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Formulation and Evaluation of Amoxicillin Nanosuspension

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HUMAN

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Keywords: Amoxicillin**,** Nanosuspension, Nanoprecipitation**,** Particle Size, Solubility, Zeta Potential

ABSTRACT

Nanotechnology is one of the growing fields in medicine. “Nano” stands for the particle size ranging from 1-1000µm. Nanosuspensions are sophisticated technology in the field of nanoscience. These are simple to prepare and are more advantageous than other approaches. Other techniques like microemulsion, solid dispersions, and inclusion complexes using cyclodextrin even though showed increased solubility, but not applicable for drugs that are insoluble in both aqueous and organic media. The objective of this study was to formulate nanosuspensions to resolve the solubility issue of amoxicillin which is widely used as an antibiotic, which will improve antibiotic therapy and make the dosage form more cost-effective. These focuses on, method of preparation, physical characteristics and evaluation of nanosuspensions. The nanoprecipitation method presents numerous advantages, in that it is a straight forward technique, rapid, and easy to perform. Polymeric nanosuspensions were prepared by nanoprecipitation method by using biodegradable polymer PVP-K 30 loaded with Amoxicillin in the ratio of 1:1, 1:2, 1:3, 1:4, and 1:5 respectively and the formulation was evaluated for drug excipients compatibility study, drug content, particle size analysis, and zeta potential. Nanoparticulate drug delivery has advantages over conventional dosage forms which include improved efficacy, reduced toxicity, enhanced biodistribution, and improved patient compliance.

INTRODUCTION

Nanosuspensions are colloidal dispersions of solid drug particles in a liquid phase with average particle sizes below 1µm stabilized by the use of surfactants. Nanosuspension technology can be used to improve stability as well as the bioavailability of poorly soluble drugs. Nanosuspensions are biphasic systems consisting of pure drug particles dispersed in an aqueous vehicle, stabilized by surfactants. Techniques such as wet milling, high-pressure homogenization, emulsification-solvent evaporation, and supercritical fluid have been used in the preparation of nanosuspension(1-3). Nanosuspension engineering processes currently used are precipitation, high-pressure homogenization, and pearl milling either in water or in mixtures of water and water miscible liquids or non-aqueous media. In nanoprecipitation, the drug is dissolved in the organic phase, the ratio of drug to polymer is taken as 1:1,1:2,1:3,1:4,1:5. The mixture of polymer and water is used as an aqueous phase. The drug is added by using the syringe with a needle. Then the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type of stabilizer, concentrations of stabilizer, and homogenizer speed. To produce small particle size, often a high-speed homogenization or ultrasonication may be employed. The supersaturation is further attained by evaporation of drug solvent. This yields to the precipitation of the drug(4). For large-scale production of nanosuspensions, media milling and high-pressure homogenization technology have been successfully used. More than 40 percent of the drugs coming from High-through output screening are poorly soluble in water. One of the critical problems associated with poorly soluble drugs is too low bioavailability and or erratic absorption. Nanotechnology can be used to resolve the problems associated with these conventional approaches for solubility and bioavailability enhancement.

MATERIALS AND METHOD

CHEMICALS: Amoxicillin (Drug), Polyvinylpyrrolidone (Polymer), Tween80 (Surfactant) Bezoalkonium chloride (Preservative), Ethanol (Solvent) are obtained from Yarrow chemicals, Aurangabad, Maharashtra, India.

METHODS:

Calibration Curve –

100 mg amoxicillin was weighed accurately and dissolved in 100 ml of distilled water in a volumetric flask. Flask was shaken for 5 min to dissolve the drug properly, flask was labeled as a Stock solution was further diluted into 100 ml distilled water. Maximum wavelength was determined by scanning on UV –Visible spectrometer. Further dilutions were prepared by1 ml stock solution in 100ml, 2 ml stock solution in 100 ml, and so on. These results are surmised in tables.

Melting Point –

The melting point was measured with the use of Thiele's tube apparatus by using paraffin oil, thermometer, and placed in thiele tube containing paraffin oil, the tube is heated by using a burner. The range of temperature when the drug just start melting and till it completely melts was noted.

FTIR Spectroscopy Analysis - Fourier–transform infrared (FT–IR) spectra of a moisture-free powdered sample of amoxicillin, PVP, Tween 8, and physical mixture were obtained using a spectrophotometer (FTIR–Shimadzu, India).

Differential Scanning Colorimetry

(DSC) Analysis-

DSC scans of pure drug samples and polymer were recorded using DSC-Shimadzu 60 with TDA trend line software. All sample were weighed.

1. *FTIR*

FTIR has been used to assess the interaction between excipients and the drug molecule in the solid state. The FTIR spectra were taken by the pure drug, PVP, Tween80, reconstituted nanosuspension. The FTIR spectra of all samples show in Figure No.--. Row amoxicillin and precipitated nanoparticle exhibited the same FTIR spectra, 10mg) and heated at a scanning rate of 10^0c/min under dry nitrogen flow (100 ml/min) between 50 and 300^0c. Aluminum

pans and lids were used for all samples. Pure water and indium were used to calibrate the DSC temperature scale and enthalpy response.

Preparation of Amoxicillin Nanosuspension by nanoprecipitation - Nanosuspensions were prepared by the solvent evaporation technique (2,3). It contains an aqueous phase and organic phase, the aqueous phase containing different amounts of PVPK-30 and Tween80 maintained at room temperature as ratio 1:1, 1:2, 1:3, 1:4, 1:5 (Table No. 2). The organic phase contains amoxicillin (drug) dissolved in ethanol at room temperature. This was poured into an aqueous phase subsequently stirred on a mechanical stirrer for 4000 rpm (Remi, India) for 1 hour. Then the volatile solvent was allowed to evaporate.

Addition of organic solvent by mean of a syringe positioned with the needle directly into surfactant containing water. The organic solvent was left to evaporate off under a slow mechanical stirrer of the nanosuspension at room temperature for 8 h.

Table No. 1: Composition of Amoxicillin Suspension

Table No. 2: Composition of Various Nanosuspensions Formulation

Evaluation Parameter (6-8)

1. **Particle Size Analysis-**

Particle size and particle size distribution was determined by photon correlation spectroscopy (PCS) using a zeta sizer (z- average, measuring range: 20-1000 nm).

2. ***Viscosity determination***-

Viscosity was determined by Brookfield viscometer. The suspension is poured into a beaker without bubble then measures the reading and calculate viscosity.

RESULTS AND DISCUSSION:

The sample of amoxicillin that was procured for the study was identified and estimated for its purity. The sample of amoxicillin was identified by melting point, FTIR, Differential Scanning Colorimetry.

2. *Construction of Calibration Curve using UV spectrometer-*

The UV spectrometer method was selected for the estimation of amoxicillin, showing absorbance at ƛ max 343.43nm (Figure No. 1.1).

The standard curve of amoxicillin was constructed in distilled water using UV- visible spectrometer. Excellent linearity, precision, and reproducibility were obtained in the range of 2-10 µg/ml. A standard calibration curve was plotted (Table No. 3, Figure No. 1.1) as follow.

3. *Melting Point* –

The melting point was determined by Thiele's tube apparatus by using paraffin oil and a thermometer. The melting point was found to be 141-145^{0}C.

4. *FTIR*

FTIR has been used to assess the interaction between excipients and the drug molecule in the solid state. The FTIR spectra were taken by a pure drug, PVP, Tween80, reconstituted nanosuspension. The FTIR spectra of all samples shown in Figure No --. Raw amoxicillin and precipitated nanoparticle exhibited same FTIR spectra, the amoxicillin showed a peak at 3468 for N-H and the range is from 3300-3500, and the nanosuspension showed the peck at 3543 as shown in Figure No --., which demonstrate that the chemical structure of the drug is not changed before and after the precipitation process.

5. DSC-

The physicalproperties of amoxicillin and reconstituted nanoparticles of nanosuspension was examined by DSC and there are thermograms are shown in Figure No1.6. Raw amoxicillin exhibited a melting point with fusion enthalpy whereas a DSC scan of PVP, a broad endotherm ranging from 207-234 was observed due to the presence of a residual solvent.

6. *Particle Size Analysis* –

The mean particle size and particle size distribution affect the saturation solubility, dissolution rate, physical stability, even *In vivo* behavior of nanosuspension. The polydispersive index in the range of 0.1-0.22 indicates a fairly narrow size distribution that can be determined by photon correlation spectroscopy(9,10).

CONCLUSION

Nanoprecipitation technique was employed to produce nanoparticles of amoxicillin, a poorly water soluble drug, for the improvement of solubility. In this process, the particle size of amoxicillin can be obtained in the micro and nanosize ranges, by adjusting the operation parameter, such as polymer concentration, and organic to aqueous solvent ratio. The best nanosuspension of particle size of 261 nm can be obtained by a 1:1 ratio of drug to polymer using a solvent evaporation technique at a laboratory scale. Nanosuspension can thus be a simple and effective approach to produce submicron particles of poorly water soluble drugs.

Table No. 1: Composition of Various Nanosuspension

Formulation code	Drug mg	Polymer (mg)	Surfactant	Preservative	Solvent(ml) Ethanol	Solvent(ml) water
F1	200	100	2	0.04	2	20
F2	200	200	2	0.04	2	20
F3	200	300	2	0.04	2	20
F4	200	400	2	0.04	2	20
F5	200	500	2	0.04	2	20

Table No. 2: Composition of Amoxicillin Suspension

Sr. No.	Ingredient	Quantity	Use
1	Amoxicillin	200mg	Antibiotic
2	Polyvinyl pyrrolide	200mg	Polymer
3	Ethanol	2ml	Solvent
4	Tween-80	0.04g	Surfactant
5	Bezoalkonium chloride	0.04%	Preservative
6	Pineapple essence	0.1ml	Flavoring agent
7	Saccharine	0.1ml	Sweetening agent
8	Distilled water	20ml	Vehicle

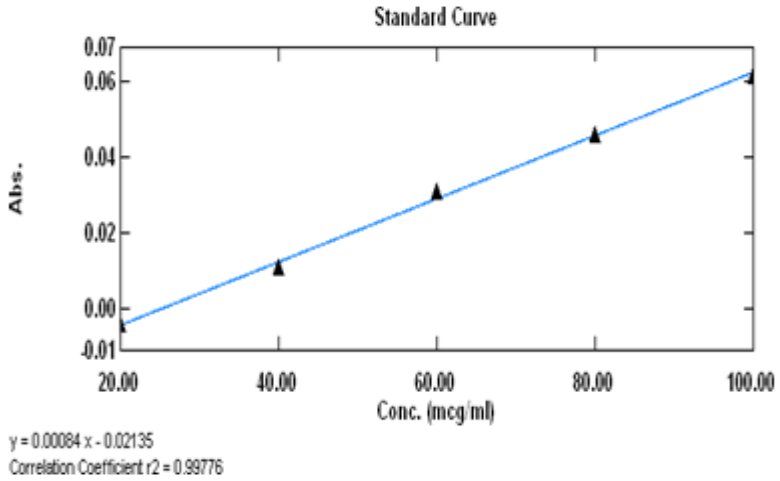

Figure No. 1.1: Construction of Calibration Curve

FTIR

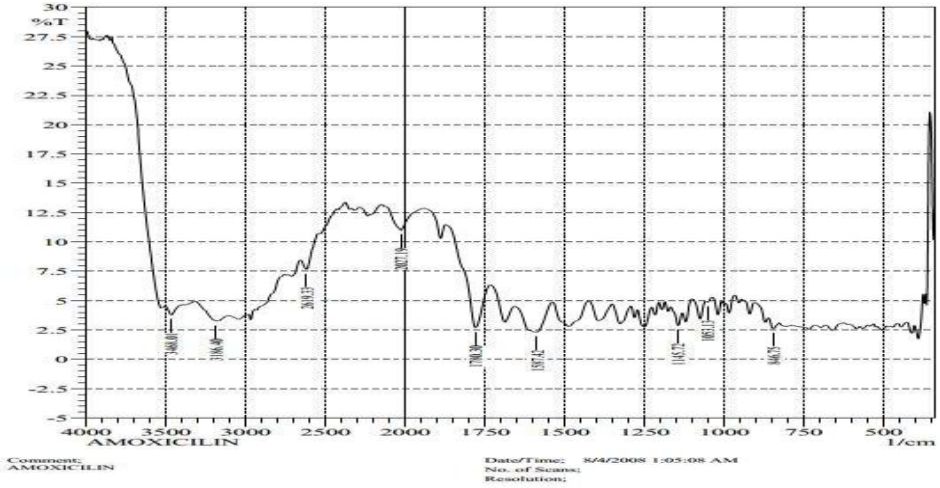

Figure No. 1.2: Amoxicillin

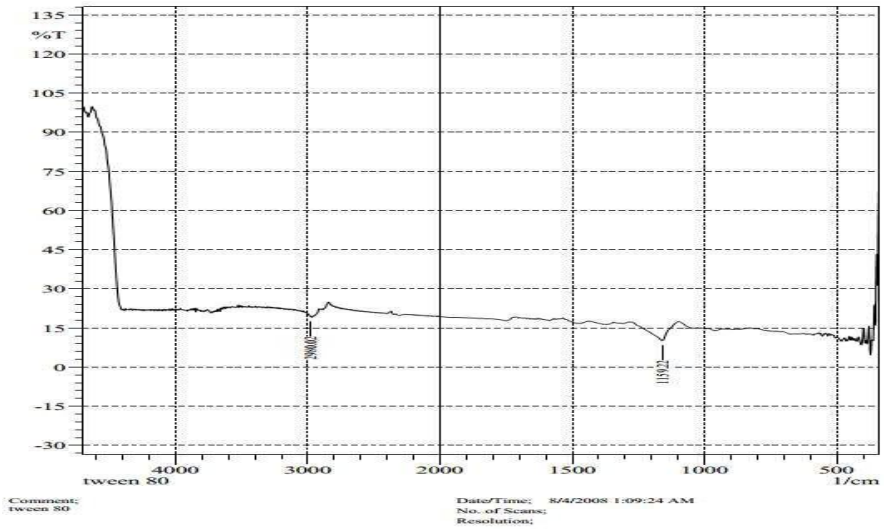

Figure No. 1.3: Tween80

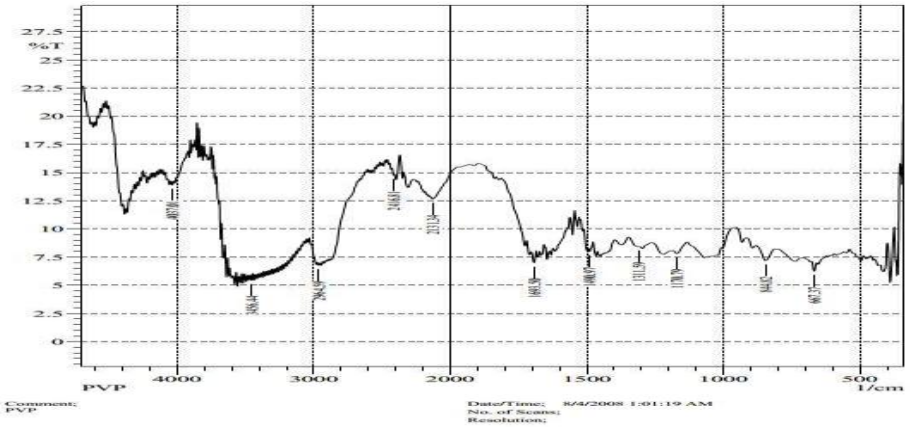

Figure No. 1.4: PVP

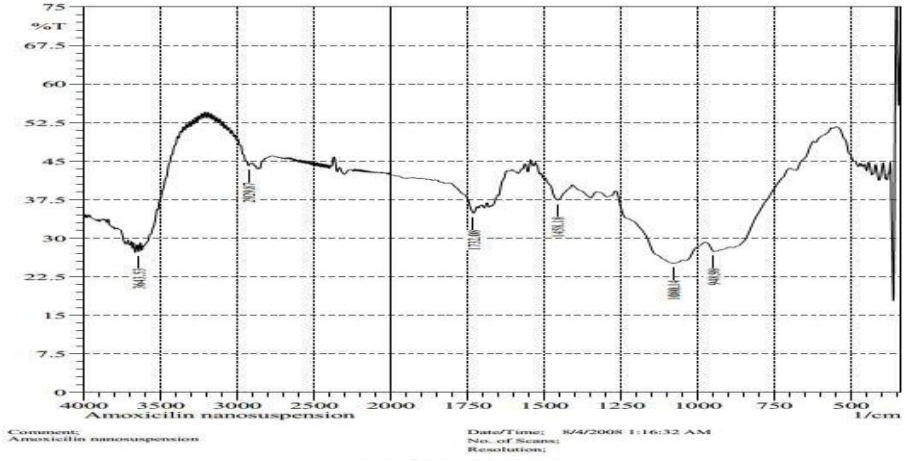

Figure No. 1.5: Amoxicillin Nanosuspension

1. DCS Result

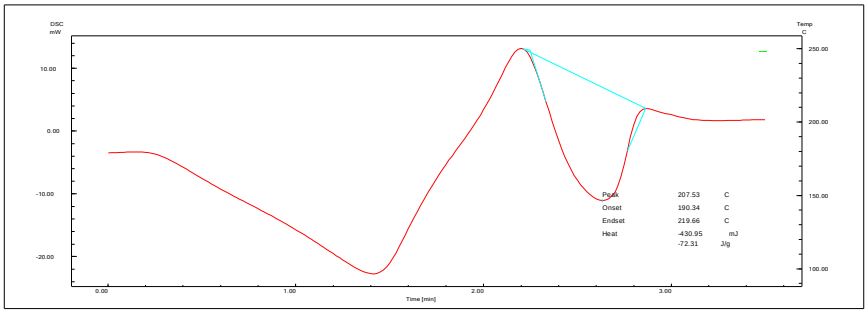

Figure No. 1.6: Amoxicillin

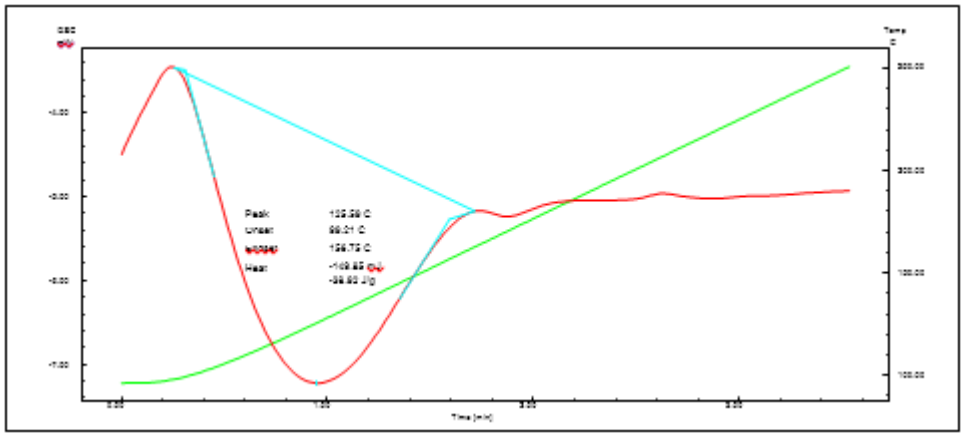

Figure No. 1.7: PVP

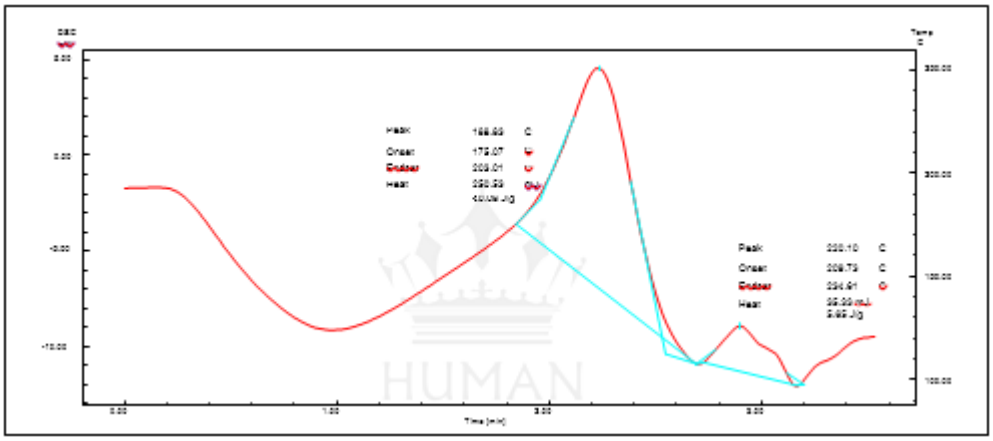

Figure No. 1.8: Amoxicillin + PVP

2. PARTICLE SIZE DETERMINATION

Formulation	Particle Size (nm)
F1	833
F2	261
F3	682.3
F4	401.7
F5	1245.7

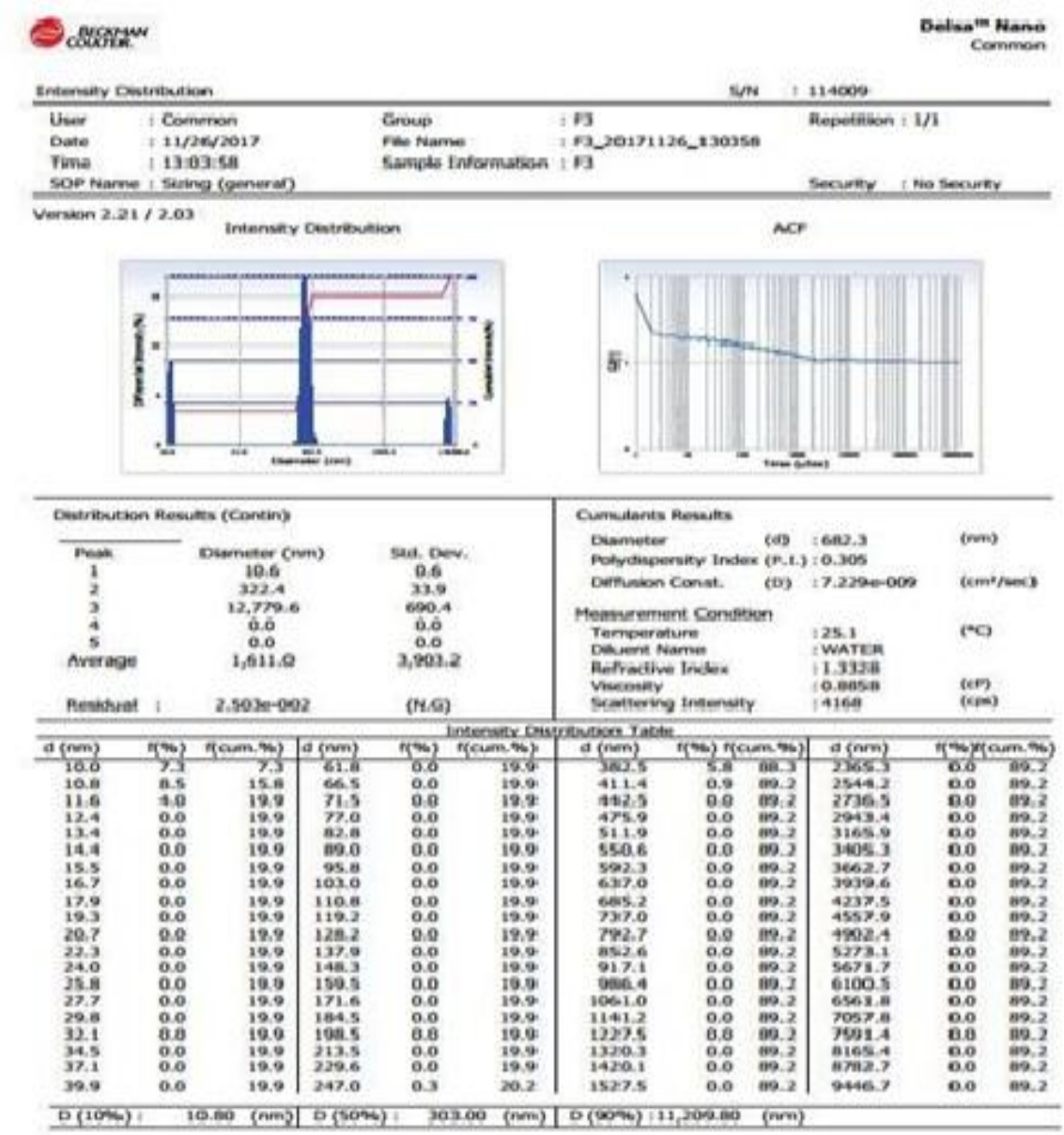

Figure No. 1.9: Particle Size Formulation F2

BECKMAN COULTER

Delsa™ Nano
Common

Intensity Distribution S/N : 114009

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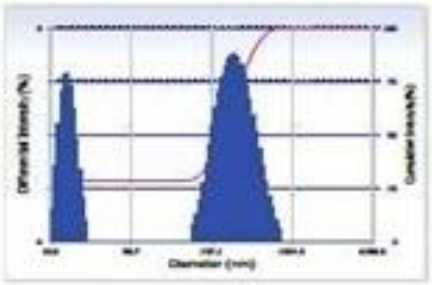
Version 2.21 / 2.03

Intensity Distribution



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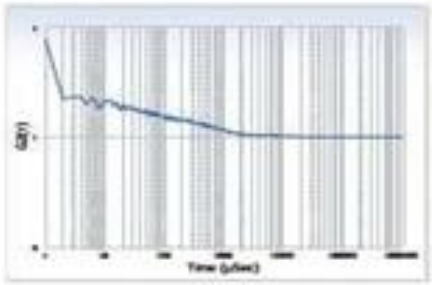

Distribution Results (Contin)

Peak	Diameter (nm)	Std. Dev.
1	14.1	2.4
2	437.1	169.8
3	0.0	0.0
4	0.0	0.0
5	0.0	0.0
Average	314.5	239.4

Residual : 2.176e-002 (N.G)

Cumulants Results

Diameter	(d)	:401.0	(nm)
Polydispersity Index	(P.I.)	:0.184	
Diffusion Const.	(D)	:1.230e-008	(cm²/sec)

Measurement Condition

Temperature	:25.1	(°C)
Diluent Name	:WATER	
Refractive Index	:1.3328	
Viscosity	:0.8858	(cP)
Scattering Intensity	:3792	(cps)

Intensity Distribution Table

d (nm)	f(%)	f(cum.%)	d (nm)	f(%)	f(cum.%)	d (nm)	f(%)	f(cum.%)	d (nm)	f(%)	f(cum.%)
10.0	0.7	0.7	50.7	0.0	29.0	257.2	2.7	39.3	1304.5	0.0	100.0
10.7	1.8	2.5	54.1	0.0	29.0	274.5	3.1	42.4	1392.0	0.0	100.0
11.4	2.8	5.3	57.8	0.0	29.0	292.9	3.5	45.9	1485.5	0.0	100.0
12.2	3.5	8.8	61.6	0.0	29.0	312.5	3.8	49.8	1585.1	0.0	100.0
13.0	3.9	12.7	65.8	0.0	29.0	333.5	4.1	53.9	1691.5	0.0	100.0
13.8	3.9	16.6	70.2	0.0	29.0	355.9	4.3	58.2	1805.0	0.0	100.0
14.8	3.6	20.3	74.9	0.0	29.0	379.8	4.4	62.5	1926.1	0.0	100.0
15.8	3.1	23.4	79.9	0.0	29.0	405.3	4.4	66.9	2055.4	0.0	100.0
16.8	2.4	25.8	85.3	0.0	29.0	432.5	4.3	71.2	2193.3	0.0	100.0
17.9	1.7	27.5	91.0	0.0	29.0	461.5	4.2	75.4	2340.5	0.0	100.0
19.1	1.0	28.5	97.1	0.0	29.0	492.4	3.9	79.3	2497.5	0.0	100.0
20.4	0.5	29.0	103.6	0.0	29.0	525.5	3.7	83.0	2665.1	0.0	100.0
21.8	0.0	29.0	110.6	0.0	29.0	560.8	3.3	86.3	2843.9	0.0	100.0
23.3	0.0	29.0	118.0	0.0	29.0	598.4	3.0	89.3	3034.8	0.0	100.0
24.8	0.0	29.0	125.9	0.0	29.0	638.5	2.6	91.9	3238.4	0.0	100.0
26.5	0.0	29.0	134.4	0.0	29.0	681.4	2.2	94.0	3455.7	0.0	100.0
28.3	0.0	29.0	143.4	0.0	29.0	727.1	1.8	95.8	3687.6	0.0	100.0
30.2	0.0	29.0	153.0	0.0	29.0	775.9	1.4	97.3	3935.0	0.0	100.0
32.2	0.0	29.0	163.3	0.0	29.0	828.0	1.1	98.3	4199.1	0.0	100.0
34.3	0.0	29.0	174.2	0.4	29.4	883.5	0.8	99.1	4480.9	0.0	100.0

D (10%) : 12.40 (nm) D (50%) : 313.70 (nm) D (90%) : 609.30 (nm)

Figure No. 2: Particle Size Formulation F3

Intensity Distribution S/N : 114009

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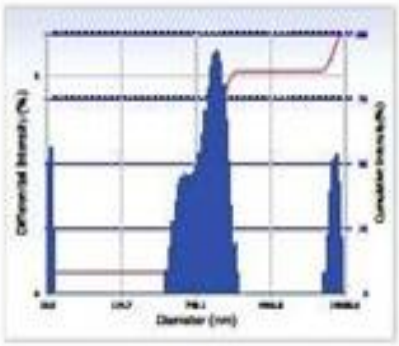
Version 2.21 / 2.03

Intensity Distribution



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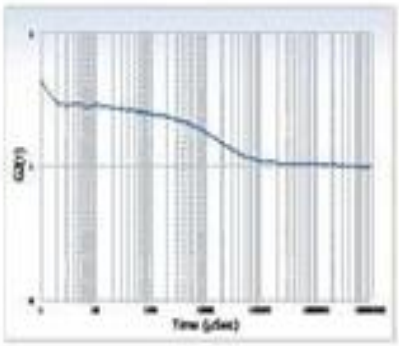

Distribution Results (Contin)

Peak	Diameter (nm)	Std. Dev.
1	21.2	1.1
2	526.8	74.8
3	1,234.7	356.0
4	24,078.6	2,741.3
5	0.0	0.0
Average	4,301.0	8,172.0

Residual : 2.695e-002 (N.G)

Cumulants Results

Diameter	(d)	: 1245.7	(nm)
Polydispersity Index	(P.I.)	: 0.417	
Diffusion Const.	(D)	: 3.959e-009	(cm²/sec)

Measurement Condition

Temperature	: 25.1	(°C)
Diluent Name	: WATER	
Refractive Index	: 1.3328	
Viscosity	: 0.8858	(cP)
Scattering Intensity	: 11918	(cps)

Intensity Distribution Table

d (nm)	f(%)	f(cum.%)	d (nm)	f(%)	f(cum.%)	d (nm)	f(%)	f(cum.%)	d (nm)	f(%)	f(cum.%)
20.0	3.0	3.0	125.7	0.0	7.8	790.1	2.9	32.4	4966.0	0.0	85.7
21.5	3.4	6.4	135.3	0.0	7.8	850.4	3.3	35.7	5344.9	0.0	85.7
23.2	1.5	7.8	145.6	0.0	7.8	915.3	3.7	39.4	5752.7	0.0	85.7
24.9	0.0	7.8	156.7	0.0	7.8	985.1	4.2	43.6	6191.6	0.0	85.7
26.8	0.0	7.8	168.7	0.0	7.8	1060.3	4.8	48.4	6664.0	0.0	85.7
28.9	0.0	7.8	181.6	0.0	7.8	1141.2	5.2	53.6	7172.5	0.0	85.7
31.1	0.0	7.8	195.4	0.0	7.8	1228.2	5.5	59.1	7719.8	0.0	85.7
33.5	0.0	7.8	210.3	0.0	7.8	1321.9	5.6	64.7	8308.8	0.0	85.7
36.0	0.0	7.8	226.4	0.0	7.8	1422.8	5.4	70.1	8942.7	0.0	85.7
38.8	0.0	7.8	243.6	0.0	7.8	1531.4	4.8	74.9	9625.0	0.0	85.7
41.7	0.0	7.8	262.2	0.0	7.8	1648.2	4.0	78.9	10359.4	0.0	85.7
44.9	0.0	7.8	282.2	0.0	7.8	1774.0	3.1	82.0	11149.9	0.0	85.7
48.3	0.0	7.8	303.8	0.0	7.8	1909.3	2.1	84.0	12000.6	0.0	85.7
52.0	0.0	7.8	327.0	0.0	7.8	2055.0	1.2	85.2	12916.2	0.0	85.7
56.0	0.0	7.8	351.9	0.0	7.8	2211.8	0.5	85.7	13901.7	0.0	85.7
60.3	0.0	7.8	378.7	0.5	8.4	2380.5	0.0	85.7	14962.4	0.0	85.7
64.9	0.0	7.8	407.6	1.1	9.5	2562.2	0.0	85.7	16104.0	0.0	85.7
69.8	0.0	7.8	438.7	1.7	11.1	2757.7	0.0	85.7	17332.7	0.0	85.7
75.1	0.0	7.8	472.2	2.2	13.3	2968.1	0.0	85.7	18655.2	0.5	86.2
80.9	0.0	7.8	508.3	2.5	15.8	3194.5	0.0	85.7	20078.6	1.4	87.5

D (10%) : 417.40 (nm) D (50%) : 1,085.00 (nm) D (90%) : 21,664.10 (nm)

Figure No. 2.1: Particle Size Formulation F5

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