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Comparative Carvedilol Nanomicelle Preparation Method: Thin-Film Hydration and Direct Dissolution using Soluplus and PVP K25

Noor Mohammed Dawood [*,1], Abeer H. Khasraghi[1], Mowafaq M. Ghareeb[1] and Ilaf Jabbar Attosh[2]

[1] Department of pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq

[2] Ministry of Health, Baghdad, Iraq.

***Corresponding author**

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Abstract

The present work aims to formulate carvedilol as nanomicelle and study variables effect on the particle size of nanomicelle, and on the entrapment efficiency (EE%). The formulations were performed by two methods; thin film hydration method and direct dissolution method using soluplus® and polyvinylpyrrolidone (PVP K-25) as polymers. The results revealed that formulations prepared by direct dissolution method exhibits lower size and higher EE% as compared with thin film hydration method, it was found that soluplus® produces larger size of nanomicelle and lower EE% as compared with PVP K-25, it was found that as the amount of polymer raised, the size of nanomicelle increased in both polymers, the effect of solvent indicates that methanol solvent produced lower particle size as compared with ethanol. From all the results obtained, it was found that F9 is selected as the best formula that characterized by a low particle size (14.83 nm), low PDI (0.31), higher percentage of drug entrapment efficiency (96.3%) and drug content (98.83%), also we concluded that the direct dissolution was the best method for preparation of carvedilol nanomicelle and PVP K-25 in a concentration of 1:5 considered the best polymer that gave the best result for preparation concerning nanomicelle size, and EE%.

Keywords: Carvedilol, Nanomicelle, preparation method, PVP K-25, Soluplus.

Introduction

In an aqueous medium, about 40% of newly discovered chemical entities are poorly soluble, and many of them are even in an organic medium [(1)]. Low intestinal absorption and a very slow rate of drug dissolution are caused by low solubility, which lowers the oral drug's bioavailability [(2)]. Micelles are a type of colloidal dispersion that are part of the broad category of dispersed colloidal systems. They are made up of a continuous phase called the dispersing medium and a dispersed phase. Colloidal dispersions are created where surfactants aggregate to micelles at concentrations higher than their critical micelle concentration (CMC), at concentrations lower than this one ; the amphiphilic molecules called monomer. Therefore, CMC is the lowest concentration at which an amphiphilic molecule needs to start micellizing, and it has a unique value for every monomer [(3)]. Amphiphilic block copolymers self-assemble to form a polymeric micelle in an aqueous environment. Low CMC values (10−7 mol/l) of amphiphilic polymers are favorable for the formation and stability of micelles. The micelle is composed of an inner hydrophobic structure and an outer hydrophilic structure. Since the polar portion of the forming polymer formed the shell and the lipophilic portion was included in the core, a lipophilic compound can be incorporated into the micelle's core in aqueous solutions; in fact, the lipophilicity of an amphiphilic polymer incorporated molecule determines where it is located inside the micelle [(4)].

One of the most promising delivery methods in nanomedicine is polymeric micelles. Most polymeric micelles are between 10 and 100 nm in size; this nano-size disperses the poorly soluble compound in water and shields the poorly soluble drug with its own outer shell. As a result, nanomicelle technology has been developed as a potential means of efficiently delivering hydrophobic drugs and used with poorly soluble drugs because of their unique structure, which produces formulations with high dissolution velocities and increased saturation solubility, which in turn lengthens the circulatory residence time of the drugs and increases their therapeutic efficacy. Furthermore, polymeric micelles offer a high drug filling amount, a narrow particle size distribution, a

polyethylene glycol backbone as the hydrophilic part and vinylcaprolactam/vinyl acetate side chains as the low dissociation rate, a low critical micelle concentration and low toxicity [5-8].Soluplus® is a polyvinyl caprolactampolyvinyl acetatepoly-ethylene glycol graft copolymer, having the lipophilic moiety. Because of its amphiphilic nature, it can form micelles in aqueous solution above the 7.6 mg/lCMC value. Soluplus® has been suggested as a safe and adaptable material among the many uses for creating nanomicelles in the pharmaceutical industry, either by itself or in conjunction with other polymers [9,10].

PVP K-25 is a large, non-ionic, non-toxic, water soluble polymer with functional groups C=O, CN, and CH2 that is frequently used in the synthesis of nanoparticles. The pyrrolidone moiety of the PVP K-25 molecule is highly hydrophilic, while the alkyl group is a significant hydrophobic group. PVP in nanomicelle can serve as in micelle formation and a surface stabilizer [11,12].

Carvedilol is a non-selective β-blocking agent, acting as a competitive antagonist against β1-, β2- and α1 adrenergic receptors [13]. As shown in Figure 1, carvedilol is ((2RS)-1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl]amino]propan-2-ol) one example of the BCS Class II drug candidates . This medication has a pH-dependent solubility and is a lipid soluble compound that has high permeability. The pKa values of Carvedilol are 7.8 for basic and 15 for acidic. It dissolves readily in the stomach's acidic media but may precipitate in the small intestine's basic pH. It is extensively used to treat a range of cardiovascular conditions, such as hypertension, heart failure with reduced ejection fraction, and left ventricular dysfunction after myocardial infarction; however, because of extensive hepatic first-pass metabolism by cytochrome P-450, it has a short plasma half-life and only 25–35% systemic bioavailability [14,15]. Carvedilol was prepared with different nanocarrier like carvedilol mucoadhesive nanosponge[16]and carvedilol-loaded nanocapsules[17]in order to improve solubility and bioavailability.

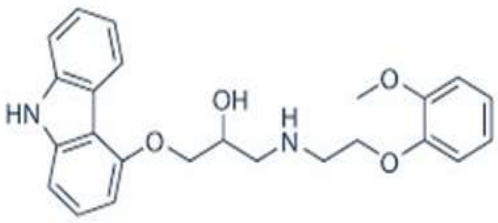


Figure 1. Chemical structure of Carvedilol [15]

Materials and methods

Materials

Carvedilol was purchased from Wadi Al-Rafidian Factory for pharmaceutical products. PVP K-25 was supplied by Hangzhou hyper chemicals limited, Zhejiang, China. Soluplus® (graft copolymer of polyethylene glycol; polyvinyl caprolactam; and polyvinyl acetate) provided from BASF, Germany. Ethanol and Methanol provided from Sigma Aldrich, Germany. and deionized water also was used in this study.

Methods

Preparation of carvedilol nanomicelle

Polymeric micelles were prepared by two different methods (Evaporation or thin film hydration method and Direct dissolution).Table 1 shows ten different formulas prepared by these two methods by using poly (vinyl caprolactam)-poly (vinyl acetate)-poly (ethylene glycol) (Soluplus) and PVP K-25.In the thin film hydration methods(F1-F6), nanomicelles were prepared by dispersing the appropriate amount of polymer (Soluplus and PVP K-25) with carvedilol (3.125 mg) in ethanol to obtain a transparent solution in the form of the thin film, this can be obtained after the removal of organic solvents under a high vacuum(175 mbar for 40º C) by using rotary evaporator (BUCHI rotavapor® R-300). After organic solvent evaporation, the thin film hydrated by deionized water under magnetic stirring (1000 rpm, 25°C and for 1 hour) [18,19].

The second method was direct dissolution also known as a simple equilibrium method. In this method (F7-F10), the drug and the polymers dissolved in distilled water, so the simultaneous dissolution of drug and copolymer with the appropriate ratio occurs in the aqueous solution under magnetic stirring (1000 rpm, 35°C and for 24 hour). During stirring and heating, the core of the structure undergoes dehydration that leads to the formation of nanomicelles [19,20].

Table 1. Composition Carvedilol nanomicelle formulation

Formulas	Drug:polymer	Polymer	Solvent	Method of preparation	D.W
F1	1:5	Soluplus	Ethanol	Thin film hydration	10
F2	1:10	Soluplus	Ethanol	Thin film hydration	10
F3	1:5	PVPK-25	Ethanol	Thin film hydration	10
F4	1:10	PVPK-25	Ethanol	Thin film hydration	10
F5	1:5 (1:2.5:2.5)	Soluplus+PVPK-25	Ethanol	Thin film hydration	10
F6	1:5	Soluplus	Methanol	Thin film hydration	10
F7	1:5	Soluplus	---------	Direct dissolution	10
F8	1:10	Soluplus	---------	Direct dissolution	10
F9	1:5	PVPK-25	----------	Direct dissolution	10
F10	1:10	PVPK-25	----------	Direct dissolution	10

Evaluation of the Prepared Nanomicelle

Particle size and size distribution of Carvedilol nanomicelles

Particle size diameter was obtained using Zetasizer ULTRA Red Label (Malvern Panalytical Ltd., Malvern, UK). In a plastic cell, each experiment was conducted at 25°C. Every sample was utilized in the studies in a total of 1 ml. the angle of the incident light was 173° to decrease back scattering and it was equipped with optical filter [21]. Zetasizer relies on light diffraction technique. Each solution was being done in three separate studies, each involving five measurements. The polydispersity index (PDI), a measurement of the spread or variation or width within the particle size distribution, is a measure of the particle size distribution of nanoparticles obtained from a particle analyzer. [21,22].

Determination of entrapment efficiency (EE)

A 10-milliliter of formula was centrifuged for 30 minutes at 40000 rpm (Thermo Scientific, Mumbai, India). Filtration and separation were done on the supernatant solution by ultrafiltration membrane (Millipore, Billerica, MA). A UV spectrophotometer was used to determine the absorbance at maximum λ max (284 nm) after diluting 1 milliliter of this filtrate with water and using blank water [23]. After measuring the amount of free drug in each formulation (indirect method), the entrapment efficiency is computed using Equation 1.

$$\text{E. E\%} = \frac{(total\ drug\ in\ formula - free\ drug) \times 100}{total\ drug\ in\ formula} \quad (1)$$

The results were analyzed in triplicate and standard deviations are reported.

Determination of drug content of carvedilol nanomicelles

An accurate volume (1ml) of each formula was measured and mixed in 9 ml of ethanol and was sonicated in a sonication bath for 5min. From this, 1 ml of the solution was taken and further diluted with ethanol. The solution was assayed for drug content using a UV/VIS spectrophotometer (model UV-1900I PC, Shimadzu, Kyoto, Japan). The percentage of drug content in the nanomicelle was calculated by using Equation 2 [24].

Drug content

$$\text{\%} = \frac{The\ actual\ amount\ of\ carvidilol}{The\ theoretical\ amount\ of\ carvidilol} \times 100$$

equation (2)

Determination of Fourier Transform Infrared Spectroscopy (FTIR)

The Fourier transform infrared (FTIR) spectra of carvedilol pure drug, and physical mixture at a ratio (1:1) of drug: polymer was carried out by using an FTIR spectrometer (FTIR-8300 Shimadzu, Japan), and then scanned in the wave numbers range from 4000 cm-1 to 400 cm^{-1}. The FTIR analysis was conducted to detect any evidence of interaction or complexation between carvedilol and the excipients used in the nanomicelle formulation [25].

Statistical analysis

The experimental results are given as mean triplicate samples standard deviation (SD) and were analyzed according to one-way analysis of variance (ANOVA) using Sigma Plot 11 software at which the results would be significant if $p<0.05$, and the results would be non-significant if $p>0.05$.

Results and Discussion

Particle size analysis and polydispersity index measurement

The effect of the 2 methods of preparation (thin film hydration and direct dissolution) by using soluplus and PVP K-25 on the particle size and polydispersity index was studied using ten different formulations. The mean particle size (effective diameter) for formulations varied in the wide range from 14.83±0.0 nm to 231.7±0.0 nm. The particle size and PDI for different formulations of different parameters are shown in Table 2.

Table 2. The particle size, and PDI of different formulations

Formula no.	P. S.(nm)±SD*	PDI±SD*
F1	178.8±0.005	0.33±0.008
F2	231.7±0.003	0.48±0.006
F3	15.79±0.008	0.32±0.003
F4	79.88±0.008	0.005±0.009
F5	16.84±0.006	0.36±0.009
F6	66.57±0.009	0.15±0.008
F7	66.46±0.008	0.003±0.008
F8	128.5±0.009	0.267±0.009
F9	14.83±0.009	0.31±0.004
F10	15.21±0.007	0.33±0.009

*SD standard deviation, n=3, P. S: Particle size, PDI: Polydispersity index

Effect of polymer type on the nanomicelle size and polydispersity index

Eight formulations were used to show this effect F1, F2, F7 and F8 which compared with F3, F4, F9 and F10 respectively. Figure 2 which appeared the effect of polymer type on nanomicelle size shown that nanomicelle size were significantly decreased ($p<0.05$) from 66.46nm -231.7 nm in F1, F2, F7and F8 to (14.83- 79.88) nm in F3, F4, F9 and F10, therefore the best polymer that used in preparation of carvedilol nanomicelle was PVP K-25. Polydispersity index values of formulas that contain soluplus (F1, F2, F7and F8) were 0.003- 0. 48 that decreased significantly ($p<0.05$) to be 0.005-0.33 in formulas that contain PVP K-25 (F3, F4, F9 and F10). The effect of polymer on nanomicelle size is complex and depends on a variety of factors, but in general, it can be said that polymers can significantly influence the size, stability, and properties of nanomicelles [26].

PVP K-25 has been shown to have a number of effects on the size and stability of nanomicelles, PVP K-25 can adsorb to the surface of nanomicelles due to that PVP K-25 molecules create a steric barrier around the micelles, which prevents them from coming close together and aggregating so prevent increasing the particle size. This is because the PVP K-25 molecules coat the surface of the micelles and protect them from attack [27,28].

Effect of method of preparation on the nanomicelle size and polydispersity index

Figure 3 represents a comparative view of an influenced method of preparation on the nanomicelle's size of carvedilol using two different polymers (soluplus and PVP K-25). F1- F4 showed the particle size when thin film hydration used as a preparation method, While F7-F10 were prepared by direct dissolution method. The particle size of F7-F10 were 66.46 nm, 128.5 nm, 14.83 nm and 15.21 nm respectively; which appeared significantly decreased ($p<0.05$) in particle size compared with F1- F4 (178.8 nm, 231.7 nm ,15.79 nm and 79.88 nm respectively). Polydispersity index values of formulas that prepared by thin film hydration (F1-F4) were 0.005- 0. 48 that decreased significantly ($p<0.05$) to be 0.003-0.33 in formulas that prepared by direct dissolution method (F7- F10).

From above results, it seems that direct dissolution methods generally lead to a larger decrease in nanomicelle size compared to thin film hydration. This is because direct dissolution disrupts the pre-formed nanomicelles, allowing for greater shrinkage, while thin film hydration controls the size through self-assembly during hydration [29]. However, it's important to note that the effectiveness of each method depends on various factors, such as the nanomicelle composition, solvent properties, and processing conditions [30].

Effect of polymer concentration on the nanomicelle size and polydispersity index

(F1, F3, F7 and F9) of drug: polymer 1:5 and (F2, F4, F8 and F10) of drug: polymer 1:10, all of these formulas studied the effect of concentration of polymers on change the nanomicelle's size as showed in Figure 4. It was observed that the nanomicelle's size significantly ($p<0.05$) increases with the increase in polymer concentration in the nanomicelle from 178.8 nm, 15.79nm and 66.46nm in F1, F3 and F7 to 231.7 nm, 79.88 nm and 128.5 nm in F2, F4 and F8 respectively. Except F9 and F10 the increased in polymer concentration was slightly ($p>0.05$) changing (14.83nm to 15.21nm). Therefore, we prefer to use 1:5 carvedilol: polymer to get smaller nanomicelle.

In many cases, increasing the polymer concentration does lead to decrease in nanomicelle size. This is a common phenomenon observed in nanomicelle formation and has been reported in numerous studies across various polymer systems [31]. But in this study the opposite relationship has been occur, this due to; As the polymer concentration increases, there are more polymer chains available to form the micelle core. This can lead to the incorporation of more polymer chains into each micelle, resulting in a larger aggregate [32]. Also higher polymer concentrations may lead to changes in the hydration layer surrounding the micelles. This can alter the repulsive interactions

between micelles, allowing them to pack closer and potentially grow in size [26]. At higher polymer concentrations, the system may reach a point where it becomes more energetically favorable to form new micelles rather than just grow existing ones. This can lead to an increase in both the number and size of micelles in the population [33].

Effect of polymers combination on nanomicelle size and polydispersity inde

F5 was used to show the effect of combination of soluplus with PVP K-25 as compared with F1and F3 that used these polymers alone (figure 5). When soluplus is utilized as the primary polymer in formulation F1 (178.8 nm), it dramatically reduces micelle size ($p<0.05$) to nanosized particles when paired with PVP K-25 in formulation F5 (16.84 nm); thus, it cannot serve as the sole polymer for the nanomicelle.

The non-significant effect ($p>0.05$) of PVP K-25 combination with soluplus (F5) was shown in formulas that contain PVP K-25(F3) as primary polymer (15.79 nm).

The combination of different polymers with complementary properties can indeed influence the size of micelles, and in many cases, it can lead to a decrease in micelle size. This might due to synergistic effects, so can lead to more efficient packing at the core-corona interface, resulting in smaller or more stable micelles than either individual component. This is because the different block lengths can interdigitate and fill in gaps, reducing the overall size of the micelle core [34].

Effect of solvent type on nanomicelle size

Two formulations were used to show this effect F1, and F6. In figure 6 the nanomicelle size of F6 using methanol as organic solvent decreased significantly ($p<0.05$) from 178.8 nm in F1(using ethanol as a solvent) to 66.57 nm in F6 (using methanol as a solvent). It was observed that with using methanol as organic solvent the nanomicelle size decrease; because methanol is a polar solvent, meaning it has both a positive and negative end due to the hydroxyl group (OH). This polarity allows methanol to interact with the hydrophilic head groups of the surfactant molecules that make up the nanomicelle. When methanol interacts with the head groups, it can weaken the hydrophobic interactions between the surfactant tails. This weakening can cause the nanomicelle to shrink in size [35].

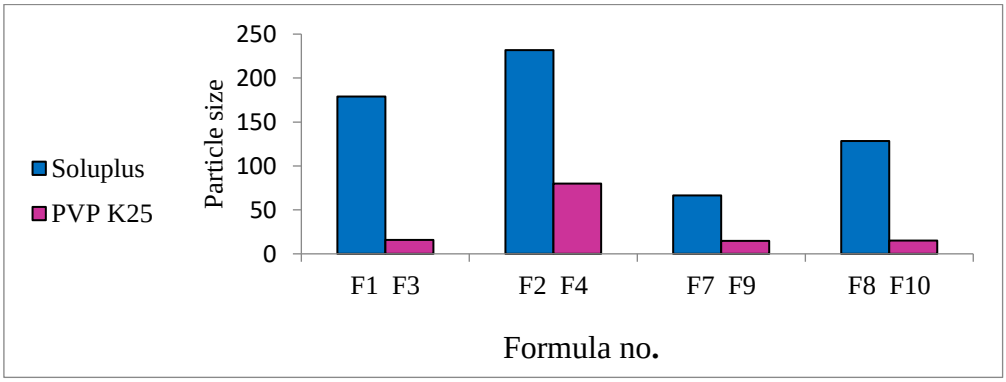


Figure 2. Effect of polymer type on the nanomicelle size of (Results as an as mean, n=3)

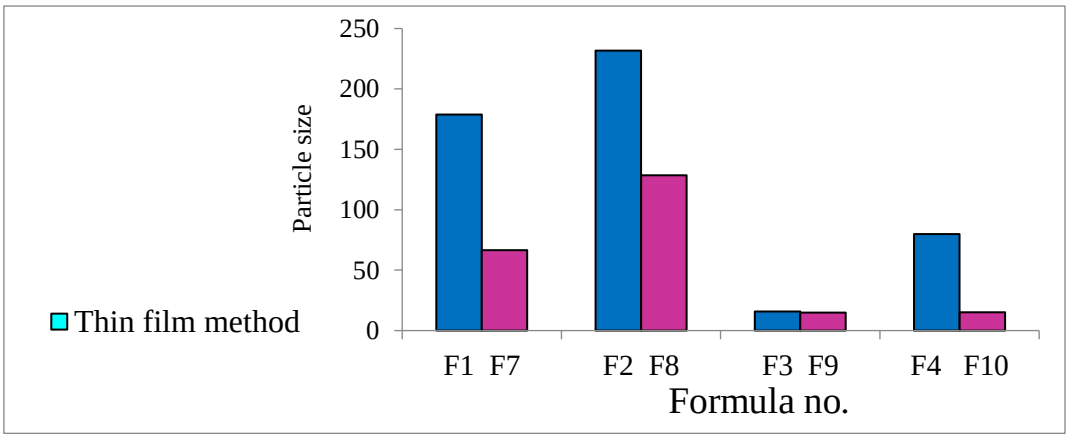


Figure 3. Effect of method of preparation on the nanomicelle size of (Results as an as mean, n=3)

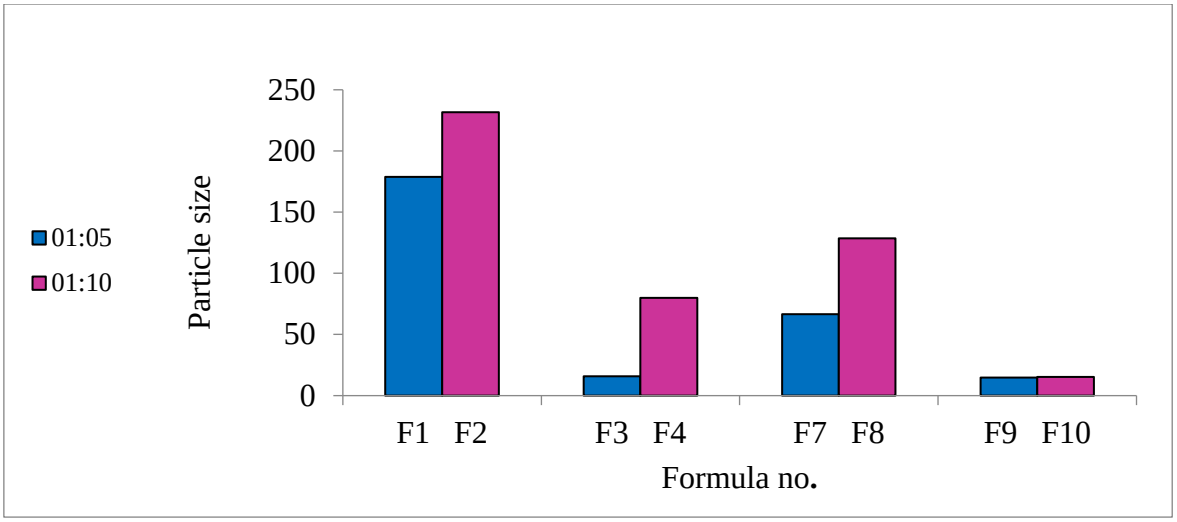


Figure 4. Effect of polymer concentration on the nanomicelle size of (Results as an as mean, n=3)

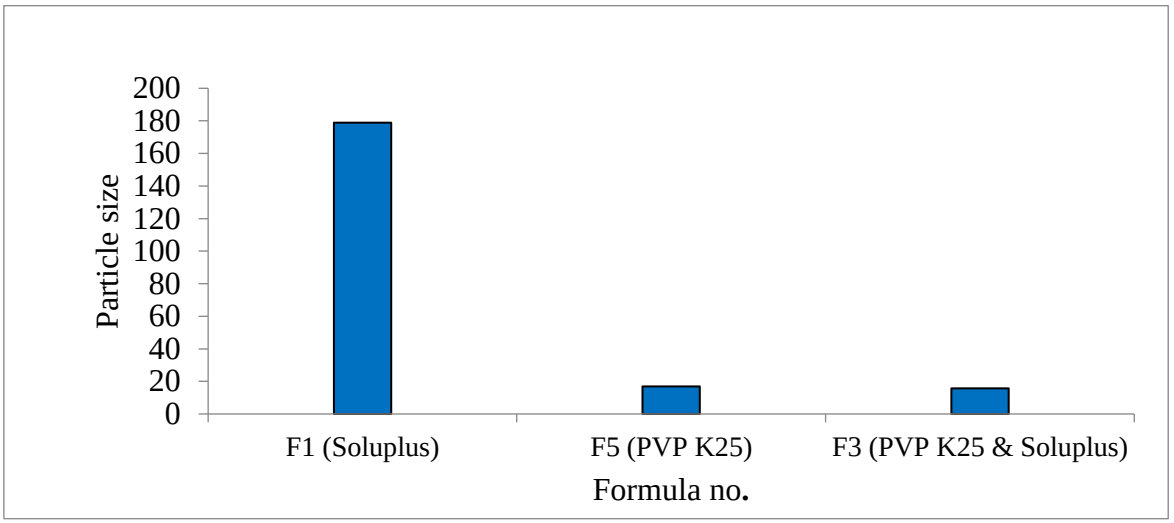


Figure 5. Effect of combination of polymers on the nanomicelle size of (Results as an as mean, n=3)

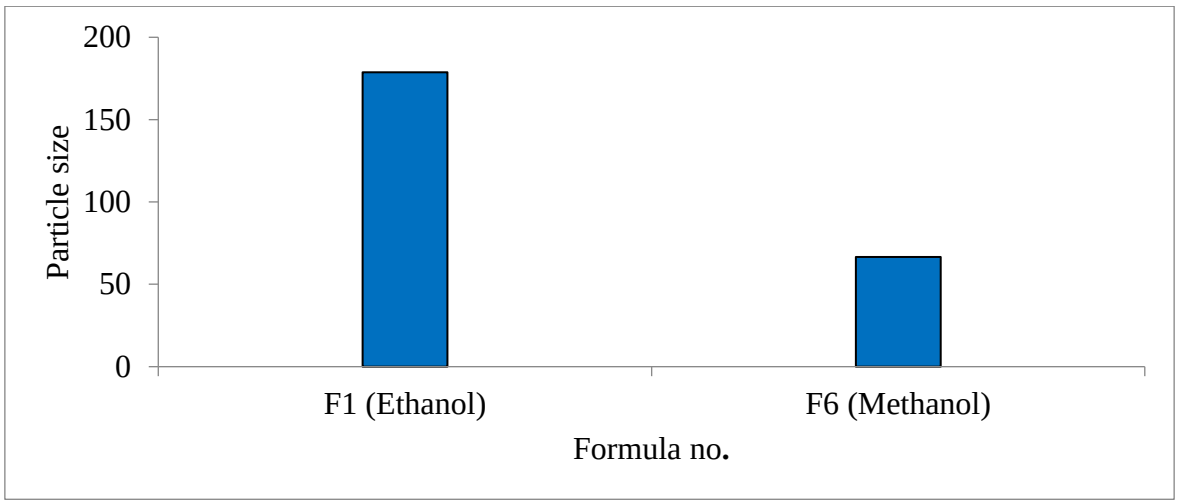


Figure 6. Effect of type of solvent on the nanomicelle size of (Results as an as mean, n=3)

Drug entrapment efficiency

The percentage drug entrapment efficiency of the formulations was calculated and the results of F1-F10 were ranged from 80.09%± 0.05 to 96.3%± 0.07 as shown in the Table 3.

Table 3. Entrapment Efficiency% (EE), drug content of Formulas (Mean of EE% ± Sd , mean of drug content ± Sd ,n=3)

Formulas no.	EE%± Sd	Drug content%± Sd
F1	85.6± 0.06	92.02±0.07
F2	80.09± 0.05	92.43±0.02
F3	95.6± 0.02	96.89±0.008
F4	90.8± 0.009	93.3±0.008
F5	95.4± 0.009	96.81±0.05
F6	86.2± 0.02	92.08±0.007
F7	93.0± 0.1	96.5±0.04
F8	89.6± 0.09	93.98±0.1
F9	96.3± 0.07	98.83%±0.2
F10	95.21± 0.03	97.0±0.5

Figure 7 demonstrated that polymer type (soluplus or PVP K-25) had a significant effect ($p<0.05$) on the EE%. Moreover, this study appeared that PVP K-25 is more affected and it gave higher EE% due to it has a higher surface area, so there are more binding sites available for carvedilol molecules to attach and the result stronger interaction between PVP K-25 and carvedilol molecules. Soluplus is more susceptible to degradation: This means that it may break down over time, releasing the entrapped carvedilol molecules so it gave less EE %of drug [36,37].

The results showed that the direct dissolution significantly ($p<0.05$) more EE % of carvedilol into nanomicelle as shown in Figure 8, this due to that in the direct dissolution method, the drug encounters pre-formed micelles immediately, promoting rapid encapsulation before significant aggregation or degradation occurs. This contrasts with thin film hydration, where drug diffusion and micelle formation occur simultaneously, potentially leading to incomplete drug incorporation [25].

Carvedilol entrapment efficiency was significantly($p<0.05$) increased by the combination of PVP K-25 with soluplus than polymer alone (Figure 9), this because that the presence of PVP K-25 could help to form a more stable inclusion complex with Soluplus (synergistic effect), which would further improve the entrapment efficiency of carvedilol [38].

It is clear that the decreased in polymer concentration increased the drug entrapment efficiency (Figure 10), the experimental data indicated that the concentration of polymer had critical effects ($p<0.05$) on the drug entrapment of nanomicelle formation, this study revealed that the concentration of polymer at ratio 1:5 drug: polymer was sufficient to give the optimized entrapment efficiency. This may be due to the presence of optimum polymer concentrations [39]. Figure 11 demonstrated that methanol not significantly ($p>0.05$) effect on EE % of carvedilol nanomicellenot.

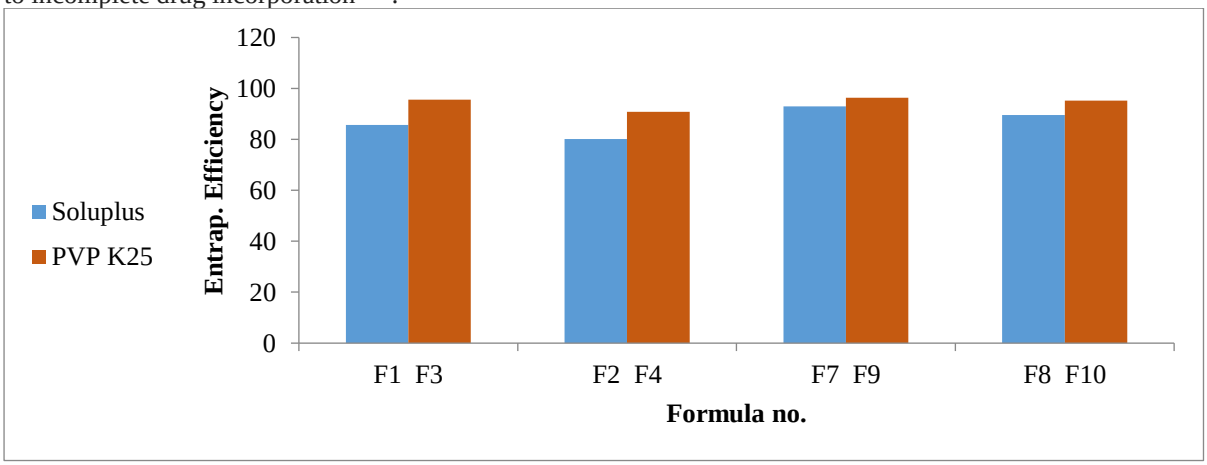


Figure 7. Effect of polymer type on entrapment efficiency

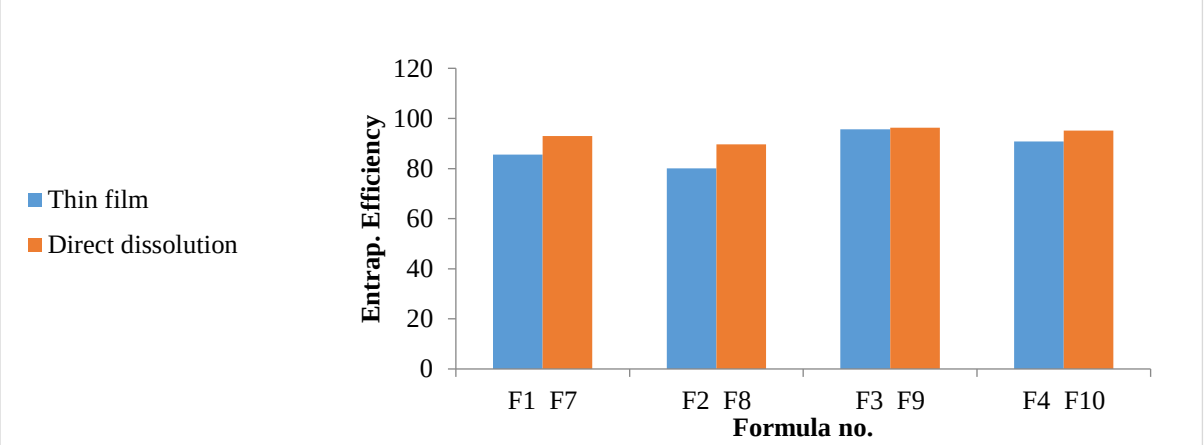


Figure 8. Effect of method of preparation on entrapment efficiency

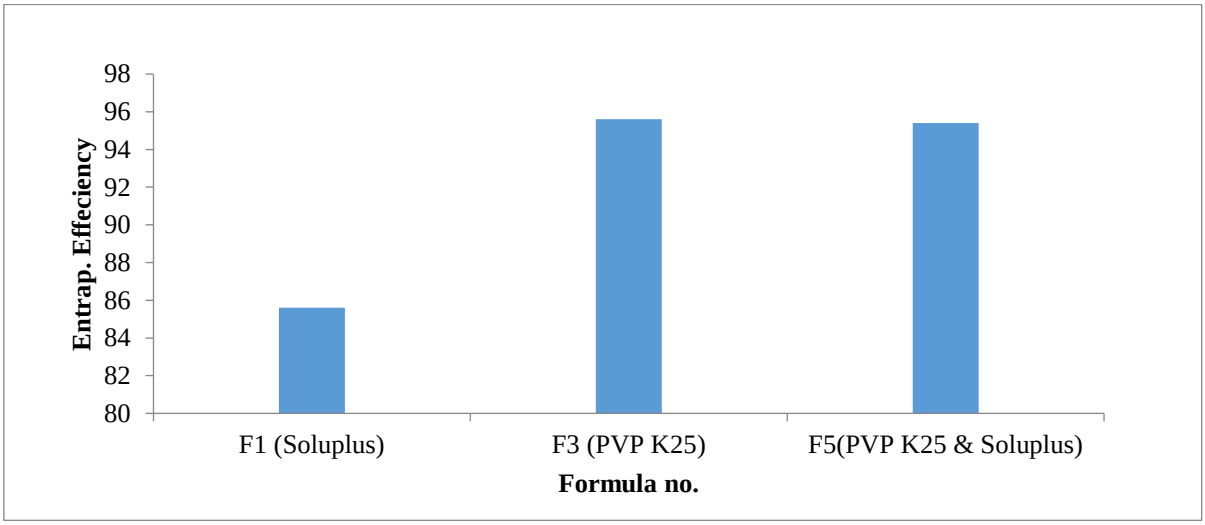


Figure 9. Effect of polymer combination on entrapment efficiency

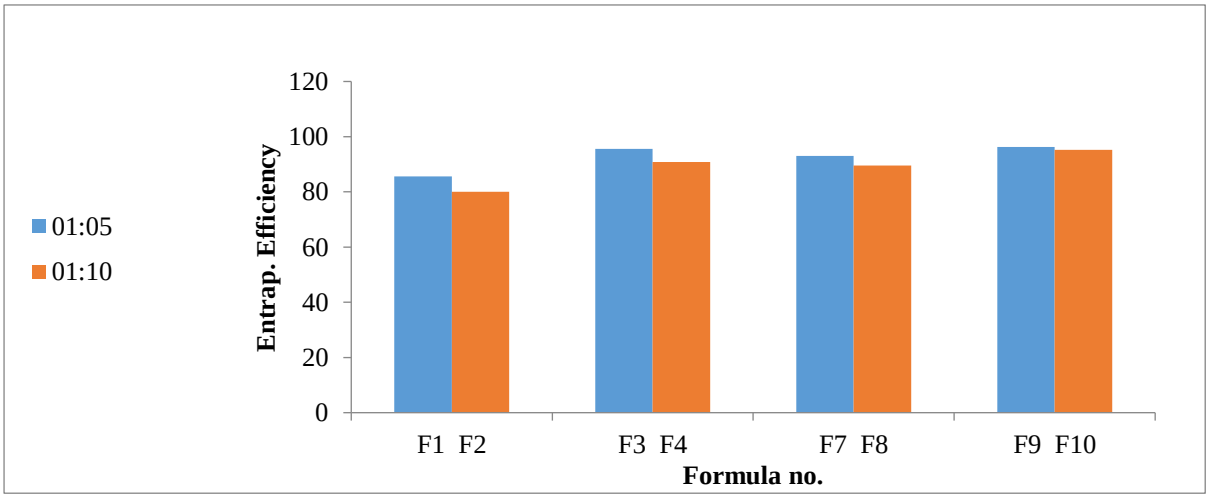


Figure 10. Effect of drug/ polymer ratio on entrapment efficiency

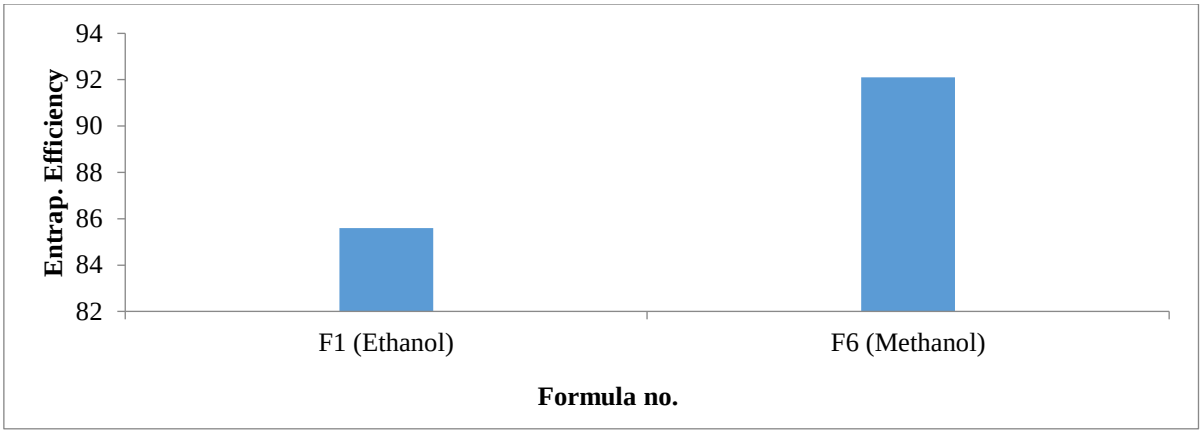


Figure 11. Effect of type of solvent on entrapment efficiency

Drug content estimation

The results of drug content were in a range of (92.02%-98.83%) as presented in Table 3 and Figure 12. The results showed all the prepared carvedilol nanomicelle formulas are within the accepted limit and contain more than 90% of carvedilol.

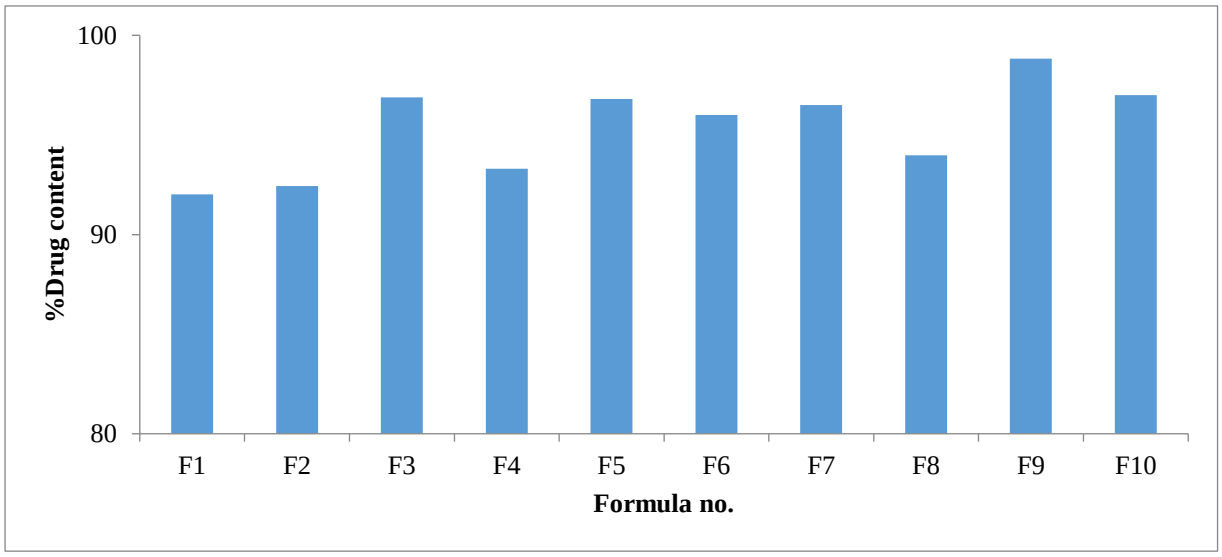


Figure 12. Percentage drug content of Carvedilol nanomicelle formulas

Selection of optimized formula

From the study of particle size , polydispersity index, entrapment efficiency and drug content , it was found that F9 is selected as the best formula that characterized by a low particle size (14.83 nm),low PDI (0.31), higher percentage of drug entrapment efficiency (96.3%) and drug content (98.83).

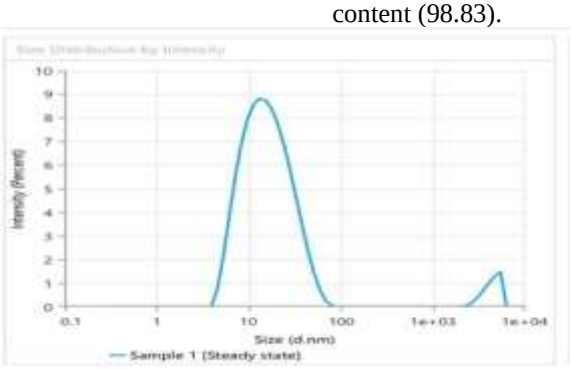


Figure 13. Nanomicelle size of selected formula (F9)

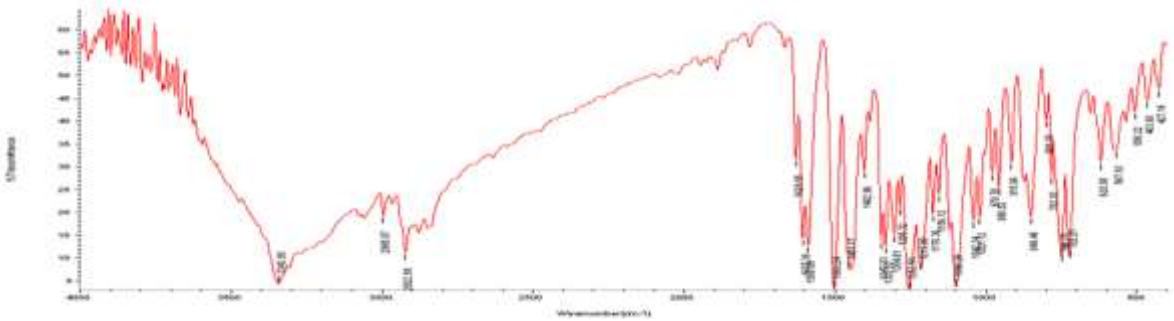
Fourier transforms infrared spectroscopy

The Fourier transforms infrared spectrum of pure carvedilol shown in Figure 14 (A), the physical mixture 1:1 of carvedilol: soluplus intensity in Figure 14 (B), the physical mixture 1:1 of carvedilol: PVP K-25 appeared in Figure 14 (C) and the physical mixture 1:1:1 of carvedilol: soluplus: PVP K-25 are shown in Figure 14 (D).

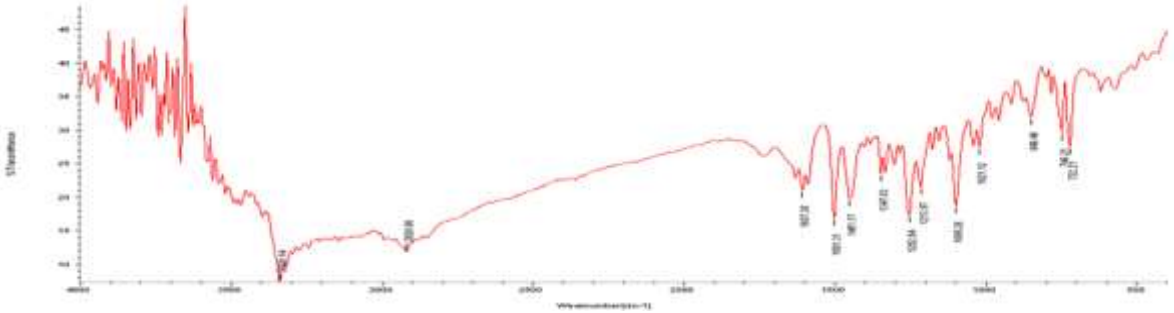
FTIR spectra of physical mixture of 1:1 carvedilol: polymers showed that that the major peaks of pure carvedilol and physical mixture not affected and predominantly observed in the theoretical range, and this will indicate there was no an interaction between the drug and the polymer PVP K-25 and soluplus used in the formulation The change in the near and mid IR region due to presence of (OH) group in the carvedilol and formula polymers [40].

Table 4. Theoretical and analyzed FTIR spectra values of the pure carvedilol [41]

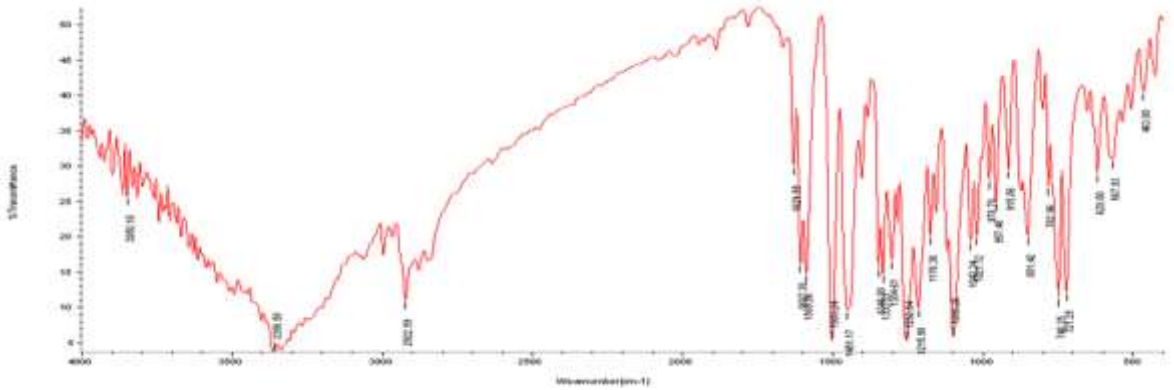
No.	Assignmented groups	Theoretical value wave number (cm^{-1})	Analyzed value wave number(cm^{-1}) of carvedilol pure drug
1	Aliphatic Secondary amine, NH Stretch	3360–3310	3342.75
2	Secondary amine, NH bend	1650–1550	1629.9
3	Secondary amine, CN stretch	1190–1130	1174.69
4	Aromatic Secondary amine, CN stretch	1350–1280	1346.36
5	Aromatic Secondary amine, NH stretch	~3450	3450
6	Hydroxy group, H-bonded (broad) OH stretch	3570–3200	3203.87
7	Secondary alcohol, C-O stretch	~1100	1097.53
8	Primary or secondary, OH in-plane bend	1350–1260	1303.92
9	Alcohol, OH out-of-plane bend	720–590	617.24
10	Methoxy, C-H stretch (CH3-O-)	2820–2810	2820
11	Aromatic ethers, Aryl-O stretch	1270–1230	1253.77
12	Methylene C-H asymmetric stretch	2935–2915	2922.25
13	Methylene C-H symmetric stretch	2865–2845	2847.03
14	Methylene C-H bend 1485–1445 1448.66		
15	Aromatic ring stretch(C=C)	1615–1580, 1510–1450	1606.76, ,1587.47,1502.6
16	Aromatic C-H stretch	3130–3070	3090
17	Aromatic C-H in-plane Bend	1225–950	1213.27
18	Aromatic C-H out-of-plane bend	900–670	748.41



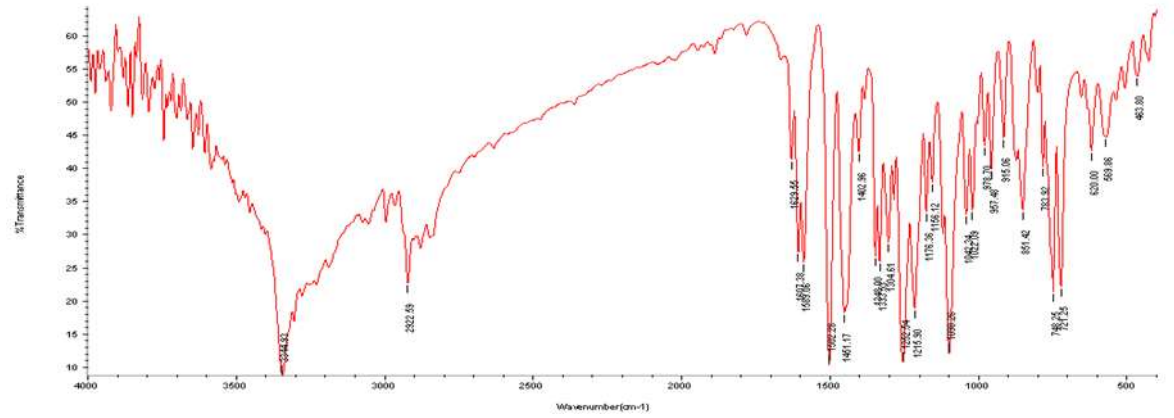
A



B



C



D

Figure 14. Fourier transforms infrared spectroscopy of A) pure Carvedilol, B) physical mixture 1:1 of Carvedilol: Soluplus, C) physical mixture 1:1 of Carvedilol: PVP K-25, D) Selected formula (F9)

Conclusion

PVP K-25 produces lower nanomicelle size as compared with Soluplus®. Direct dissolution method produces lower size of nanomicelle as compared with thin film hydration film. The higher concentration of polymer produces larger size of nanomicelle as in F2, F4, F8 and F10 with drug: polymer ratio (1:10). So, the desired size of nanomicelle as nanocarier can be obtained by considering several factors like, polymer type and concentration, solvent type and method of preparation. From all the results we have obtained, we conclude that the direct dissolution was the best method for preparation of carvedilol nanomicelle and PVP K-25 in a concentration of 1:5 considered the best polymer that gave the best result for preparation concerning nanomicelle size, PDI, and EE.

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Conflicts of Interest

We want to declare the absence of any conflict of interest during the experimental work, and the work proceed smoothly.

Funding

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Ethics Statements

This study is performed without subjecting a human or an animal to any test.

Author Contribution

The contribution of authors was as follow: Noor Mohammed Dawood performed most of the lab work, recorded the results and wrote the manuscript. Abeer H. Khasraghi did the evaluation tests, constructed the figures, did the statistical analysis study and participated in editing the article, Mowafaq M. Ghareeb: provided the drug, gave the idea of the work, and provided us by supervision, and Ilaf Jabbar Attosh prepared two formulas in the beginning of our work.

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مقارنة تحضيرالجسيمات المذيلة النانوية لدواء الكارفيديلول بطريقتي: ترطيب الاغشية الرقيقة والذوبان المباشر باستعمال السولبلس والبولي فينيل بايروليدون ك ٢٥

نور محمد داود [١،*] ، عبير حسن خزعل[١] ، موفق محمد غريب [١] و ايلاف جبار عطوش [٢]

[١]فرع الصيدلانيات، كلية الصيدلة، جامعة بغداد، بغداد ، العراق

[٢]وزارة الصحة ، بغداد ، العراق

الخلاصة

يهدف هذا البحث إلى صياغة الكارفيديلول على شكل جسيمات مذيلة نانوية ودراسة تاثير عوامل التصييغ على حجم الجسيمات وعلى كفاءة الانحباس وعلى مؤشر التشتت المتعدد. تم تصنيع الجسيمات المذيلة النانوية بطريقتين هما طريقة ترطيب الأغشية الرقيقة وطريقة الذوبان المباشر باستخدام بوليمرات مختلفة وهي بولي فينيل بايروليدون ك-٢٥ والسولبلس . وجد ان الصيغ المحضرة بطريقة الذوبان المباشر تمتلك احجام اصغر وكفاءة انحباس اعلى من الصيغ المحضرة بطريقة ترطيب الاغشية الرقيقة .كما وجد ان الصيغ التي تم تحضيرها باستعمال السولبلس لها حجم اكبر وكفاءة انحباس اقل من تلك التي استخدمت فيها البولي فينيل بايروليون ك-٢٥, كما بينت هذه الدراسة انه كلما ازدادت كمية البوليمر ادى الى ازدياد حجم الجسيمات, وان مذيب الميثانول اعطى حجم اصغر للجسيمات مقارنة بالايثانول. من هذه الدراسة نستنتج ان طريقة الذوبان المباشر و استخدام بولي فينيل بايروليدين ك-٢٥ بتركيز ١:٥ اعطوا نتائج افضل من حيث حجم الجسيمات و كفاءة الانحباس.

الكلمات المفتاحية: كارفيديلول, الجسيمات المذيلة النانوية ,طريقة تحضير, بولي فينيل بايروليدون ك٢٥, سولبلس .