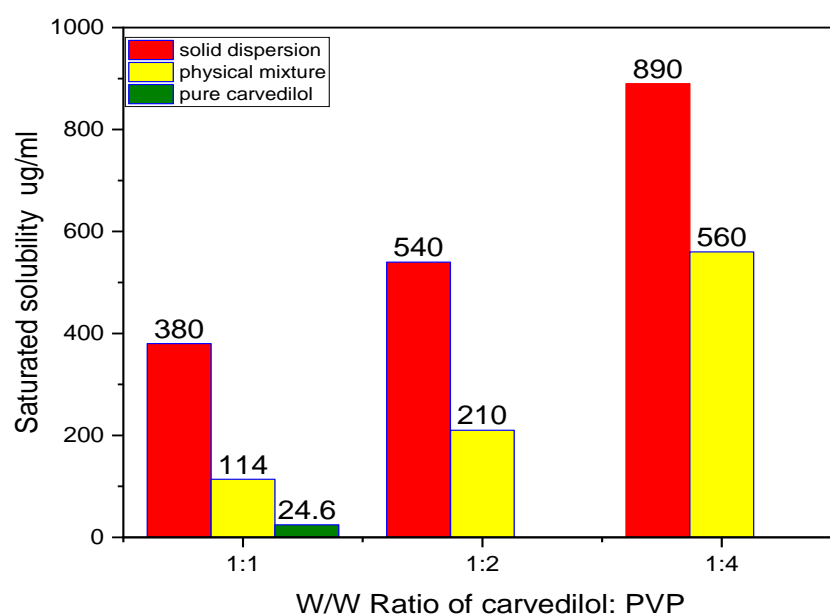
The drug content was tested to assess the homogeneity of active ingredient distribution and ensure precise dose for solid dispersion and physical mixture formulations, The results of this test are shown in Table 2.

On the other hand, the saturated solubility was tested in HCl, "pH 1.2", at  $37^\circ\text{C} \pm 0.5$  for pure CVD, solid dispersion formulations, and physical mixture formulations of CVD with PVP K30 polymer (25) and the results are illustrated in Table 2 and Figure 1. According to the results, the highest solubility was found with SD3, which shows a significant difference ( $p = 0.03$ ) in drug solubility compared to other formulations.

**Table (2) Drug content and saturated solubility of physical mixtures and solid dispersion formulations, and pure carvedilol.**

Sample	Saturation solubility in HCl pH 1.2 at $37^\circ\text{C}$	Drug content %
Carvedilol	$24.59 \pm 0.83 \text{ } \mu\text{g/ml}$	--
SD1	$380 \pm 3.59 \text{ } \mu\text{g/ml}$	$95 \pm 0.79 \%$
SD2	$540 \pm 5.27 \text{ } \mu\text{g/ml}$	$93 \pm 0.34\%$
SD3	$890 \pm 4.51 \text{ } \mu\text{g/ml}$	$97 \pm 0.48 \%$
PM1	$114.45 \pm 2.24 \text{ } \mu\text{g/ml}$	$98 \pm 0.5\%$
PM2	$210 \pm 1.79 \text{ } \mu\text{g/ml}$	$99.6 \pm 0.76\%$
PM3	$560 \pm 4.71 \text{ } \mu\text{g/ml}$	$98 \pm 0.68\%$

\*Data represent mean ( $\pm$ SD) (n=3)

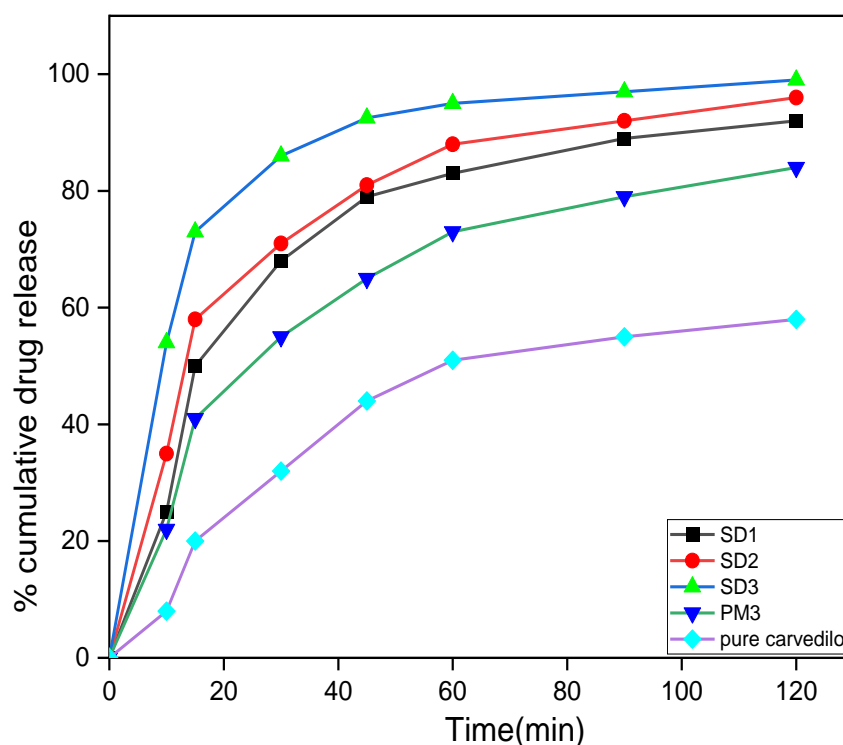


**Figure 1. Saturated solubility of pure carvedilol, solid dispersion, and physical mixture in 0.1N HCl (pH1.2).**

## 2.2. In-vitro dissolution of pure carvedilol, solid dispersion formulations and PM3 formula.

To investigate the *in-vitro* dissolution of CVD and impact of polymer concentration on drug release, the formulations of solid dispersion (SD1, SD2, and SD3), PM3 and pure drug were used. They showed that there is a highly significant difference ( $p = 0.01$ ) in the release of drug, the CVD solid dispersion formulations in general have a faster dissolution rate than the pure medication and PM3 (Figure 2). However, the dissolving rates of various CVD solid dispersion formulations varied. After the same duration of time, the SD3 indicated the faster drug release and the release completed after 2 hours compared to the SD1 and SD2. It was hypothesized that increasing the concentration of carrier in the solid dispersion formulation would

increase the drug dissolution and solubility. These results are in agreement with results of A. Sharma and C.P. Jain, 2010 they obtained that the carvedilol release and solubility increased with increase of PVP K30 concentration(26). Also, the increasing dissolution of carvedilol from solid dispersion could be caused by a number of factors, such as the lack of crystallinity, improved wetting, decreased interfacial tension between the hydrophobic drug and the dissolution medium, and efficient surface adsorption of the drug on the hydrophilic carrier are all results of the particle size reduction and formation of a higher energy metastable state with a higher degree of amorphization of the drug(27). According to finding of saturated solubility and *in-vitro* release the optimum formula from solid dispersion is SD3. Therefore, the other ratios have been excluded from further characterization.



**Figure 2. *In-vitro* dissolution profiles of pure carvedilol, solid dispersions and physical mixture of different drug: carrier ratios.**

### 2.3. Fourier transforms infrared spectroscopy (FT-IR)

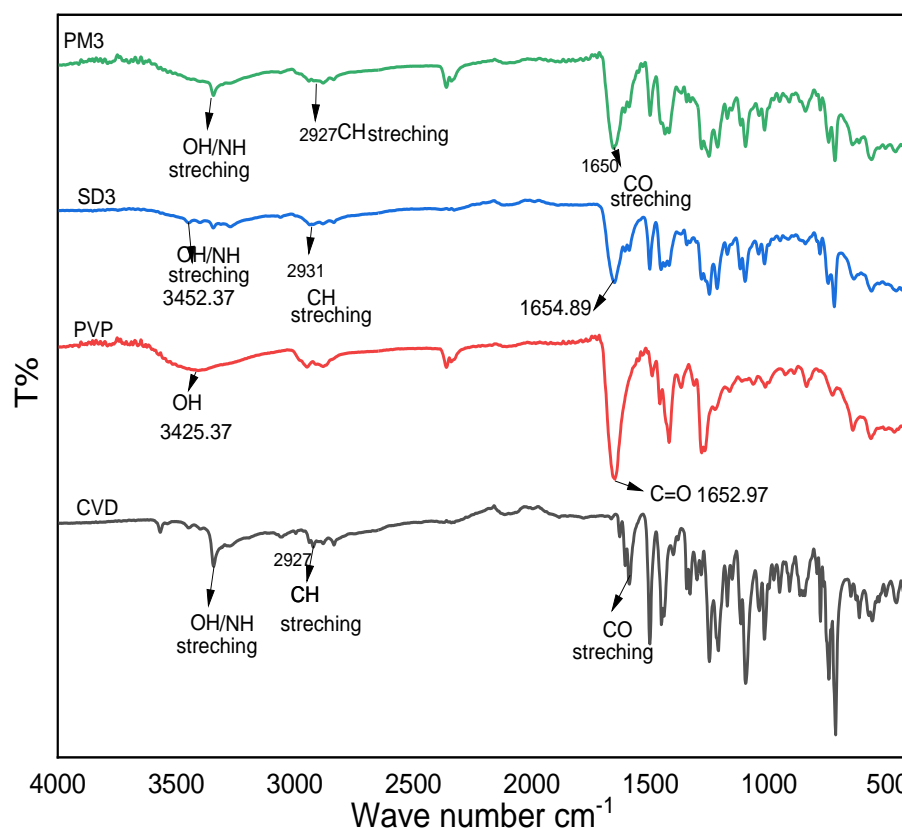
Infrared spectroscopy was used to get a clearer understanding of the interaction between CVD and PVP K30 (1:4 w/w ratio) in solid dispersions and physical mixture formulations. Figure 2 represents the FT-IR spectroscopy of the SD3 and PM3, in addition to the reference spectra of drug and PVP K30. CVD had characteristic peaks at  $3346.27\text{ cm}^{-1}$  (combined O-H and N-H stretching vibration peaks),  $2925.81\text{ cm}^{-1}$  (C-H stretching vibrations),  $1598.88\text{ cm}^{-1}$  (N-H bending vibrations), and  $1246.64\text{ cm}^{-1}$  (C-H bending vibrations) (O-H bending and C-O stretching vibrations)(28). The absorption bands of the C=O group were most visible in the IR spectrum of PVP K30 at  $1652.53\text{ cm}^{-1}$ . PVP's FTIR spectrum shows a wide peak at  $3425.37$

$\text{cm}^{-1}$  related to the stretching vibration of hydroxyl in absorbed water. Figure 3 reveals the existence of CVD and PVP K30 peaks based on the distinct absorption peaks in the SD3 and PM3 infrared spectra. All distinctive peaks of the medication and PVP K30 were detected in the spectra of SD3; the FTIR spectra of PM3 were identical to those of carvedilol and PVP K30 alone, showing that there was no chemical interaction between the substances. The assortment SD3 revealed the existence of a weak-OH stretching vibration peak at  $3452.37\text{ cm}^{-1}$  and a C=O peak at  $1652.97\text{ cm}^{-1}$ (29). The SD3 spectrum demonstrated a change in the crystallized drug from  $1652.97\text{ cm}^{-1}$  (C=O) to  $1656.89\text{ cm}^{-1}$ (30). This discovery suggested that CVD and PVP K30 interacted through hydrogen bonding. It is important to keep in mind that this type of



interaction between the drug and the carrier has an added benefit for solid dispersion because it may increase the

drug's solubility in the hydrophilic carrier when it is in solid form(31).

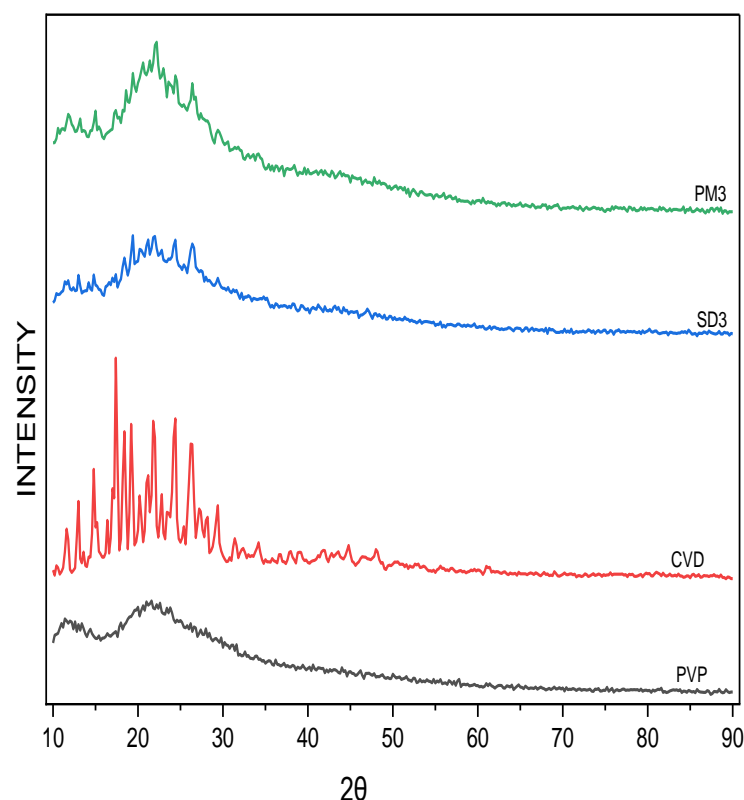


**Figure 3. FT-IR of carvedilol (CVD), PVP K30, SD3, and PM3.**

#### 2.4. Powder x-ray diffraction (PXRD)

Figure 4 illustrates the PXRD for CVD, PVP, PM3, and SD3. Numerous CVD diffraction peaks were found at  $2\theta$  with angles of  $12.8^\circ$ ,  $15.62^\circ$ ,  $17.46^\circ$ ,  $18.56^\circ$ ,  $20.1^\circ$ ,  $24.3^\circ$ , and  $26.2^\circ$ , suggesting its crystalline structure. While the diffractograms of PVPK30 power showed two halo-shaped patterns consisting of weak intensity peaks (31), this was due to the fact that PVP K30 is an amorphous polymer. The PM3 also exhibited crystallization. In contrast, SD3 exhibited

no crystallinity. In the case of SD3, peak intensity was similarly lowered. For pure CVD, the peak intensity was 2500 counts; however, it was only 1800 counts in the case of PM3 and 1050 counts in the case of SD3. The decrease in CVD's diffraction intensity in SD3 at these angles indicates that the drug's crystallinity has decreased. This research suggests that medication into an amorphous state(32). In addition, there are no further diffraction peaks, eliminating the possibility of chemical interaction between the ingredients or the presence of another kind of crystal (33).



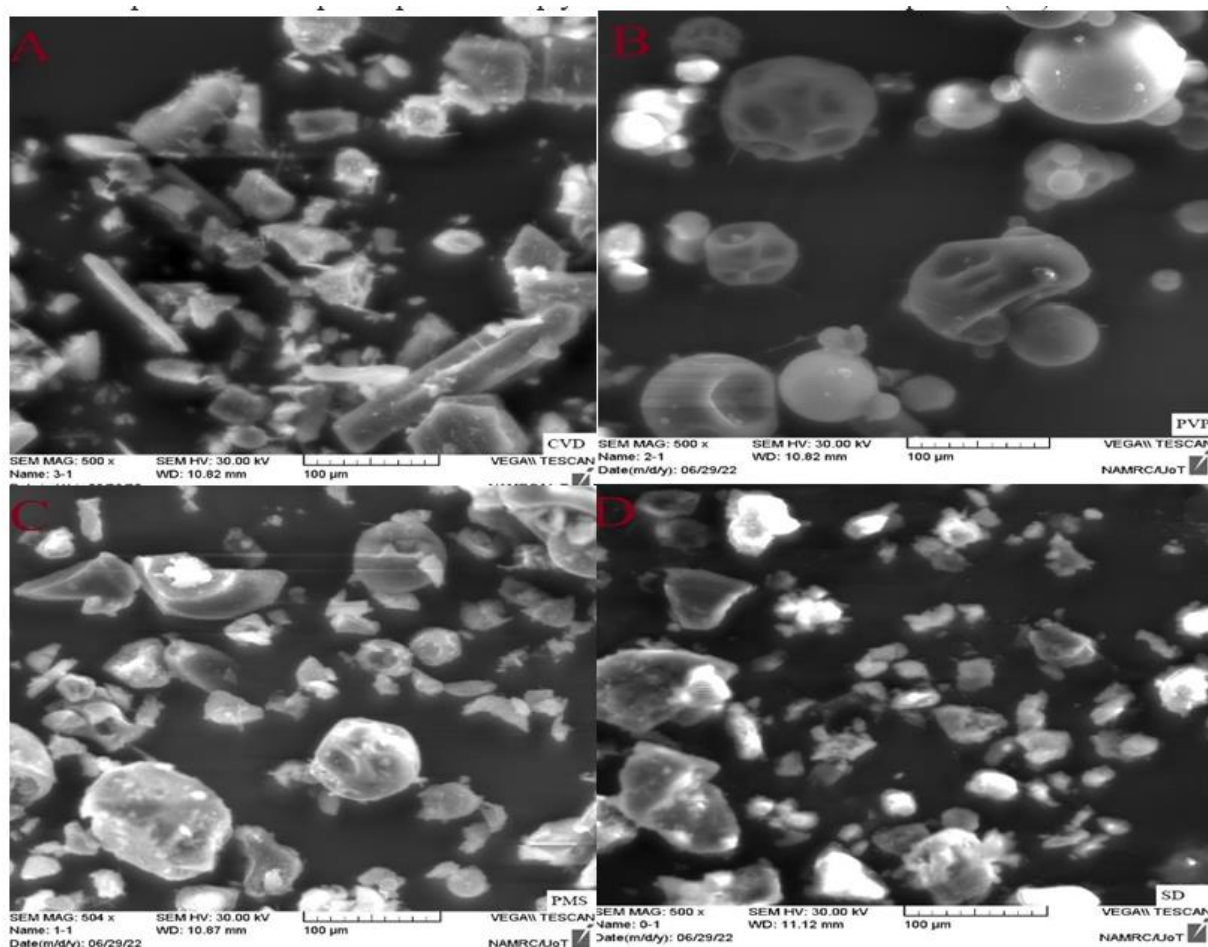
**Figure 4. XRD of pure carvedilol (CVD), PVP, PM3, SD3.**

### 2.5. Scanning electron microscopy (SEM)

Using SEM at 500x, the drug, PVP K30, PM3, and SD3 were all investigated under the microscope. According to micrographs, the CVD particles in the physical mixture are about as small as those in the drug alone and still contain free PVP K30 and crystalline CVD particles. Compared to a pure medication and PM3, a solid dispersion has smaller particles and all particles are in amorphous form. therefore, the enhanced in solubility could be resultant

from reduced in particle size and crystallinity of the drug(34). The micrograph of the drug reveals that it is crystalline (Figures 5), but the physical combination comprises both amorphous and crystalline particles. In the instance of a solid dispersion, the smaller particles of drug, some of which are in spherical shape, may improve the dissolution and solubility of CVD by providing a larger surface area than the surrounding drug particles given by the hydrophilic PVP K30 particles. Amorphous particles imply the formation of a solid dispersion (13).





**Figure 5. SEM of A- pure carvedilol powder (CVD), B- PVPK 30, C-PM3 and D- SD3 investigated using magnification power 500x.**

## Conclusion

Solid dispersion using kneading method was succeeded in improving the solubility and dissolution rate of CVD. Increasing the ratio of carrier (PVPK30) used in the solid dispersion had a significant effect on accelerating the release of the drug from solid dispersion. FTIR analysis revealed no interaction between the CVD and carrier. Reduced in crystallinity and changing the drug into amorphous form as PXRD, and SEM studies showed could be the main reasons for enhancing the solubility and dissolution of the drug by solid dispersion.

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