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ORIGINAL ARTICLE

Preparation and Ex-Vivo Evaluation of Stabilized Cefdinir Nanosuspension

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ABSTRACT

Purpose: The objective of this research is to prepare cefdinir as a nanosuspension formulation to improve its solubility and dissolution rate. Cefdinir is a class IV drug with low solubility and low permeability.

Methods: Eight formulations were prepared with different types of stabilizers and different concentrations including poly vinyl pyrrolidone (PVP-K90), poly vinyl alcohol (PVA), D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) and soluplus ®. Ratio of drug to stabilizer used to prepare the nanosuspension were 1:1 and 1:2. The prepared nanosuspension formulations were evaluated for particle size, entrapment efficiency, dissolution study, atomic force microscopy (AFM), transmission electron microscope (TEM), field emission scanning electron microscopy (FESEM) and differential scanning calorimetry (DSC).

Results: The dissolution rate was enhanced due to a reduced particle size. The prepared nanosuspension was homogenous with a uniform size and stable cefdinir nanoparticles. Drug entrapment efficiency of F1-F8 was ranged from (78.4 ±0.1) nm to (95.11±0.01) nm.

Conclusion: Enhanced solubility and better dissolution profile of cefdinir result from using solvent evaporation method.

Keywords: Cefdinir, nanosuspension, Antisolvent precipitation, Stabilizer , In vitro Evaluation.

INTRODUCTION

Oral administration is the most convenient, extensively used, and favored form of systemic medication delivery. One of the most difficult elements of medication research is improving the oral bioavailability of poorly water soluble medicines. To enhance solubility and partition within the gastrointestinal barrier, all medicinal molecules in the biopharmaceutical classification system (BCS) classes II and IV can be formulated using nano-sized particles [1]. Lipophilic chemicals account for more than 40% of novel chemical entities (NCE). Currently, poorly soluble pharmaceuticals account for one-third of all US Pharmacopeia-recognized medications. Poorly soluble medicinal compounds are referred to as "grease ball" and "brick dust" molecules. Brick dust molecules have a high melting point and a low partition coefficient. Their low water solubility is due to high intermolecular interaction and high lattice energy in the solid-state. Since there are no interactions with water, grease ball molecules are very lipophilic and have a high partition coefficient [2]. One approach to the delivery of water-insoluble medications is the creation of drug nanosuspensions. Nanosuspensions are drug carriers with particle sizes ranging from 10 to 1000 nm. As a result, research into new dosage forms to attain acceptable bioavailability has become a critical and difficult scientific, industrial, and medical challenge [3]. The pharmaceutical nanosuspension is described as a suspension of extremely finely colloidal, biphasic, dispersed, and solid drug particles in an aqueous medium with a particle size of fewer than 1 µm and no matrix material, stabilized by a surfactant and polymer. Solid particles in nanosuspensions typically have a distribution of particle size of less than one micron, with averaged sizes varying between 200 and 600 nanometers. Miscellaneous routes of drug administration utilize nanosuspension like oral, ocular, parenteral, topical, and pulmonary routes of drug administration. Multiple methods are used to prepare nanosuspension for different drug delivery uses [4].

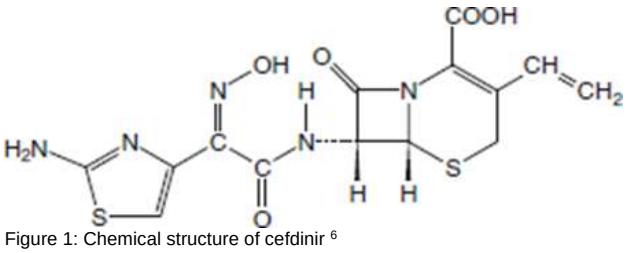


Figure 1: Chemical structure of cefdinir [6]

Cefdinir is a third generation cephalosporins group characterized by having a broad spectrum of activity. It belongs to class IV which is characterized by low solubility and low permeability. Its half-life is short (1.7 ± 0.6 hr). For these reasons, cefdinir has low bioavailability (16–21%) due to a deficient absorption [5]. In this research, cefdinir is prepared as nanosuspension using solvent evaporation technique or anti-solvent precipitation to enhance its solubility, dissolution, and bioavailability. The above method proved its success in improving drug solubility, dissolution , and bioavailability. The chemical structure of cefdinir is shown in figure (1).

MATERIALS AND METHOD

Materials: Cefdinir powder was purchased from (Sigma, USA), Soluplus® was obtained from (BASF, Germany), polyvinyl alcohol (PVA) (JP & SB converting Services, Spain), D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) was obtained from (Mumbai, India), Polyvinylpyrrolidone K-90 (PVP-K90) was provided by (Hangzhou hyper chemicals limited, Zhejiang, China). Dimethyl sulfoxide (DMSO) was provided by (Scharlau Chemie, S.A. Spain). All other chemicals are of analytical grade.

Table 1: Composition of Cefdinir Nanosuspension Using Different Stabilizers at a Drug: Stabilizer Ratio 1:1

Formula	Cefdinir (mg)	PVP-K90 (mg)	PVA (mg)	TPGS (mg)	Soluplus® (mg)	DMSO (ml)	Distilled water (ml)	Rotation speed (rpm)
F1	300	300				2	20	1500
F2	300		300			2	20	1500
F3	300			300		2	20	1500
F4	300				300	2	20	1500

Table 2: Composition of Cefdinir Nanosuspension Using Different Stabilizers at a Drug: Stabilizer Ratio 1:2

Methods: Preparation of cefdinir nanosuspension: Nanosuspensions of cefdinir were prepared by the solvent evaporation method which is known as the anti-solvent precipitation method. Cefdinir powder was dissolved in 2 ml DMSO at room temperature. This was poured into 20 ml of distilled water containing different types of stabilizers maintained at 25°C and subsequently stirred at an agitation speed of 1500 revolutions per min (rpm) for 2 hr and 24 min to allow the volatile solvent to be

evaporated. The resultant organic solution of the drug (organic phase) was added drop by drop using a plastic syringe positioned with the needle directly into an aqueous solution of a stabilizer [7]. The ratios of drug to stabilizer used to prepare the nanosuspensions were 1:1 and 1:2 as shown in table (1) and table (2).

Formula	Cefdinir (mg)	PVP-K90 (mg)	PVA (mg)	TPGS (mg)	Soluplus® (mg)	DMSO (ml)	Distilled water (ml)	Rotation speed (rpm)
F5	300	600				2	20	1500
F6	300		600			2	20	1500
F7	300			600		2	20	1500
F8	300				600	2	20	1500

Evaluation of the prepared nanosuspension: Particle size and size distribution: Particle size measurement was achieved by using Malvern Zetasizer instrument (Malvern, UK). This instrument has a dynamic light scattering work by measuring the intensity of light scattered by the molecules in the sample as a function of time, at scattering angle 90°C and at a constant temperature of 25°C. The polydispersity index (PDI) which is a measure of the width of the size distribution of each formula of cefdinir nanosuspension was measured and it represents the distribution of particle size of the nanoparticles obtained from the particle size analyzer, PDI is an index of spread or variation or width within the particle size distribution [8]. Each formulation was measured in triplicate at 25°C.

Zeta Potential: Zeta potential of the selected formulation of cefdinir nanosuspension was measured. For nanosuspension using electrostatic stabilizer, ± 30mV value of zeta potential is sufficient to stabilize the nanosuspension. On the other hand, for nanosuspensions stabilized by both of steric and electrostatic stabilizer, ± 20 mV value of zeta potential is needed to maintain stable nanosuspension formulation [9]. Zeta potential of the optimum nanosuspension is measured by Malvern Zetasizer instrument (Malvern, UK). The laser is the heart of the zetasizer, as it provides a light source to brighten the particles within the sample. This light divides to give an incident and reference beam for zeta potential investigations.

The incident laser beam passes through the sample cell's center, and the scattered light is discovered at an angle of around 130 degrees. The zeta potential is determined using the frequency spectrum generated by the Zetasizer software in addition to the electrophoretic mobility [10].

Determination of the drug entrapment efficiency (EE) of nanosuspension: The fresh prepared cefdinir nanosuspension : stabilizer ratio 1:1 and 1:2 was centrifuged at 6000 rpm for 20 min using ultracentrifuge. The amount of unincorporated drug was measured by taking an absorbance of an appropriately diluted 25 ml with water at 287 nm using UV-visible spectrophotometer. The amount of free drug in the formulation was measured and the entrapment efficiency was calculated by subtracting the amount of free drug in the supernatant from the total amount of the drug in the formulation. The result will be divided by the total drug in the formulation, then multiplied by 100. For each formulation, the experiment was repeated in triplicate and the average was calculated [9].

In vitro dissolution profile of nanosuspension: The in vitro dissolution study was performed using USP dissolution test apparatus- II (paddle assembly). The dissolution test was performed using cefdinir nanosuspension in 900 ml of 0.1 N HCL (pH 1.2) maintained at 37°C ± 0.5 °C, 50 rpm and samples (5 ml) were withdrawn at scheduled time intervals of (5, 10, 15, 30, 60, 90 and 120) min and replaced by a freshly prepared media. Samples were filtered through filter paper and assayed spectrophotometrically on UV-Visible spectrophotometer at 281 nm wave length [9]. All of the measurements were done in triplicate. The similarity factor f2 was used to determine the similarity in the percent of drug dissolution between two curves according to the following equation:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}|R_t - T_t|^2\right]^{-0.5} \times 100\right\}$$

Where: n represents the number of sampling points, while Rt and Tt is the average percentage of dissolved drug in the reference and test sample at time t. If the f2 value is less than 50, both dissolution profiles can be considered dissimilar according to FDA guidelines [11].

Atomic Force Microscope (AFM): An atomic force microscope (Angstrom Advanced Inc. AA3000) with a scanner of 3.1 m and three piezo electrodes for three axes X, Y, and Z in noncontact mode was used to undertake a more in-depth morphological study. In distilled water, sample suspensions (1 percent w/v) were made, and a drop was impregnated onto aluminum sheet (2 cm x 2 cm). The dried region was tested after it was allowed to dry in a HEPA filter zone [12].

Field emission scanning electron microscopy (FESEM): On an aluminum stub, double-sided carbon tapes were glued. The nanosuspensions were dropped onto the tape and set aside to dry in a desiccator. They were gold- sputtered for 10 min in a row. A scanning electron microscope (Carl Zeiss SMT- Super Ultra Model Gemini Ultra 55) with a vacuum chamber was used to position the aluminum stub. Surface properties of the particles were examined [13].

Transmission electron microscope (TEM): The morphological properties of the obtained optimum drug nanosuspension were studied using a transmission electron microscope (TEM) (Model JEM-1230, JOEL, Tokyo, Japan). A few drops of the sample were placed on a carbon-coated grid, left for two min to allow greater adsorption on the carbon film, and the surplus liquid was removed using filter paper [14].

Freeze drying of nanosuspension: Using freeze-drying to eliminate the water from the best formula, nanosuspension can be converted to powder. A total of 400 mL of the best formulation was made. Four flasks were frozen for 24 hr at - 20°C in a deep freezer. The frozen flasks were connected to the device's vacuum port, followed by four flasks each containing 100 ml of nanosuspension, and the instrument was run until dry powder was obtained. Solvent sublimation from frozen samples required 48 to 72 hr [15].

Differential scanning calorimetry (DSC): Using an automatic thermal analyzer device, a DSC scan of the pure drug was performed, and about 5 mg of cefdinir, soluplus®, physical mixture and lyophilized powder was accurately transferred and the scans were recorded. From 25 to 250

C, the samples were scanned at a rate of 10 °C min. The DSC was used to determine compatibility issues as well as the final formulation [16].

RESULTS AND DISCUSSION

Particle size analysis and polydispersity index measurement: Malvern Zetasizer instrument was used to determine the particle size of the eight formulations. The particle size was within the nano range for all of the formulations. The mean particle size (effective diameter) for formulations was varied in the wide range from 80.42 ±0.2 nm to 368.8 ± 0.2 nm. The particle size and PDI for different formulations of different parameters is shown in table (3). According to the results, smallest particle size was observed (with the F4 and F8) 109.4±0.8 and 80.42 ±0.2 nm respectively.

Table 3: Particle Size, Polydispersity Index and Entrapment Efficiency of Different Cef-NS Formulations

NS formulation No.	Particle size (nm) ±SD	PDI ± SD	EE% ± SD
F1	368.8± 0.2	0.322±0.1	78.4 ±0.1
F2	296.6±0.3	0.1226±0.2	87.32±0.02
F3	239.6±0.7	0.316±0.1	81.43±0.1
F4	109.4±0.8	0.1819±0.4	95.11±0.01
F5	292.7±0.8	0.4487±0.2	90.7 ±0.02
F6	289.1±0.1	0.3718±0.4	90.81±0.04
F7	180.8±0.2	0.4061±0.1	91.69±0.2
F8	80.42±0.2	0.1794±0.1	93.41±0.07

Polydispersity index analysis: Polydispersity index values determine particle size uniformity, with the lowest value indicating the best uniformity. Polydispersity index is a parameter used to determine the particle size distribution obtained from the particle size analyzer [17]. The range of PDI values (0 - 0.05) indicates a monodisperse system, (0.05 – 0.08) indicates a nearly monodisperse system, (0.08 – 0.7) indicates a mid-range polydisperse system, and > 0.7 indicates a polydisperse system (very polydisperse) [17]. In this research, polydispersity index was found ranging from 0.1226±0.2 for F2 to 0.4487±0.2 for F5, as shown in table (3).

Effect of stabilizer type on the particle size of Cefdinir nanosuspension: The good stabilizer is required for preparation of nanosuspension because of the significant role of stabilizer in maintaining nanosuspension stability [18]. The main function of the stabilizer is inhibition of Ostwald's ripening by making hydrating drug particles. Aggregation of drug particles can occur if a stabilizer is not added to the formulation due to the elevated surface energy of nano sized drug particles [19]. In this study, four types of stabilizers were employed in preparing nanosuspension formulations. All of the four stabilizers provided nano size formulations. PVA can produce large size nanoparticles due to the network formation with the polymer at the interface in spite of frequent washings. Other reason for the formation of large drug particles is the presence of low energy during homogenization that results in inability to conquer the viscous forces. High viscosity of the dispersion resulted from hydrogen bonding formation with the solvent molecules due to the OH groups of PVA [20]. PVA is very efficient in reducing the interfacial strain due to the presence of hydrophilic and hydrophobic functional groups compared with acetic acid derived groups and hydroxyl groups. This helps in getting organized at the interface and reducing the interfacial strain even with maintaining low molecular size of nanoparticles [21]. Also, PVA acts as a steric stabilizer and produces thermodynamically stable formulation. Adsorption of PVA molecules on drug particles can prevent particle aggregation. Steric repulsion between particles resulted by PVA due to efficient surrounding drug molecules [22]. On the other hand, PVP-K90 is a hydrophilic polymer and acts as a stabilizer in nanosuspension formulation. It has a steric stabilization function [9]. It results in larger particle size compared with other stabilizers used in this research. In addition to that, the inadequate affinity of stabilizer to drug molecules is the reason for developing larger particle size. This low affinity is due to polymer depletion from the gap between the drug particles (depletion forces) and the supreme attractive forces between the particles[9]. The esterification of vitamin E succinate with polyethylene glycol (PEG) 1000 produces TPGS, a water-soluble derivative of natural vitamin E. TPGS is a non-ionic surfactant with high surface activity and a noticeable effect on the lipid membrane. It has been widely employed in wetting, emulsification, solubilization, and absorption enhancer functions because it can solubilize a variety of water-insoluble compounds [23]. TPGS can enhance drug solubility because it acts as nonionic surfactant. By decreasing CYP3A4 and CYP2C9-mediated metabolism, TPGS has been shown to improve medication stability. In solid dispersion, TPGS can improve drug bioavailability due to its role as adsorption enhancer [24]. In this study, TPGS provided nanosuspension with nano-sized particles lower than produced with both of PVA and PVP-K90. Soluplus® is a graft copolymer composed of polyethyleneglycol (PEG), polyvinyl caprolactam and polyvinylacetate [13,25]. It is predicted to work as an ideal matrix to dissolve poorly soluble medicines in aqueous medium due to its amphiphilic character resulting from its bifunctional nature [13]. A hydrophilic part (polyethylene glycol backbone) and a lipophilic part (vinyl caprolactam/vinyl acetate side chain) make up Soluplus®, an amphipathic graft copolymer. Soluplus® adsorption on drug particles lowers the interfacial tension of the surface particles, resulting in steric hindrance, which prevents freshly generated nanoparticles from aggregating. The nanosuspension stabilized by Soluplus® had the lowest particle size compared with the other stabilizers. This can be due to the chemical structure of Soluplus® in addition to its wettability and dominant surface activity [11].

Effect of stabilizer concentration on the particle size and polydispersity index: Eight formulations were used to show the effect of increasing polymer concentration. Different ratios of (drug: surfactant) were utilized. It is found that increasing polymer concentration will reduce the particle size of the nanosuspension formulation. These results were achieved with four types of polymers used as shown in figure (2). For colloidal systems to be stable, the concentration of stabilizer in the dispersion fluid is critical. By affecting the stabilizer's absorption affinity on the surface of drug particles, the quantity of stabilizer contributes to the suspension's stability. The surfactant's molecular structure influences the effective concentration required for stabilization [26]. The sufficient stabilizer concentration is highly needed. When the stabilizer concentration is insufficient, steric repulsion between the particles may be compromised because of the insufficient stabilizer available for complete coverage of drug particle surface. On the other hand, surfactants with a longer hydrophobic chain and a larger hydrophilic head have been shown to require a lower molar concentration because they provide superior steric hindrance and hence minimize the likelihood to agglomerate [26].

In this study, it had been shown that increasing the concentration of stabilizer provided better coverage of particle surface (drug: stabilizer) (1:2) ratio. This ratio provided less particle size measurement compared with (drug: ratio) (1: 1). Using of soluplus® at the ratio (1 : 1) and (1: 2) resulted in low particle size compared with the other stabilizers used. It had been noted that the low particle size resulted with increasing surfactant concentration in the nanosuspension can be due to low viscosity and low hydrodynamic diameter of the particles with increasing surfactant concentration [9].

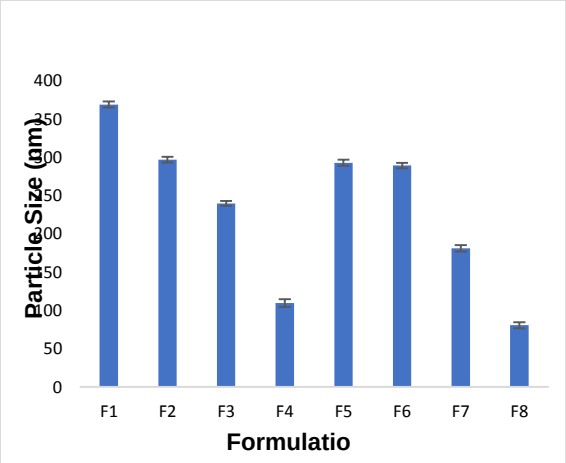


Figure 2: Effect of stabilizer concentration on the particle size of nanosuspension (results are expressed as the mean ±SD (n= 3)

Determination of drug entrapment efficiency of nanosuspension (EE%): The entrapment efficiency of all formulations was ranged from (78.4% to 95.11% as shown in table

(3). Also, the drug entrapment efficiency of F4 was high compared with other formulations. In this study, increasing stabilizer concentration results in an increase in drug entrapment efficiency. This comes in agreement with a previous studies reporting that a high drug entrapment efficiency can be achieved with increasing stabilizer concentration[18]. Therefore, the formulation with highest entrapment efficiency was chosen as the selected formulation (F4) (95.11%). This can be due to the addition of hydrophilic polymer and low ability of the drug to dissociate into the aqueous layer resulting in good dispersion [9].

The Zeta potential: The zeta potential of optimized nanosuspension formulation is shown in figure (3). The particle size of the selected formulation is shown in figure (4). The zeta potential (ζ) is a powerful indicator of the physical stability of the nanosuspension. Zeta potential is determined at the shear plane. It may not provide a significant idea about the physical stability in the presence of electrostatic stabilization. This can be due to the breakup of the charged functional groups present on particle surface and this breakup is responsible for the electrical properties present on the surface. Several factors like medium pH and PKa of the drug can affect the breakup of the charged functional groups [27].

It should be noted that zeta potential measures the degree of repulsion present between the equivalent charged neighboring particles in the system [27].

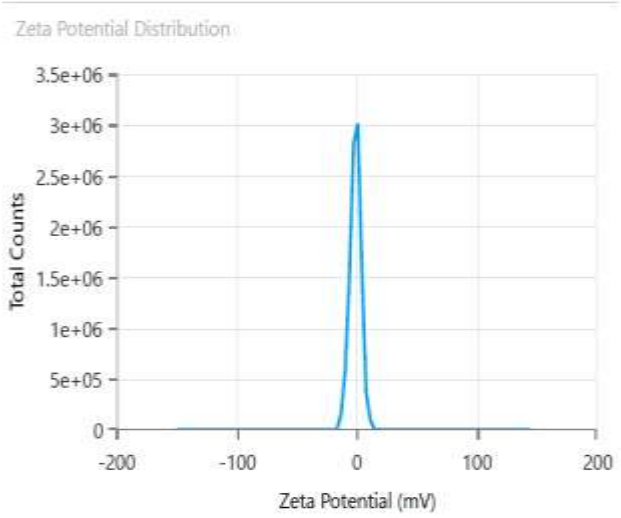


Figure 3: Zeta potential of the selected formulation (F4)

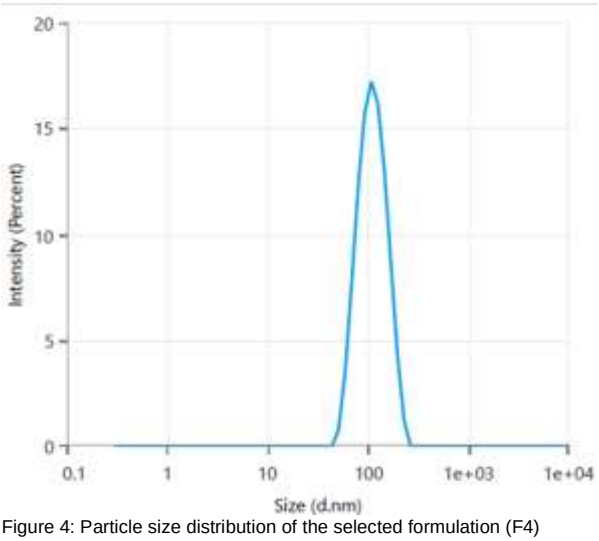


Figure 4: Particle size distribution of the selected formulation (F4)

Statistics Table

Name	Mean	Standard Deviation	RSD	Minimum	Maximum
Z-Average (nm)	109.4	-	-	109.4	109.4
Polydispersity Index (PI)	0.1819	-	-	0.1819	0.1819
Intercept	0.9589	-	-	0.9589	0.9589
Fit Error	0.0007494	-	-	0.0007494	0.0007494
In Range (%)	95.15	-	-	95.15	95.15
Peak One Mean by Intensity (nm)	115.4	-	-	115.4	115.4

In-vitro drug release study of Cefdinir nanosuspension: The dissolution profile of the eight cefdinir nanosuspension formulations were studied using in 0.1 N HCl (pH 1.2) to determine the best release for all of the formulations. Figure (5) shows the release profile of F4 and the pure drug (cefdinir) in 0.1 N HCl (pH 1.2). Maximum cumulative drug release (100%) was observed with F4 within 60 min. The release of pure drug reached approximately 45% in 90 min. F4 had the composition of 300 mg cefdinir and 300 mg soluplus®

(drug: polymer)(1:1) ratio and it is selected as the best formulation from all the prepared formulations in this study. According to the Noyes-Whitney equation, dissolution velocity will be highly improved when the drug particles are decreased to the nano-size due to the resultant higher surface area. The ability of soluplus® to improve drug dissolution in nanosuspension formulation is due to its ability in hydrating the drug particles that are poorly water soluble comparing with pure drug release [11].

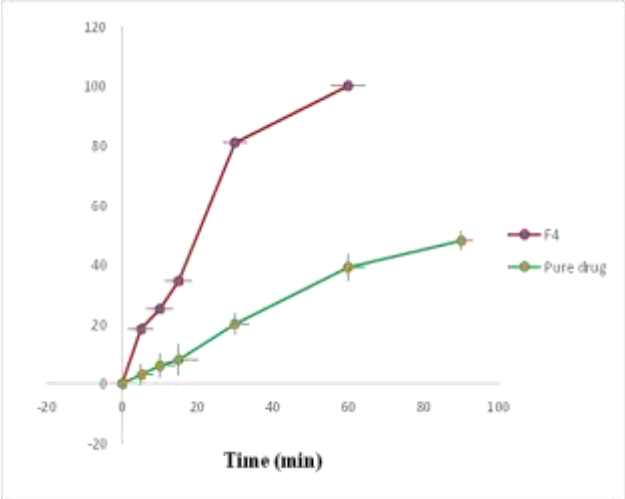


Figure 5: Dissolution profile of cefdinir nanosuspension (F4) and pure drug in 0.1 N HCl (pH 1.2) at 37°C

The differences between the dissolution profiles of the selected formula (F4) and the pure drug dissolution profile were evaluated by measuring the similarity factor f2 using cefdinir pure drug as a reference. The range for f2 values is between 0 and

100. When the value of f2 is higher than 50, both dissolution profiles are similar [11].

In this study, the result of comparison between the dissolution profile of the selected formulation and the pure drug was less than 50 as shown in table (4). The result indicated the dissimilarity between the dissolution profile of F4 and pure cefdinir powder.

Table 4: Similarity factor f2 for cefdinir nanosuspension

Formulation Name	*f2* value in 0.1 N HCl pH 1.2
F4	20.9

Atomic force microscope (AFM): AFM had been employed to study the molecular structure of the selected formulation (F4). AFM imaging is a complementing technique to scanning electron imaging (SEM) since it can analyze surfaces in controlled situations. It is theoretically feasible to calculate the dimensions of nanoparticles with great precision using the AFM's high precision. In air or submerged settings, AFM allows for the viewing of samples with resolution in three dimensions (x, y, and z) [8]. AFM of the selected formulation (F4) was seen in figure (6) and figure (7). The formulation was determined to be stable, with no evidence of particle aggregation. The particle size of cefdinir nanosuspension measured by AFM was nearly equal to that obtained by the Malvern Zetasizer instrument. This gives an indication about the cefdinir nanoparticles stability and the proper size distribution of the selected nanosuspension (F4) [8].

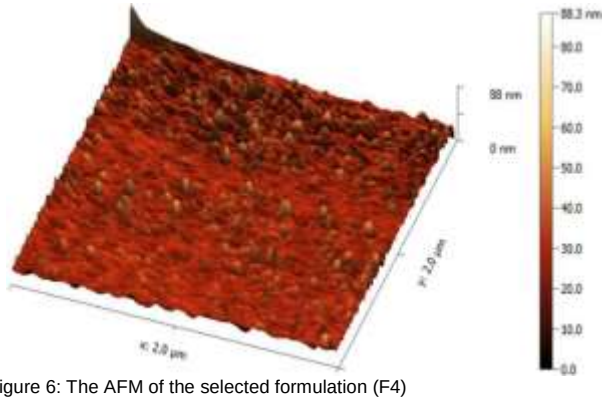


Figure 6: The AFM of the selected formulation (F4)

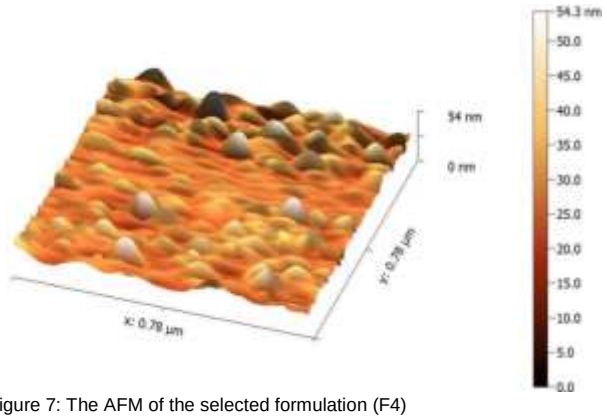


Figure 7: The AFM of the selected formulation (F4)

Field emission scanning electron microscopy (FESEM): FESEM for the selected formulation (F4) was obtained and shown in figure (8). The figure showed the uniform particle size and the small particles. The surface was smooth [28].

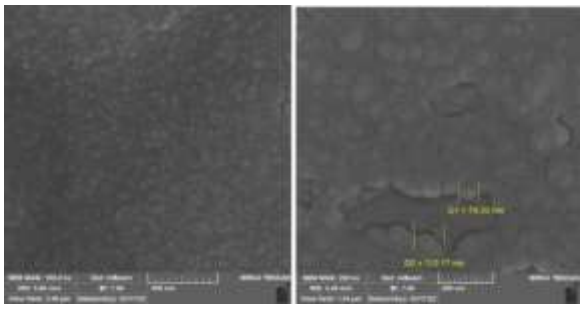


Figure 8: FESEM of the selected nanosuspension formulation (F4) (A and B) at 100K and 200K magnification respectively

Transmission electron microscope (TEM): The morphology of the nanosized drug particles was evaluated using transmission electron microscopy. The selected formulation (F4) was examined by TEM to analyze the surface characteristics of the drug particles. Figure (9) showed TEM of F4. There was no sign for aggregation. The figures showed the round shape and good dispersion of the suspended drug nanoparticles [29].

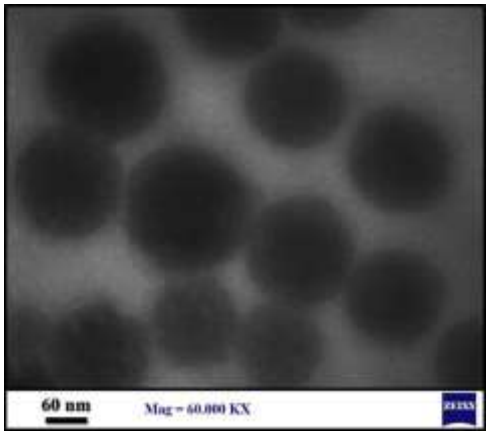
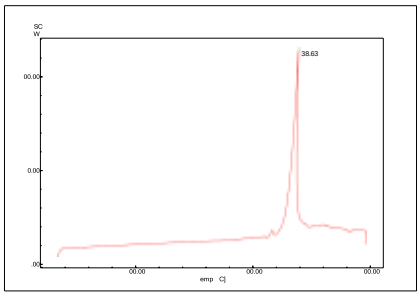


Figure 9: TEM images of selected nanosuspension formulation (F4)

Differential scanning calorimetry (DSC): Figure (10-a) demonstrated DSC of cefdinir pure drug powder. The DSC thermogram of cefdinir pure drug revealed the presence of sharp exothermic peak at 238 °C. This value comes in accordance with the melting point of the pure drug powder. In a previous study, DSC thermogram of pure cefdinir powder was detected at 220°C and showed a sharp exothermic peak [30]. In the physical mixture of cefdinir and soluplus® powder, DSC thermogram remained at the exothermic decomposition with slight change into lower temperature [31] as shown in figure (10-b). On the other hand, both of cefdinir and soluplus® showed separated peaks indicating the absence of interaction [5]. For lyophilized powder, the melting point of cefdinir was disappeared and this indicated cefdinir conversion into the amorphous form. The drug lost its crystallinity and become amorphous as shown in figure (10-c) [20].



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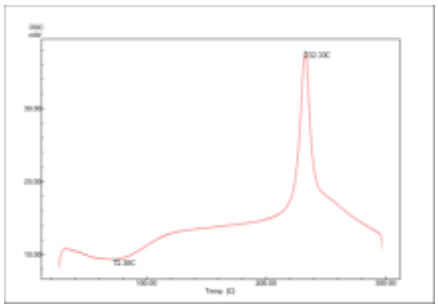

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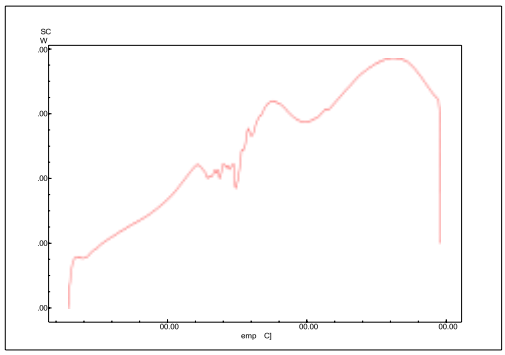

c

Figure 10: DSC thermograms of a) Cefdinir pure drug, b) Physical mixture of cefdinir and soluplus® c) Lyophilized powder of F4

CONCLUSION

Anti-solvent precipitation method was highly efficient in preparation cefdinir as nanosuspension formulation. This method will enhance the solubility and dissolution of the poorly water soluble drugs. Cefdinir nanosuspension was successfully prepared using different types of stabilizers. The used drug stabilizer ratios were (1:1) and (1:2) of drug : stabilizer ratio. The drug: stabilizer ratio (1:1) using soluplus® was highly efficient to stabilize cefdinir nanosuspension. The selected formulation (F4) had reduced particle size, high entrapment efficiency and improved dissolution profile compared with the pure drug. AFM, and TEM showed smooth surface of the prepared nanosuspension with homogenous and

uniform particle size. Finally, analysis of DSC reveals the absence of crystalline structure of cefdinir and the drug becomes in amorphous form.

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