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Formulation optimization and evaluation of Cefdinir nanosuspension using 2^3 Factorial design

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ABSTRACT: Poor water solubility and slow dissolution rate are the prime issues for the majority of upcoming and existing biologically active compounds. Cefdinir is a poorly water-soluble drug and its bioavailability is very low from its crystalline form. The purpose of the present investigation was to increase the solubility and dissolution rate of Cefdinir by preparation of its nanosuspension by solvent evaporation technique. The prepared formulation of nanosuspension was evaluated for its particle size, total drug content, entrapment efficiency, saturation solubility and in vitro dissolution. The optimized formulation was spray dried to obtain nanoparticles. The prepared nanoparticles were then evaluated for their particle size, saturation solubility and in-vitro drug release and the results were compared with the pure drug. A 2^3 factorial design was employed to study the effect of independent variables, amount of PVPK-30 (X1), Poloxamer-188 (X2) and stirring rate (X3) on the dependent variables, particle size (nm,Y1) and in-vitro drug release (%, Y2). Validity of the developed mathematical equation was assayed by designing to check point. The results indicated the suitability of solvent evaporation method for Cefdinir with improved in vitro dissolution rate and thus perhaps enhance fast onset of action for the drug.

KEYWORDS: Cefdinir; nanosuspension; solvent evaporation; factorial design; spray dryer.

1. INTRODUCTION

Nanoparticle technologies have been used as important strategies to deliver drugs, including peptides and proteins, vaccines and more newly nucleotides. In the pharmaceutical field, nanosuspension, nanoemulsion, self nanoemulsifying drug delivery system, solid lipid nanoparticle (SLN) etc are covered under nanotechnology area [1]. It can be used successfully to resolve the problems associated with these conventional approaches for solubility and bioavailability enhancement.

Nanosuspensions are the biphasic systems which comprise of pure drug particles dispersed in an aqueous vehicle, stabilized with the aid of surfactants. They exhibit several advantages namely an increase of solubility, reduced variability caused by food intake for oral administration, an increased adhesiveness to surface/cell membranes, an improvement in bioavailability, ease of formulation, ease of scale-up, narrow size distribution of the nano-sized drugs, controllable drug quantity, general applicability to most drugs (especially drugs that are poorly soluble in both aqueous and non-aqueous media), and no blockade of blood capillaries [2-6]. Moreover, the nanosuspension drug delivery system can be employed as a liquid dosage form or transformed into solid dosage form such as powder, tablet, pellet, capsule, and film dosage forms [7]. Thus, nanosuspension can be safely administrated by a variety of routes including oral, intravenous, ocular, dermal, pulmonary etc.

Cefdinir is a semisynthetic, broad-spectrum, third-generation cephalosporin. It possess a broad spectrum of activity, excellent therapeutic action against susceptible Gram-positive and Gram negative bacteria. It exhibits potent antimicrobial activity, excellent efficacy, convenient dosing and favourable tolerability compared with other antimicrobial agents [8,9]. It belongs to BCS Class IV with low solubility and low permeability characteristics. Cefdinir is available in only two dosage forms: capsules and suspension

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forms. Due to its crystalline nature, it exhibits compressibility problem and thus, not formulated easily in tablet dosage form [10]. Quality by design is a vital component of the modern approach which contributes to pharmaceutical quality. It encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications [11].

2. RESULTS AND DISCUSSION

Cefdinir belongs to BCS Class IV which exhibits low solubility and low permeability characteristics. It is available in only two dosage forms: capsules and suspension forms. Due to its crystalline nature, it exhibits compressibility problem and thus, not formulated easily in tablet dosage form. The current investigation aimed to increase the solubility and dissolution rate of Cefdinir by preparation of its nanosuspension by solvent evaporation technique using PVP K-30, Poloxamer 188 and DMSO. The fresh nanosuspensions were transformed into solid by spray drying to provide a stable solid form. The obtained Cefdinir nanosuspension powder with smooth loose appearance could be easily redispersed after gently shaking. According to result F4 batch exhibited better particle size than others. Zeta potential gives certain information about the surface charge properties and further the long-term physical stability of the nanosuspensions. It is a significant index, which has an effect on the stability of dispersion system, as it reflects electrostatic barriers preventing the nanoparticles from aggregation and agglomeration. Particle aggregation may occur when particles possess too low zeta potential to provide sufficient electric or steric repulsion between each other. Usually, a zeta potential of 30 mV at least for electrostatically stabilized systems or 20 mV for sterically stabilized systems is considered to be sufficient to obtain a physically stable nanosuspension [12]

2.1. Calibration plot in 0.1 N HCl

Cefdinir in 0.1 N HCl showed absorption maximum at 289 nm and it was chosen as the analytical wavelength. Beer's law was obeyed between 0 and 5 µg mL^{-1}. Regression analysis was performed on the experimental data. Regression equation for standard curve was y = 0.047x-0.020. Correlation coefficient for the developed method was observed to be 0.997, which signifies existence of a linear relationship between absorbance and concentration of the drug. Interference studies with formulation excipients studies indicated that no difference exists in the in absorbance recorded at 289 nm. The calibration plot in 0.1 N HCl is depicted in **Figure 1.**

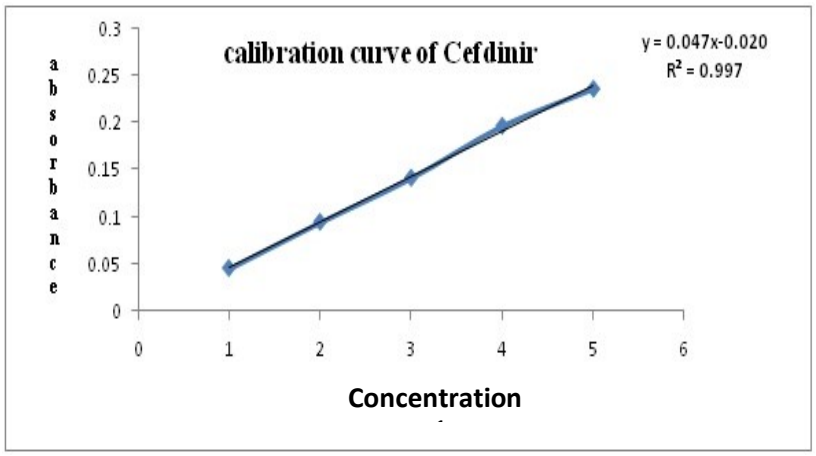

Figure 1. Calibration plot in 0.1 N HCl

2.2. Fourier transforms infrared spectroscopy (FT-IR)

Fourier–transform infrared (FT–IR) spectra of moisture free powdered samples of Cefdinir, PVPK-30, Poloxamer -188 and physical mixture were obtained using a spectrophotometer (FT-IR Jasco 4100, Japan) by potassium bromide (KBr) pellet method. The scanning range was 750-4000 cm-1 and the resolution was 1 cm^{-1}. FTIR analysis was used to evaluate the possible intermolecular interaction between Cefdinir, PVPK-30, Poloxamer -188 and physical mixture. There was no significant difference in the FTIR spectra of pure drug and the physical mixture. Cefdinir structure have carbonyl group, amino, C=N, C=C and hydroxyl group. Carbonyl group has been detected at 2960 cm^{-1}, amino group showed peak at 3292 cm^{-1}, hydroxyl bending peak has also been detected at 1347 cm^{-1}. It has been used to assess the interaction between carrier and guest

molecules in the solid state. The FT-IR spectra of Cefdinir drug, PVPK-30, Poloxamer-188 and physical mixture is depicted in **Figure 2**.

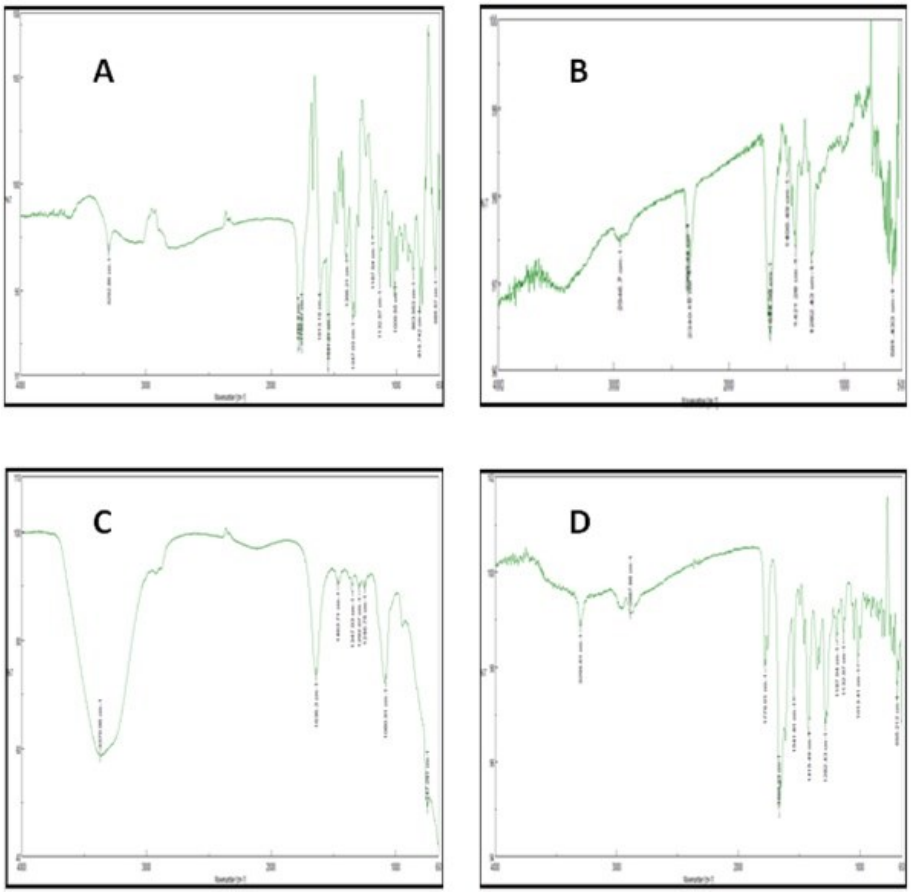

Figure 2. FT-IR spectra of (A) Cefdinir (B) Poly-Vinyl Pyrolidine K-30 (C) Poloxamer-188 (D) Physical mixture.

2.3. Particle size analysis

The shape and size of the nanosuspension were determined using field emission scanning electron microscope (SEM, JSM6490A, Jeol, Tokoyo, Japan). The particle size of the formulated optimized batches F4 of nanosuspension was carried out by using SEM (**Figure 3**). Particle size of nanosuspension batches (F1-F8) were shown in **Table 1.** The particle size of all formulated batches F1-F8 of nanosuspension was carried out by using Motic digital microscope. Particle size of nanosuspension batches (F1-F8) were shown in **Table 1.** The average particle sizes of F1-F8 are in between 0.78 to 3.05 µm. According to result F4 batch have shown better particle size than others (**Figure 4).**

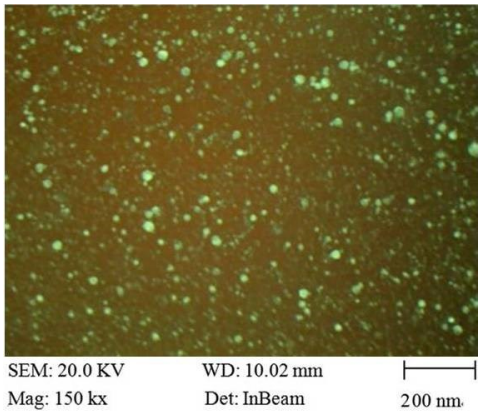

Figure 3. SEM of F4 batch

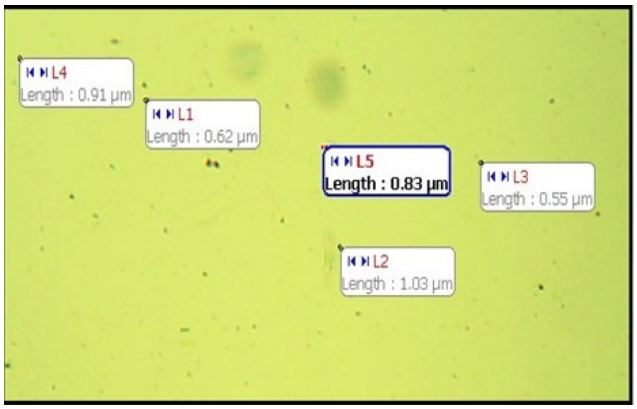

Figure 4. Particle size analysis by motic microscope of F4 batch.

Table 1. Particle size of nanosuspension batches

Batch	Particle size (µm)		
	Max	Min	Average
F1	2.85	1.41	1.89
F2	3.87	1.76	2.82
F3	3.57	0.87	2.36
F4	1.03	0.55	0.79
F5	3.47	1.25	2.30
F6	2.70	1.63	2.09
F7	2.02	1.03	1.45
F8	3.61	2.22	3.05

2.4. Entrapment efficiency

The entrapment efficiency of the formulated nanosuspension batches is highlighted in **Figure 5.** It is observed that Batch F3 showed minimum entrapment efficiency i.e. 58.33% and batch F2 exhibited maximum entrapment efficiency of 92.78%. The entrapment efficacy of the formulated nanosuspension was found to be in the range of 58.33%-92.78% respectively.

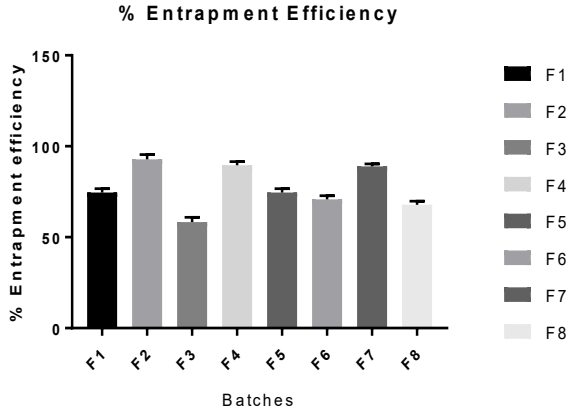

Figure 5. Entrapment efficiency of formulated nanosuspensions

2.5. Total drug content

Total drug content of all the nanosuspensions was found to be greater than 88.00 % indicating suitability of this method for particle size reduction. The optimized batch F4 showed 99.57 % of total drug content as depicted in **Figure 6.**

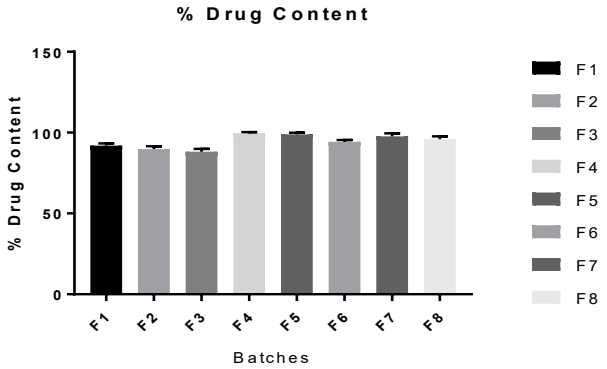

Figure 6. % Total drug content of batches

2.6. Saturation solubility study

As shown in **Figure 7**, batch F4 exhibited maximum saturation solubility of 1.05 µg mL^{-1} and therefore considered as an optimized batch and subjected to further studies. Saturation solubility of the optimized batch of nanosuspension and that of the pure drug was found to be 1.05 µg mL^{-1} and 0.41 µg mL^{-1} respectively. Thus,

there is approximately 2-fold increase in the saturation solubility of Cefdinir when it is formulated in the form of a nanosuspension [23].

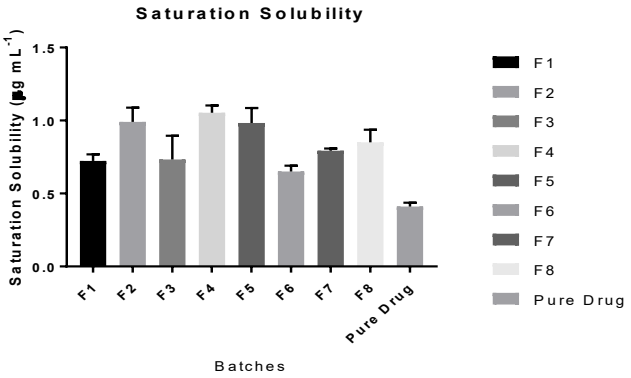

Figure 7. Saturation solubility of Batches F1-F8 and pure drug

2.7. Zeta potential

Zeta potential of the optimized nanosuspension of Cefdinir was 12.5 mV (**Figure 8)**. The non-ionic nature of PVPK-30 and poloxamer 188 resulted in a higher value of zeta potential. It suggests that PVPK-30 and poloxamer 188 result in a complete coverage as they can effectively mask the negative charge on the Cefdinir particles. Thus, it was concluded that the system had sufficient stability.

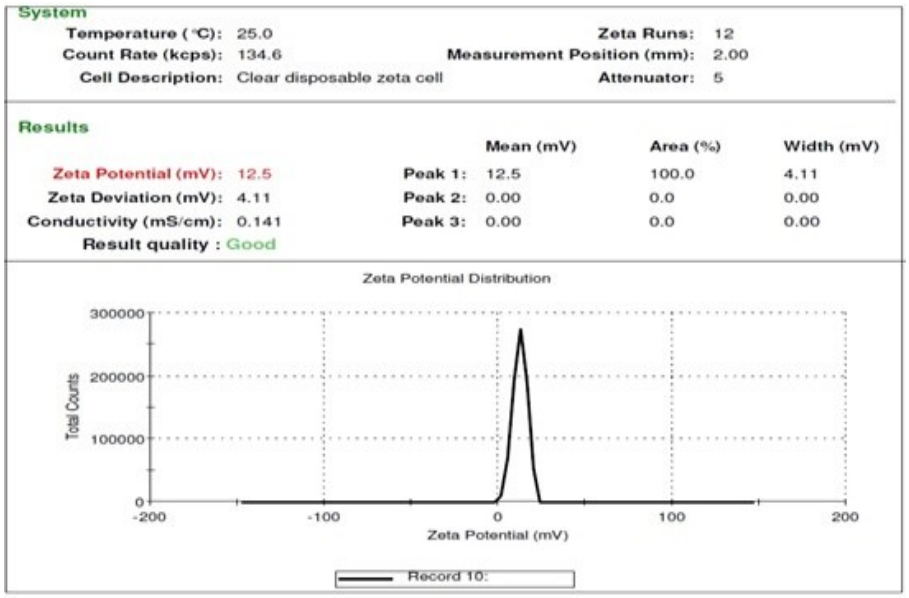

Figure 8. Zeta potential determination of Cefdinir optimized nanosuspension

2.8. Dissolution studies

Dissolution studies were compared for pure drug, nanosuspension batches and spray dried powder of F4 Batch. The amount of drug release from the pure drug was found to be 22.36% after 30 min (**Table 2)**. The optimized batch F4 of nanosuspension formulation showed 96.18% drug release after 30 min. It was greater than all the other formulated batches of nanosuspension. The spray dried powder of the optimized batch F4, showed maximum drug release of 99.90% after 30 min which was far better than the pure drug and batch F4 nanosuspension which justifies that the need of particle size reduction. An increase in the dissolution rate of the drug may be attributed to an increase in the accessible surface area to the dissolution medium and a coating of hydrophilic surfactant on the surface of drug particles. This enhanced dissolution rate can be attributed to the higher surface area of nanocrystals available for dissolution and the decreased diffusion layer thickness (**Figure 9)**.

Table 2. Dissolution study of batches F1-F8, pure drug and spray dried powder

Time (min)	0	5	10	15	20	25	30
F1	0	6.00	44.33	49.66	55.66	77.33	93.33
F2	0	13.61	32.07	47.30	66.69	76.84	92..06
F3	0	13.10	37.26	44.05	58.89	81.47	92.52
F4	0	14.81	37.68	41.43	58.12	76.31	96.18
F5	0	15.27	34.09	49.63	53.18	87.27	93.00
F6	0	9.00	36.92	55.15	62.07	81.92	93.00
F7	0	21.00	26.62	44.25	62.62	79.50	94.50
F8	0	5.25	38.43	48.37	74.43	76.68	87.18
Pure drug	0	5.72	9.00	14.18	15.27	18.00	22.36
Spray dried powder	0	16.8.0	34.20	48.60	61.20	80.40	99.80

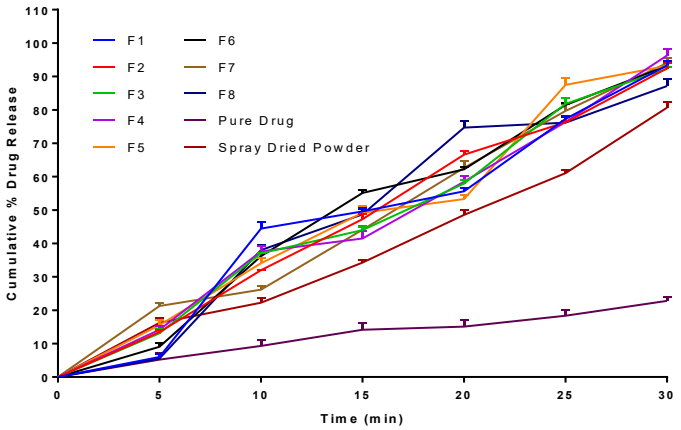

Figure 9. Cumulative %drug release of F1-F8, pure drug and spray dried powder

2.9. Data analyses of formulations

A 2^3 full factorial design was selected and the 2 factors were evaluated at 3 levels. The amount of PVP K-30 (X1), poloxamer 188 (X2) and the stirring rate (X3) were selected as independent variables and the dependent variables were particle size (Y1) and in vitro drug release (Y2). The data obtained was treated using Stat-Ease Design Expert 9.0.2.0 software and analyzed statistically using analysis of variance (ANOVA).

2.9.1. Data analysis of Y1 (Particle size nm)

Y= 412.63 -45.93X1+9.68X2+54.88X3 -2.61X1X2 -1.0875X2X3 +0.1625 X1X3 **(1)**

Regarding the particle size, the results of multiple linear regression analysis showed that both the coefficients X1 bear a negative sign and coefficients X2 and X3 bear positive sign (R2 = 0.9300). Thus, it can be concluded from the equation (1) that when the concentration of X1 was decreased with an increase in the concentration of X2 and X3 then the desired particle size could be obtained and by its controlling the stabilization of the nanosuspension for coalescence was achieved (**Figure 10)**. ANOVA for particle size (Y1) are shown in **Table 3**, which has significant for drug release due to lower particle size.

Table 3. ANOVA for particle size

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	3.4700	3	1.1600	18.86	0.0080	significant
A-PVP K-30	1.5200	1	1.5200	24.76	0.0076	
B-Polo- 188	0.1676	1	0.1676	2.73	0.1737	
C-Stirring Rate	1.7800	1	1.7800	29.08	0.0057	
Residual	0.2454	4	0.0613			
Cor Total	3.7200	7				

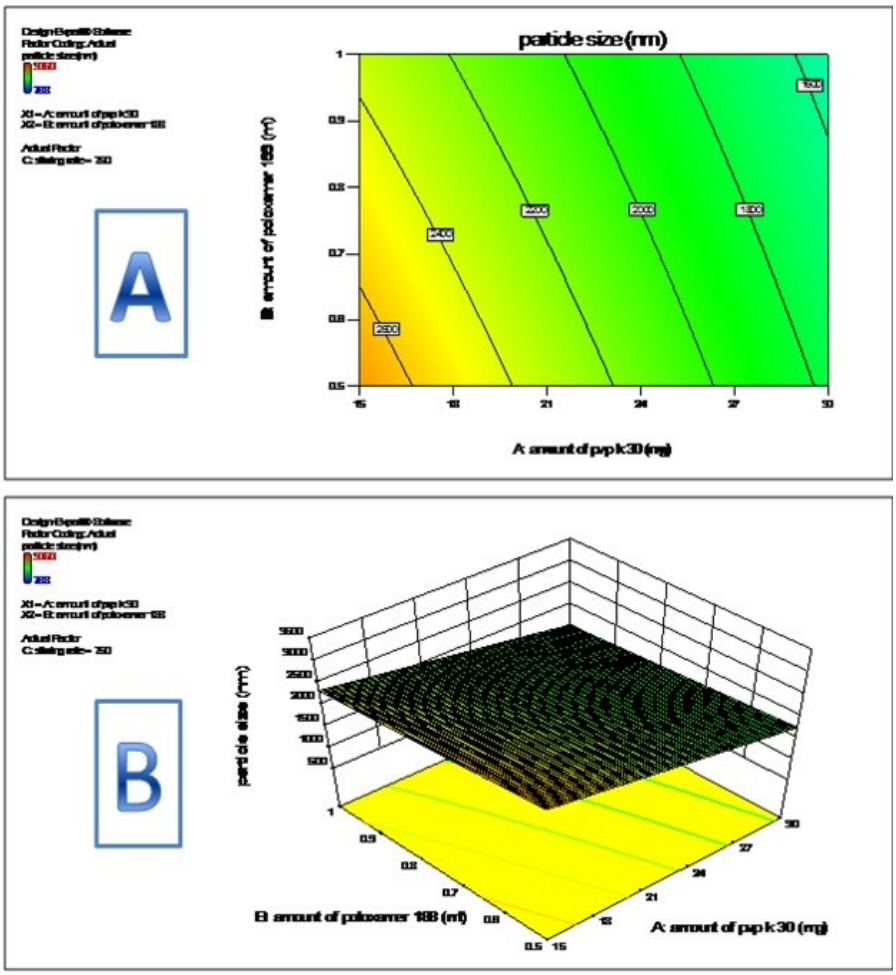

Figure 10. A) Contour plot for Particle size **B)** Surface plot for Particle size

2.9.2 Data analysis of Y2 (% in vitro drug release)

Y= 81.38 +18.30 X1 +6.809 X2 +70.20X3 –6.505 X1X2 –3.630 X2X3+0.0825 X1X3 **(2)**

Regarding the *in vitro* drug release, the results of multiple linear regression analysis showed that at the lower concentration of polymer and by increasing the stirring rate, the drug release was found to be increased (**Table 4)**. Enhancement in dissolution rate of Cefdinir from nanosuspension formulation may be attributed to its increased surface area which further enhanced its strong hydrophilic character towards PVPK-30, due to the formation of intermolecular hydrogen bonds and contributed in improving its wettability as depicted in **Figure 11.**

Table 4. ANOVA for % in vitro drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	39.47	3	13.16	7.16	0.0437	significant
A-PVP K-30	16.76	1	16.76	9.12	0.0391	
B-Polo- 188	6.81	1	6.81	3.71	0.1265	
C-Stirring Rate	15.90	1	15.90	8.66	0.0423	
Residual	7.35	4	1.84			
Cor Total	46.82	7				

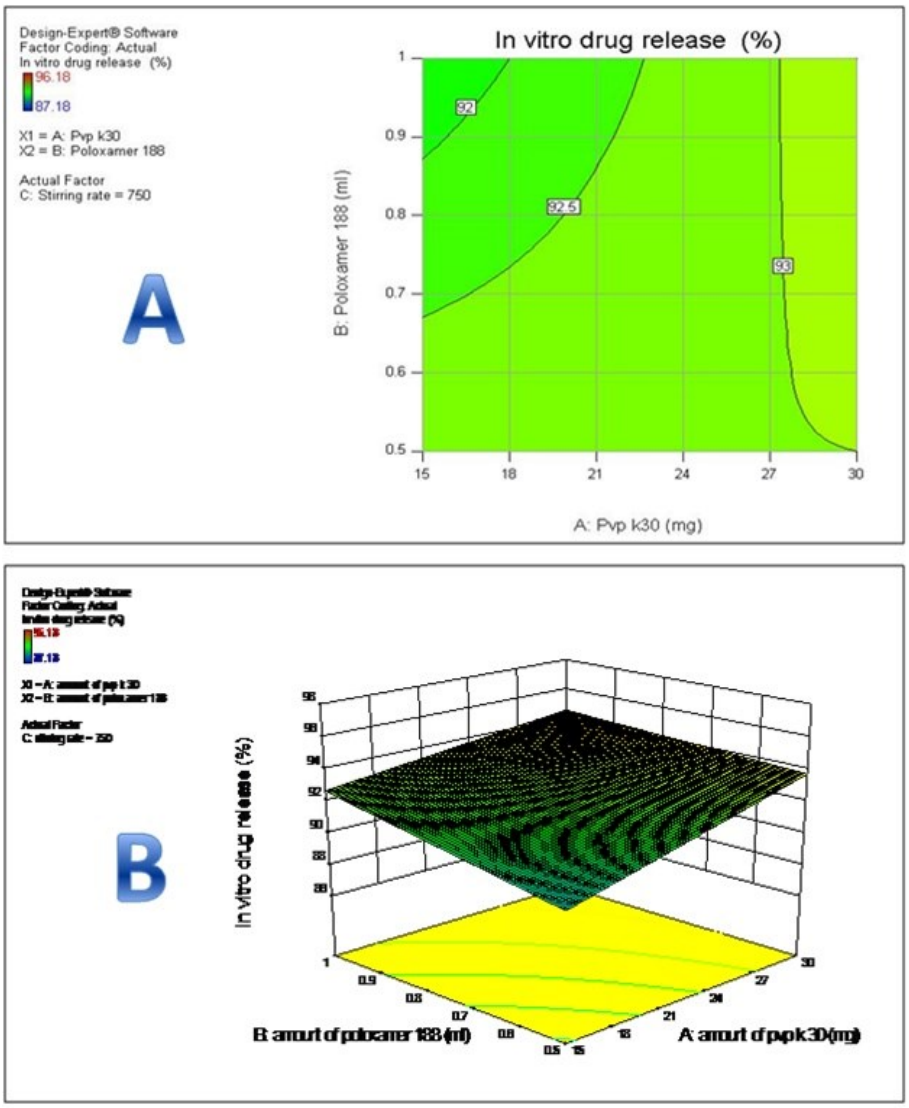

Figure 11. A) Contour plot for in vitro drug release **B)** Surface plot for in vitro drug release

2.10. Check point analysis

Two checkpoint formulations (C1 and C2) were designed to verify validity of the above equations and determine the response values for each dependent variable. The response values of the experimental results were compared with the predicted value from the model. Upon validation, the % error of variables was observed to be below 5.00%, and there was a minor difference between the experimental value and the predicted value. The check point analysis terms were highlighted in **Table 5.**

Table 5. Check point analysis

Batch	X1	X2	X3	Particle size			In vitro drug release		
				observed value	predicted value	% error	observed value	predicted value	% error
C1	19	0.7	630	1.810	1.790	1.10	98.65	97.62	1.04
C2	25	0.9	856	0.623	0..618	0.80	95.30	94.28	1.07

2.11. Optimization criteria for cefdinir nanosuspension

It was the most important part of response surface methodology. The formulation of the drug with good drug release characteristics and which exhibited minimum particle size was selected as an optimized

formulation. The criteria for optimization of formulation of Cefdinir nanosuspension is represented in **Table 6.**

Table 6. Particle size and release kinetics for optimum formulation

Property	Range
Particle size	0.5-1.5µm
Drug Release	96-100 %

2.12. Optimization of cefdinir nanosuspension

Formulation F4 was selected as an optimized formulation as it greatly fitted in the given criteria for optimization of formulation. Formulation F7 was found to possess higher particle size and achieved the release of the drug in a controlled and complete manner

3. CONCLUSION

The objective of the present study was to formulate and evaluate nanosuspension of Cefdinir. The formulations of nanosuspension of Cefdinir were developed by solvent evaporation technique by varying the compositions of stabilizers and stirring speed. Formulation F4 exhibited minimum particle size and showed good drug release characteristics. Cefdinir nanosuspension was prepared by solvent evaporation method which is relatively simple and rapid. The result of particle size, entrapment efficiency, saturation solubility, drug content and in vitro drug release justified that the method employed for preparation of nanosuspension is suitable. From the FT-IR studies, it was observed that there was no chemical interaction between the drug and polymers used, indicating that the drug was in stable form. Thus, the results of our studies indicated the suitability of solvent evaporation method for Cefdinir with improved in vitro dissolution rate and thus perhaps enhance fast onset of action for the drug.

Results should be clear and concise. Text, tables and figures must show minimal overlap, and must be internally consistent. Tables and figures should be designed to maximize the presentation and comprehension of the experimental data. Attention should be paid to the matter of significant figures (usually, no more than three). The same data should not be presented in more than one figure or in both a figure and a table. As a rule, interpretation of the results should be reserved for the discussion section of a Research Article, but under some circumstances it may be desirable to combine results and discussion in a single section.

4. MATERIALS AND METHODS

4.1. Methods

Cefdinir was obtained as a gift sample from Lupin Research Park, Pune. Polyvinylpyrrolidone K-30 and Dimethyl sulfoxide were procured from Research- Lab Fine Chem Industries (Mumbai); whereas Poloxamer 188 was purchased from Sigma Aldrich Mumbai. All the other ingredients used in the research work were of analytical grade.

4.2 Experimental Design

2^3 factorial design is one of the tools to study the effect of different variables on the quality determinant parameters of any formulation. Based on the principle of design of experiments, this design was employed to investigate the effect of three independent factors. A 2^3 factorial design for three factors at two levels each was selected to optimize the varied response variables. The three factors, amount of PVP K-30 (X1), Poloxamer-188 (X2) and stirring rate (X3) were varied and the factor levels were suitably coded. The particle size (nm, Y1), and *in-vitro* drug release (Y2) were taken as responses variables. In this design, 3 factors are evaluated, each at 2 levels are shown in **Table 7.** Experimental trials were performed at all eight possible combinations are shown in **Table 8.** All other formulation variables and processing variables were kept in variant throughout the study.

Table 7. Variable level of 2^3 factorial design for cefdinir nanosuspension

Variable level	-1 (low)	+1 (high)
PVP K-30(mg) (X1)	15	30
Polo -188 (ml) (X2)	0.5	1.0
Stirring rate (rpm)(X3)	500	1000

Table 8. Formulation of cefdinir nanosuspension using 23 factorial design

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Cefdinir (mg)	300	300	300	300	300	300	300	300
PVP K-30 (mg)	15	15	15	30	30	30	30	15
Polo -188 (ml)	1.0	1.0	0.5	1.0	1.0	0.5	0.5	0.5
DMSO (ml)	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Distilled Water (ml)	30	30	30	30	30	30	30	30
Stirring rate (RPM)	1000	500	1000	1000	500	500	1000	500

4.3 Calibration plot in 0.1N HCL

Stock solution of 100 µg mL^{-1} of Cefdinir was prepared in 0.1 N HCL and further subsequently diluted with 0.1 N HCl to get solutions with concentration range 1-5 µg mL^{-1}, six number of parallel runs of each experiment was carried out. The solutions were then filtered and analyzed spectrophotometrically at 289 nm using UV-Spectrophotometer (Jasco V630, Japan) and standard curve was plotted and values of slope, intercept and coefficient of correlation were calculated [13].

4.4 FT-IR spectroscopic analysis

Fourier–transform infrared (FT–IR) spectra of moisture free powdered samples of Cefdinir, PVPK-30, Poloxamer -188 and physical mixture were obtained using a spectrophotometer (FT-IR Jasco 4100, Japan) by potassium bromide (KBr) pellet method. The scanning range was 750-4000 cm^{-1} and the resolution was 1 cm^{-1}[14].

4.5 Preparation of cefdinir nanosuspension

Nanosuspension were prepared by solvent evaporation technique. Cefdinir nanosuspension was prepared using PVP K-30, Poloxamer 188 and DMSO by solvent evaporation method. An accurately weighed quantity of Cefdinir (300 mg), and PVP K-30 was dissolved in DMSO. Alternatively a solution of Poloxamer 188 in water was prepared. Drug solution was taken into a syringe and added drop by drop to solution of Poloxamer 188 in a beaker which was placed on a magnetic stirrer to evaporate the organic solvent. This process was carried out up to 1 hr. Further, this solution was kept for sonication for about 1 hr [15].

4.6 Conversion of nanosuspension into solid nanoparticles by spray drying

Freshly prepared Cefdinir nanosuspension were spray dried to get nano size powder using water as a solvent [16]. Spray drying was conducted using a Labultima LU-222 Advanced spray dryer (Mumbai – 400068, INDIA), at inlet temperature of 105-115 °C, outlet temperature 1000C, cool temperature 400C, aspirator flow rate of 45 nm3/hr, feed pump flow rates of 3 mL/min and cycle time 50 min. After collecting powders from the receiving chamber they were stored in glass desiccators at room temperature for further investigations.

4.7 Characterization of nanosuspension

4.7.1 Particle Size Analysis

The average particle size of the prepared nanosuspension formulation was determined by using Motic microscope and SEM [17].

4.7.2 Entrapment efficiency

This method is suitable for determining entrapment efficiency of nanosuspension when fairly high concentration of free drug is present in the supernatant after centrifugation. 10 mL portion of the freshly prepared and cooled nanosuspension was centrifuged at 1000 rpm for 10 minute using a Remi centrifuge. The supernatant was removed and the amount of unincorporated drug was measured by taking the absorbance of the supernatant solution at 289 nm by using UV spectrophotometer [18].

4.7.3 Total drug content

The percent drug content in each prepared nanosuspension was determined as per the following procedure. 5 mL of the prepared nanosuspension was taken and centrifuged at 1000 rpm for 15 min. Then 1 mL of aliquot was taken and diluted with methanol, filtered and the drug content of the diluted sample was estimated by UV spectrophotometer at λ max 289 nm [19].

4.7.4 Saturation solubility study

The solubility of Cefdinir in water was determined by addition of an excess amount of the drug to the solvent, after which the mixture was stirred on a magnetic stirrer at 25 ^{0}C for 24 hrs. The prepared nanosuspension was filled in a vial and kept for 48 hrs stirring to ensure saturation. Then 1.5 mL of nanosuspension was filled in a 2 mL centrifugation tube and centrifuged at 2500 rpm for 30 min [Remi laboratory centrifuge]. The supernatant was then filtered through 0.2 µm filter paper and thereafter analyzed spectrophotometrically using UV/visible spectrophotometer [UV-1700, Shimadzu AS, Japan] at 289 nm after suitable dilutions. Each sample was analyzed in triplicate [20].

4.7.5. Zeta potential

It was performed to investigate the surface properties of nanosuspension. It is an important parameter for prediction of stability of nanosuspension. In this study, the zeta potential was assessed by determining the electrophoretic mobility of the particles using Malvern Zetasizer NanoSeries, Nano-ZS, Malvern Instruments, UK [21].

4.7.6. Dissolution studies

Dissolution of the pure drug A sample of pure drug Cefdinir, its formulated nanosuspension batches and spray dried powder of optimized batch F4 was placed in the dissolution vessel containing 900 mL of 0.1N HCl maintained at 37 ± 5ºC. Aliquots were withdrawn at suitable time intervals for 60 min, and filtered subsequently; same volume of fresh medium was added to the dissolution vessel after each withdrawal. Quantification of the samples was done by UV analysis at 289 nm and the values were plotted versus time [22].

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