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Formulation and Evaluation of Nanosuspensions Containing Erythromycin

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ABSTRACT

In this present work Erythromycin stearate nanosuspension has been formulated. Since Erythromycin stearate is insoluble in water, it has been formulated as nanosuspension to improve bioavailability of the drug. The formulation was carried out using High Pressure Homogenization method using different variables like drug-surfactants ratio, stirring speed and rotation time, to optimize the final formulation while keeping the quantities of active ingredient constant. An optimized final formulation was prepared by using drug, poloxamer 188 and tween20 in 1:2:2 ratios with stirring speed of 25000 rpm for 25 minutes using High Pressure Homogenizer (Polytron PT 1600E) followed by lyophilisation. The optimized final formulation was subjected to *in-vitro* parameters such as compatibility, drug content, particle size analysis, zeta-potential, SEM, *in-vitro* release profile. All the *in vitro* evaluation parameters complied the limits. Stability studies were also conducted as per ICH guidelines and from the result it may be concluded that the optimized formulation is stable. Finally, it is concluded that the drug is compatible and stable with the excipients, hence Erythromycin stearate can be formulated as nanosuspension by this method.

Key words: Erythromycin stearate, Poloxamer 188, Nanosuspension, Zeta potential, DSC, SEM.

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INTRODUCTION

Advent of Nanotechnology: [1, 2]

Technology is flavour of the science fiction and popular science speculation now days. The word nanotechnology comes from the Greek prefix "Nano". In modern scientific parlance one nanometer is one-billionth of a meter. For the sake of comparison, the diameter of a single atom is ¼ nanometer and the diameter of a human hair is 10,000 nanometers. The smallest devices on commercially available chips are about 200 nanometers. Nanotechnology is about building things one atom at a time, and in doing so constructing devices with unprecedented capabilities. The history of nanotechnology began with Erwin Schrodinger physicist who received the Nobel Prize in 1933 for discovering new forms of atomic energy.

Nanosuspensions: [3,4]

Nanosuspensions are basically suspension where the particle size of the suspended materials is within the range of 10-1000nm.

Advantages of nanospensions: [5]

- Increase of drug loading in dosage from without extreme pH condition or use of toxic co-solvents, reduced toxicity and increased efficacy.
- Increase in dissolution velocity and saturation of the route used.
- Increase in drug loading with reduced administration volume for parenterals and ophthalmic administration.
- Increase in resistance to hydrolysis and oxidation and thereby improves physical stability.
- Potential for IV sustained release via monocyte phagocytic systems targeting and potential for reduced first pass metabolism for oral administration.
- Unlike nanoparticle carriers, such as polymeric nanoparticles, nanosuspensions are easy to manufacture and scale up.

Thus, these poorly soluble and poorly bio-available drugs so called "brick dust" candidates once abandoned from formulation development can be rescued by formulating into nanosuspensions which is simple technology having a higher chance to launch products on the market.

Properties of Nanosuspension: [6]

A. Physical long-term stability.

Nanosuspensions are a highly dispersed system; therefore physical instability due to Ostwald ripening would be expected. This effect is only pronounced for particles below approximately 2 µm, especially below 1 µm. A priori Ostwald ripening is reduced to the extremely low solubility of the drugs formulated as nanosuspension. An additional explanation for the absence of Ostwald ripening is that the homogenized particles are very homogeneous. There are no large differences in particles size, leading to the absence of differences in solubility sufficiently high to cause Ostwald ripening.

B. Saturation solubility of Nanosuspensions.

According to Kelvin equation, the vapour pressure above curved surface is increased compared to a flat surface. The vapour pressure increases further with increasing curvature of the surface, which means decreasing particle size. Analogously to the vapour pressure, the dissolution pressure of a substance increases with decreasing particle size (Figure 1,2).

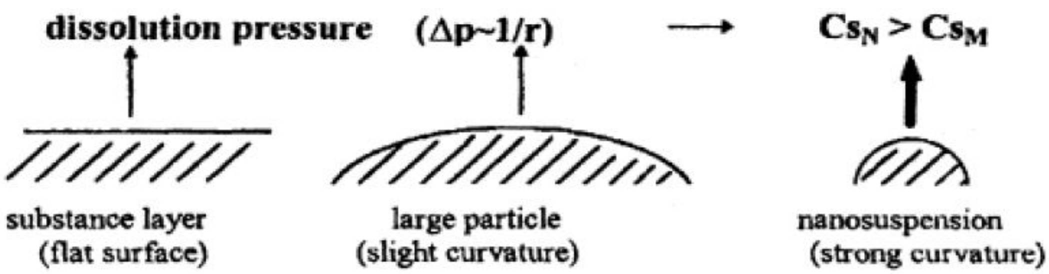
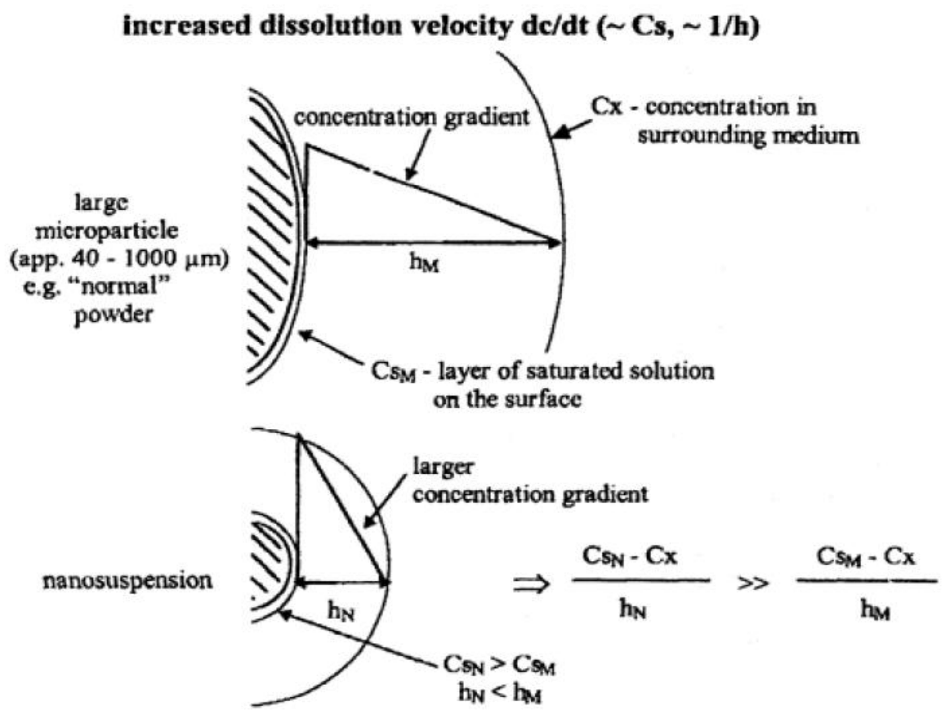


Figure 1: Mechanism of increasing dissolution velocity in Nanosuspension



Δp: dissolution pressure,

CsN: saturation solubility of nanoparticle, CsM: saturation solubility of micro particles,

hM: diffusional distance of microparticle, hN: diffusional distance of nanoparticle.

Figure 2: Mechanism of increasing saturation solubility Cs

According to the prandlt equation[7], for small particles the diffusion distance h decreases with decreasing particle size. The decrease in h and the simultaneous increase in Cs lead to an increase of the gradient (Cs-Cx)/dh and, according to Noyes-Whitneys, to an increase in the dissolution velocity. Breaking off the particles reveals new surfaces from the inside of the drug crystals. Such surfaces can be higher energetic (higher interfacial tension). Creation of highly energetic surfaces by breaking of particles can contribute to the increase in saturation solubility.

C. Internal structure of nanosuspension

The input of energy can lead to structural changes inside drug particles. Exposing the drug particles to the high power density during the transformation of drug particles into nanorange will cause internal change of the structure. The extent of internal structural change depends on the chemical nature and physical hardness of the drug, the applied power density, and time of exposure to the process.

Preparation of Nanosuspensions:[7]

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. Preparation of nanosuspensions were reported to be a more cost effective and technically more simple alternative, particularly for poorly soluble drugs and yield a physically more stable product than liposomes; conventional colloidal drug carriers. Nanosuspension engineering processes currently used are prepared by precipitation, high pressure homogenization, emulsion and milling techniques. Table 1 represents techniques for preparation of Nanosuspensions.[7]

MATERIALS AND METHODS

Materials:

Erythromycin stearate (S KANT HEALTHCARE LTD, VAP)I; Poloxamer 188 (Lincoin Pharmaceutical LTD, Gujarat); Tween 20(Loba Chemie Pvt. Ltd, Mumbai); Sodium Hydroxide(Ranbaxy Fine Chemicals LTD, Mumbai). All chemicals and solvents used were of analytical grade.

Method:

Preliminary studies:

The preliminary studies were carried out by preparing various formulations with different variables in an effort to optimize the formulations for the particle size ranging in nano scale. The High Pressure Homogenization method was adopted to prepare nanosuspension.

- 500 mg of Erythromycin stearate in acetone is kept constant in all formulation.
- Initially, the drug and different surfactants tried with different concentration at constant speed. The nanosuspensions were evaluated for effect of surfactant.
- The composition of formulation is shown in Table 2.
  - **Table 2: Preliminary Inverstigation studies of drug & different surfactant**

Sr No.	Drug (300mg)	Surfactant	Concentration of surfactant
1	Erythromycin stearate	Poloxamer 188	1%
2	Erythromycin stearate	Poloxamer 188	2%
3	Erythromycin stearate	Poloxamer 188	3%
4	Erythromycin stearate	Tween-20	1%
5	Erythromycin stearate	Tween-20	2%
6	Erythromycin stearate	Tween-20	3%

Formulation design:

Procedure for preparation of nanosuspension by High Pressure Homogenization technique:

- The Erythromycin stearate drug dissolved at room temperature in acetone and if required sonicate for 10 mins.
- The solution was slowly added drop wise with syringe, in 100 ml of distilled water containing surfactants poloxamer 188 and Tween 20 kept at room temperature with speed of 900-1000rpm speed using Mechanical Stirrers until all the drug solution completely added in to surfactant solution and acetone completely evaporate from the solution.
- The solution stirring at different speed and time using Polytron PT 1600E shown in Table 3 and 4 for reducing the particle to nano size and lyophilized the product for 24 hrs at -80°C Temperature.

Table 3: Formulation design with varied drug-surfactant ratio

Formulation	Drug (500mg)	Surfactant		Drug: Surfactant
F1	Erythromycin stearate	Poloxamer 188	Tween 20	1:6:6
F2	Erythromycin stearate	Poloxamer 188	Tween 20	1:6:4
F3	Erythromycin stearate	Poloxamer 188	Tween 20	1:4:3
F4	Erythromycin stearate	Poloxamer 188	Tween 20	1:4:2
F5	Erythromycin stearate	Poloxamer 188	Tween 20	1:2:3
F6	Erythromycin stearate	Poloxamer 188	Tween 20	1:2:2

Table 4: Formulation design with stirring speed and duration of rotation using polytron pt 1600e for formulation F6

Formulation	Stirring speed(rpm)	Duration of rotation (minutes)
F6A	15000	15
F6B	20000	20
F6C	25000	25

- The process variables chosen were:
- Drug-surfactant ratio.
- Stirring speed and duration of rotation.

Evaluation of Nanosuspension:

Particle Size Analysis: [8]

The particle size should be less than 1000 nm in nanosuspension. It can be analyzed by using malveren particle size analyzer. Particles in the size range of colloids display constant random thermal motion which is known as Brownian motion. This motion causes the intensity of light scattered by the particles to vary with time. The position of the particles can be statistically defined as being highly correlated, contrast to this with a long sample time, particles will have moved randomly from their initial positions. Therefore the particles can be described statistically as not being correlated.(Table 5)

Table 5: Formulation design with results of Paticle size and Zeta potential using polytron pt 1600e for Formulation F6

SR NO.	Formulation	speed(RPM)	Duration of rotation (minutes)	Mean particle Size (nm)	Zeta Potential (mV)
1	F6A	15000	15	566.3	-21.9
2	F6B	20000	20	519.2	-27.9
3	F6C	25000	25	415.5	-30.4

Zeta potential measurement: [9,10]

Zeta potential of the suspension is measured by malveren zetasizer. The zeta sizer mainly consists of laser which is used to provide a light source to illuminate the particles within the sample. For zetapotential measurements this light splits to provide an incident and reference beam. The incident laser beam passes through the center of the sample cell, and the scattered light at an angle of about 13^0 is detected. Zetasizer software produces a frequency spectrum from which the electrophoretic mobility hence the zeta potential is calculated. (Table 5)

Scanning Electron Microscopy (SEM):[11]

Surface morphology of the specimen will be determined by using a scanning electron microscope (SEM), Model JSM 84 0A, JEOI, Japan. The samples are dried thoroughly in vaccum desicator before mounting on brass specimen studies, using double sided adhesive tape. Gold-palladium alloy of 120°A Knees was coated on the sample sputter coating unit (Model E5 100 Polaron U.K) in Argon at ambient of 8-10 with plasma voltage about 20mA. The sputtering was done for nearly 5 minutes to obtain uniform coating on the sample to enable good quality SEM images. The SEM was operated at low accelerating voltage of about 15KV with load current about 80mA.The condenser lens position was maintained between 4.4-5.1. The objective lens aperture has a diameter of 240 microns and working distance WD=39mm.

Drug content:[12]

Take the 2.5mg equivalent of Erythromycin stearate from formulated product & transferred in to 100 ml volumetric flask and dissolved in 50ml of deionised water and 5ml of 0.005 N NaOH. Sonicate for 5 min if required, then diluted with deionised water to final volume of 100ml. From this 10 ml of solution was pipette into 25ml volumetric flask and volume was made up to 25 ml with deionised water and take UV absorbance at 285 nm.

***In vitro* release studies:** [13]

In vitro release studies were carried out for nanosuspension formulations and for the pure drug in dissolution test apparatus USP type II. Medium used was 900ml of Phosphate buffer 6.8pH was prepared. Nanosuspensions equivalent to 100mg of the pure drug was used to carry out dissolution. The tests were carried out in 900ml of Phosphate buffer 6.8pH for 1hrs at 100rpm at 37±0.5^{o}C. 5ml of the aliquot was withdrawn at different predetermined intervals and filtered. The required dilutions were made with dissolution medium and the solution was analyzed for the drug content spectrophotometrically at 285nm against suitable blank. 5ml of the dilution medium was replaced in the vessel after each withdrawal to maintain sink condition. Three trials were carried out for all the products and the average SD and SEM values were calculated. From this percentage drug release was calculated and this was plotted against function of time to study the pattern of drug release.

RESULTS AND DISCUSSION

Drug surfactant compatibility studies were carried out using FT-IR (Figure 3 to 5), XRD (Figure 8 and 9), and DSC (Figure 6 and 7) to establish the possible interaction in formulation. The spectra of the formulation were compared with pure drug. It was observed that there was no shift in the absorption peaks of Erythromycin stearate in the spectra obtained from formulation. Therefore we can conclude that there was no incompatibility between the drug and surfactant used. The preliminary studies were carried out by preparing 6 formulations with different variables which were subjected to particles size analysis. The formulations were studied for the effect of stirring speed and duration of rotation, while the concentration of surfactant was kept constant. It was observed that formulation with poloxamer 188 yielded particles in nano range at 25000 rpm speed with duration of 25 mins of rotation. So, formulation design was made by varying the surfactant- drug ratio, while keeping the others variables constant. Similarly, formulations were prepared using various speeds for different time of stirring.

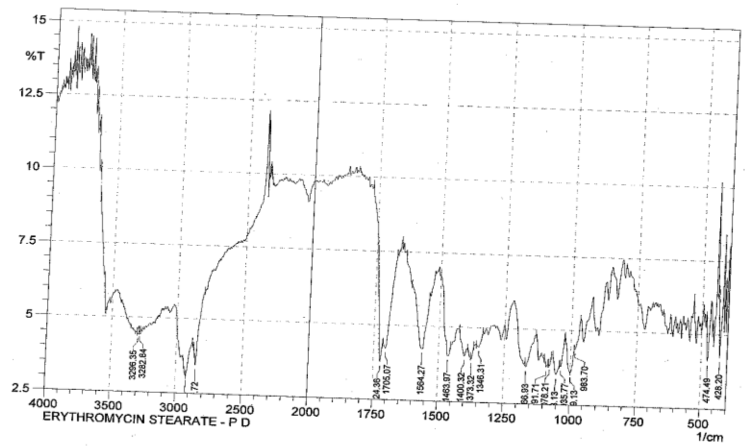


Figure 3 :FTIR Spectrum of Erythromycin stearate

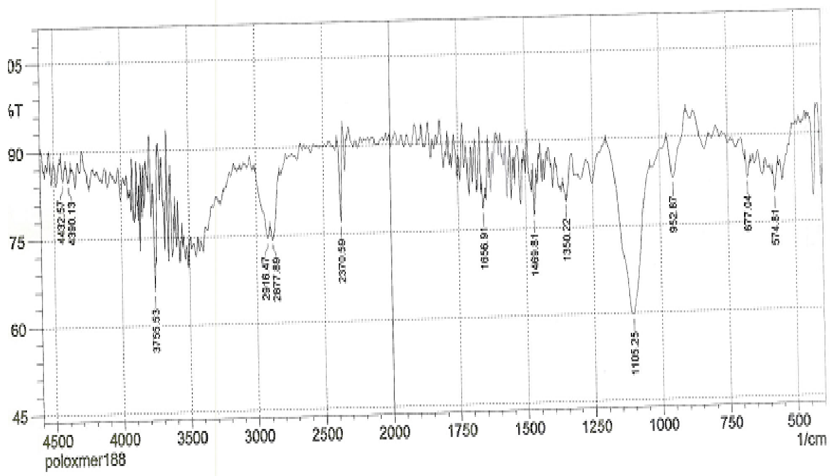


Figure 4: FTIR Spectrum of surfactant (Poloxamer 188)

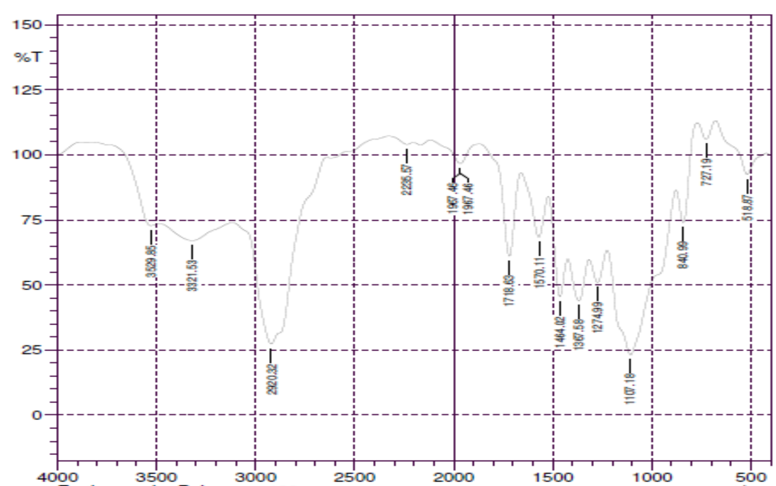


Figure 5: FTIR spectrum of Drug and Polaxomer 188

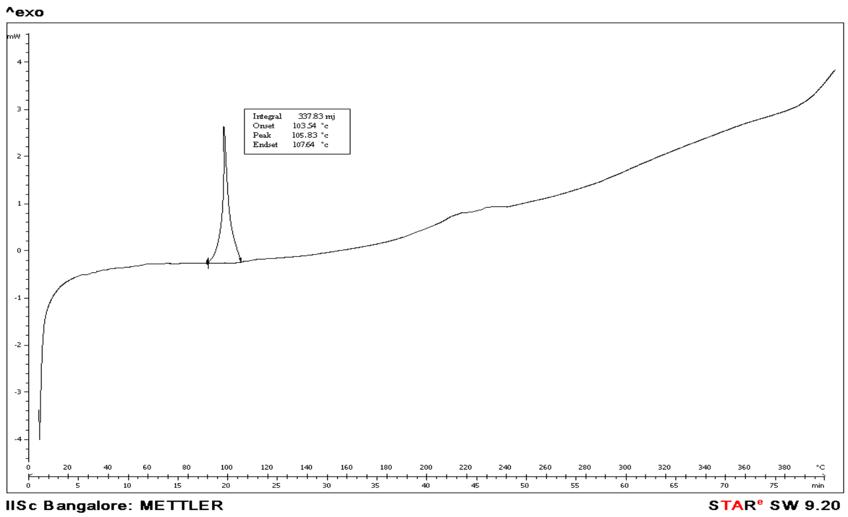


Figure 6: DSC of Pure drug Erythromycin stearate

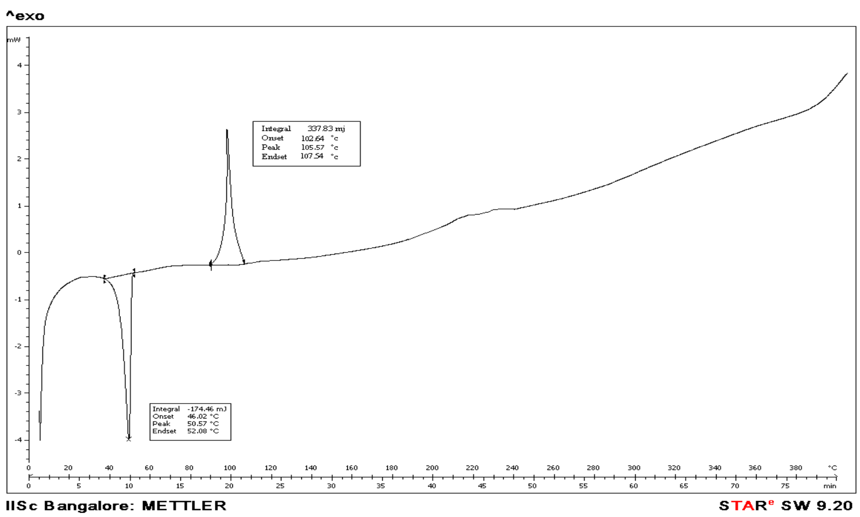


Figure 7: DSC of Optimized Formulation F6

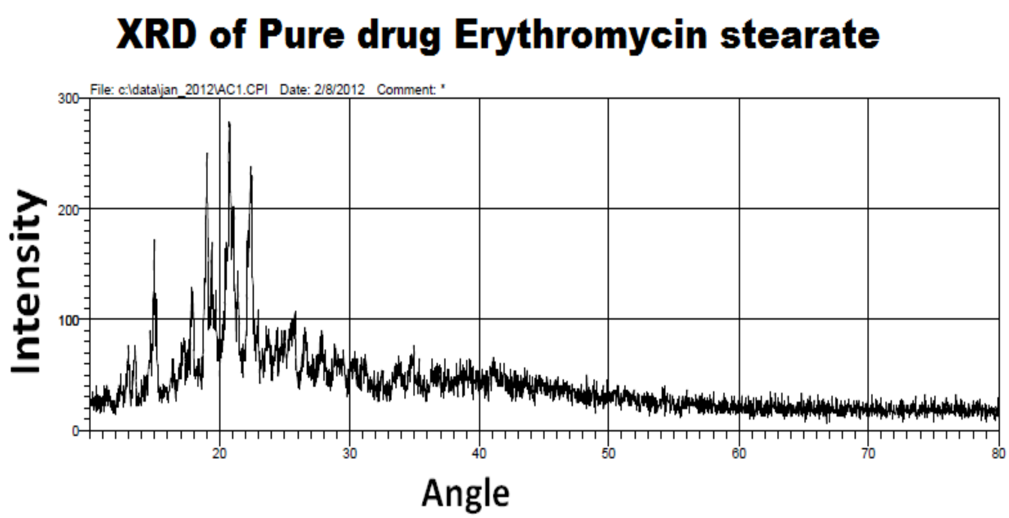


Figure 8: XRD of Pure drug Erythromycin stearate

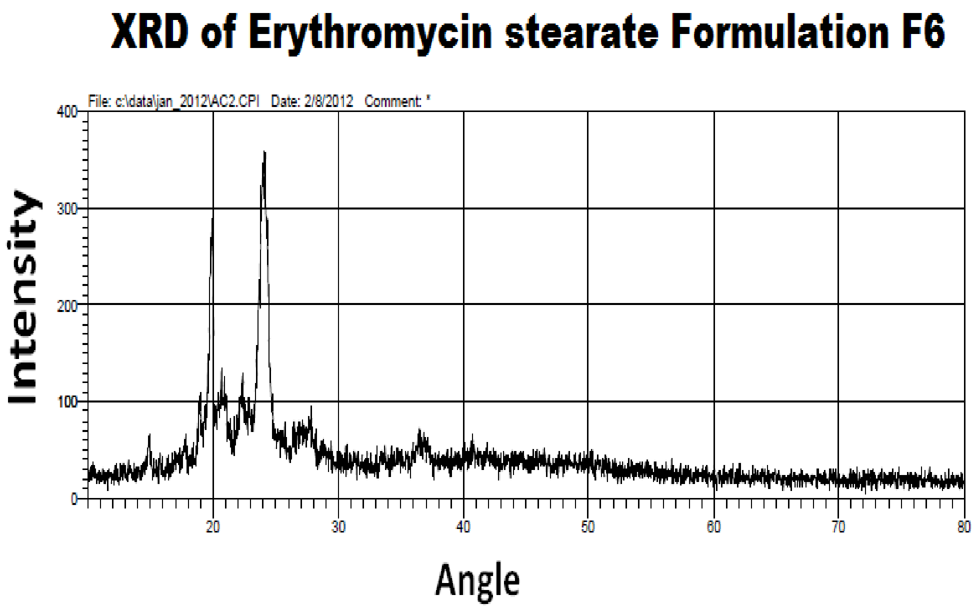
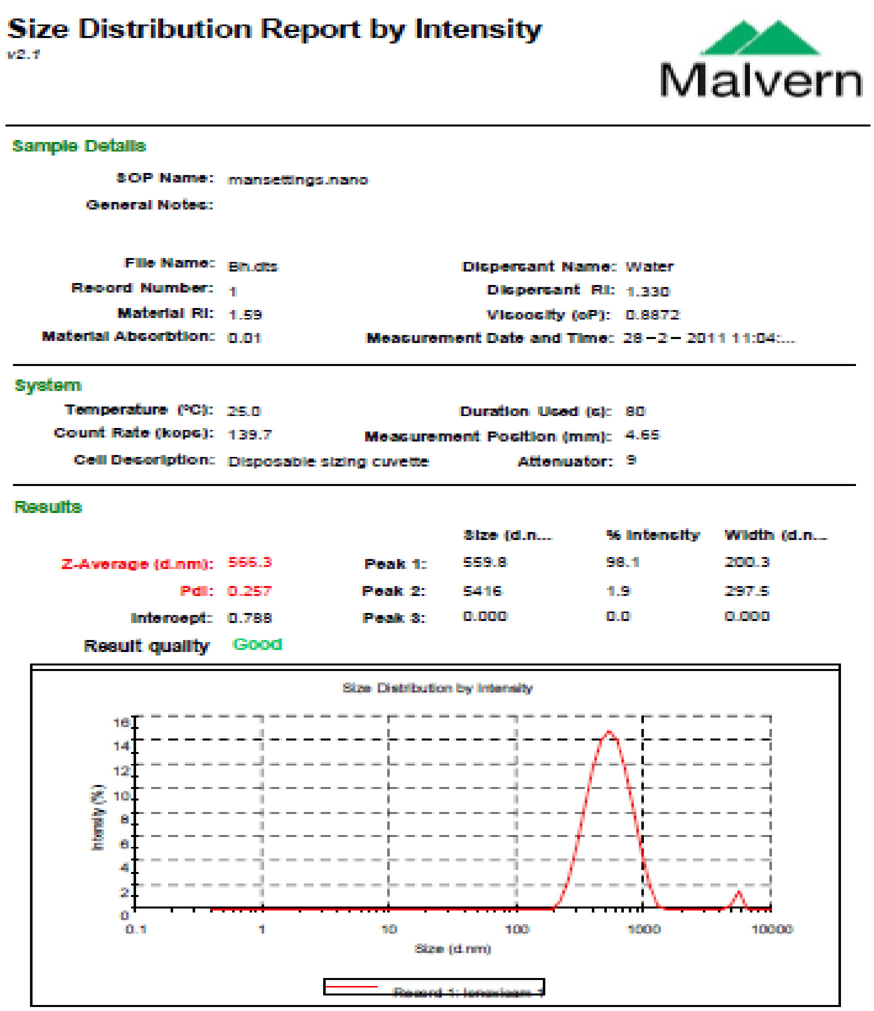


Figure 9: XRD of Erythromycin stearate Formulation F6



Size Distribution Report by Intensity
v2.1

Malvern

Sample Details

SOP Name: mansettings.nano
General Notes:

File Name: Bh.dts
Record Number: 1
Material RI: 1.59
Material Absorbtion: 0.01
Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Measurement Date and Time: 28 – 2 – 2011 11:04:...

System

Temperature (°C): 25.0
Count Rate (kcps): 139.7
Cell Description: Disposable sizing cuvette
Duration Used (s): 80
Measurement Position (mm): 4.65
Attenuator: 9

Results

			Size (d.n...	% Intensity	Width (d.n...
Z-Average (d.nm):	566.3	Peak 1:	559.8	98.1	200.3
PdI:	0.257	Peak 2:	5416	1.9	297.5
Intercept:	0.788	Peak 3:	0.000	0.0	0.000

Result quality Good

Figure 10: Size Distribution of Formulation F6A

Evaluation parameters

Particle size analysis:

For different agitation speed different duration of rotation was increased, then the particle size was reduced, but higher agitation speeds results in irregular shaped particles. The particle size in nanosuspension stabilized with poloxamer 188 is significantly greater than that stabilized with tween 80. The effectiveness of polymeric material such as poloxamer 188 is significantly smaller than tween 80 in terms of particle size (Fig 10 to 12). By combination of tween 80 and poloxamer 188 results in nanosuspension with particle size no significant different from tween 80 alone.

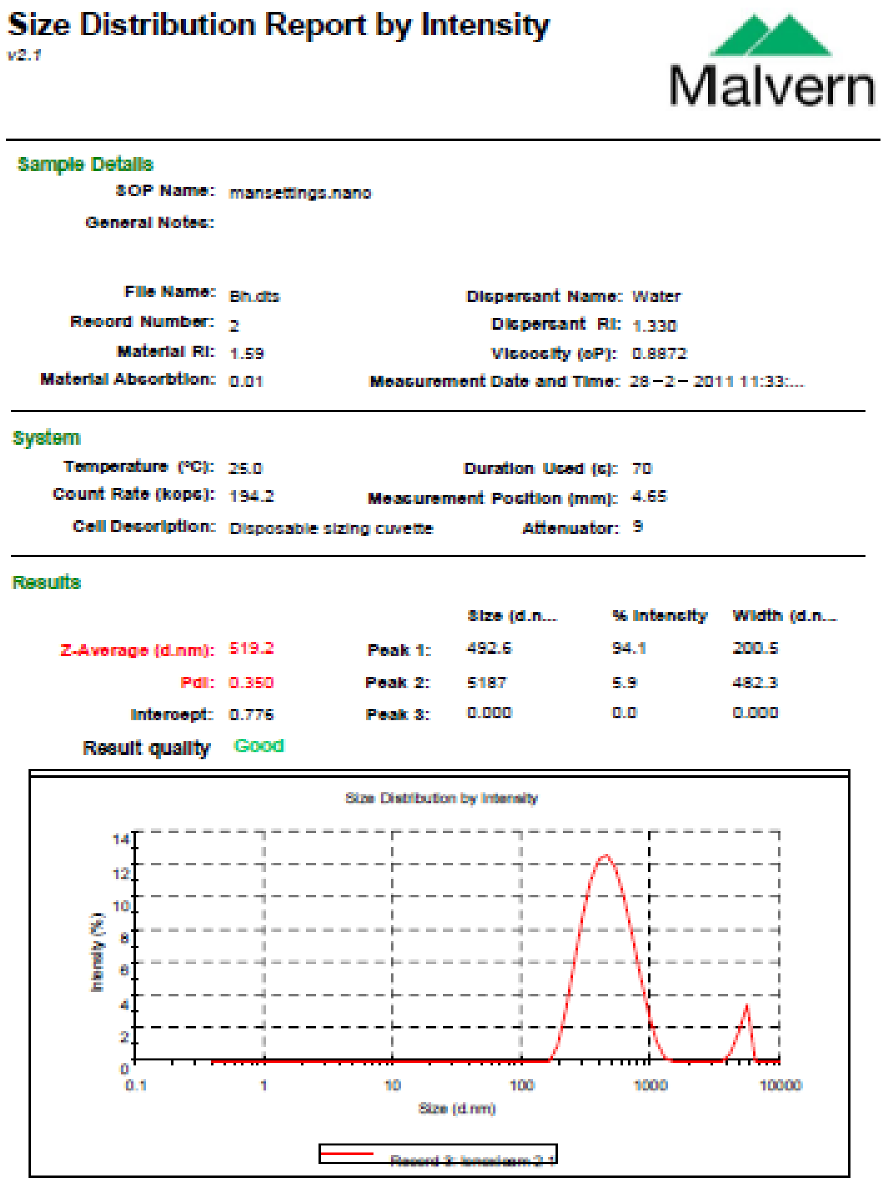


Figure 11: Size Distribution of Formulation F6B

Size Distribution Report by Intensity

v2.1

Malvern

Sample Details

SOP Name: mansettings.nano

General Notes:

File Name:	Bh.dts	Dispersant Name:	Water
Record Number:	5	Dispersant RI:	1.330
Material RI:	1.59	Viscosity (cP):	0.8872
Material Absorbtion:	0.01	Measurement Date and Time:	28-2-2011 11:44:...

System

Temperature (°C):	25.0	Duration Used (s):	80
Count Rate (kcps):	139.7	Measurement Position (mm):	4.65
Cell Description:	Disposable sizing cuvette	Attenuator:	9

Results

			Size (d.n...	% Intensity	Width (d.n...
Z-Average (d.nm):	415.5	Peak 1:	415.5	99.9	204.3
PdI:	0.251	Peak 2:	0.000	0.000	0.000
Intercept:	0.768	Peak 3:	0.000	0.0	0.000

Result quality Good

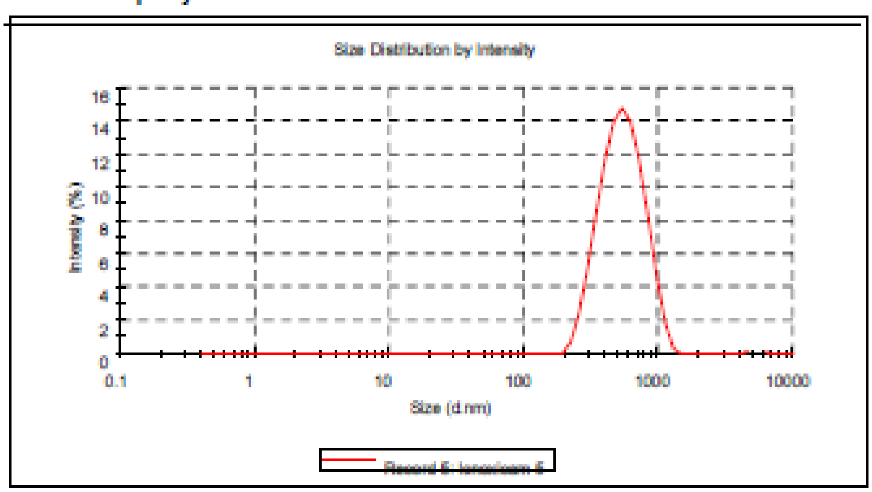


Figure 12: Size Distribution of Formulation F6C

Zeta potential measurement:

Zeta potential analysis was performed to get information about the surface properties of nanoparticles. Zeta potential is an important parameter for prediction of stability of nanosuspension. As a rule of thumb, suspensions will zeta potential around ±30 mV is physically stable. The zeta potential of F6C formulation was -30.4 mV showing excellent stability (Figure 13 to 15).

PERD Zeta Potential Re...

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Sample Details

SOP Name:	mansettings.nano	**Measured**	Pharmaceutics
General Notes:			
File Name:	Bh.dts	**Dispersant Name:**	Water
Record Number:	1	**Dispersant RI:**	1.330
Date and Time:	28 – 2 – 2011 11:16:28 ...	**Viscosity (cP):**	0.8872
		Dispersant Dielectric Constant:	78.5

System

Temperature (°C):	25.0	**Zeta Runs:**	12
Count Rate (kcps):	182.9	**Measurement Position (mm):**	2.00
Cell Description:	Clear disposable zeta cell	**Attenuator:**	6

Results

			Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV):	-21.9	**Peak 1:**	-21.9	100.0	5.67
Zeta Deviation (mV):	5.67	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm):	0.0395	**Peak 3:**	0.00	0.0	0.00

Result quality Good

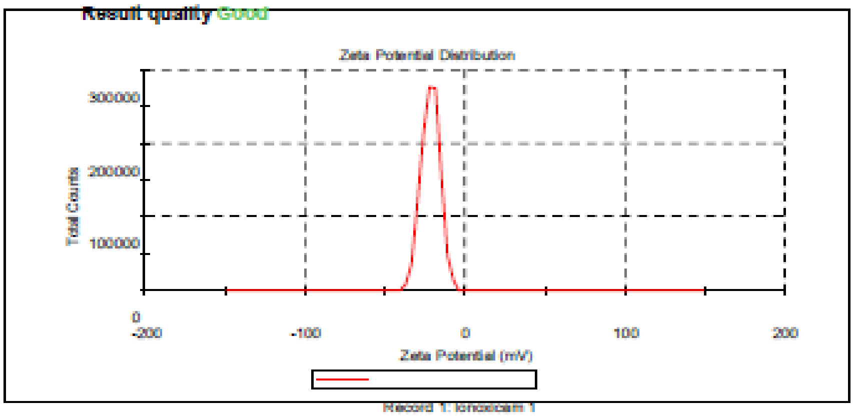


Figure 13: Zeta Potential of F6A

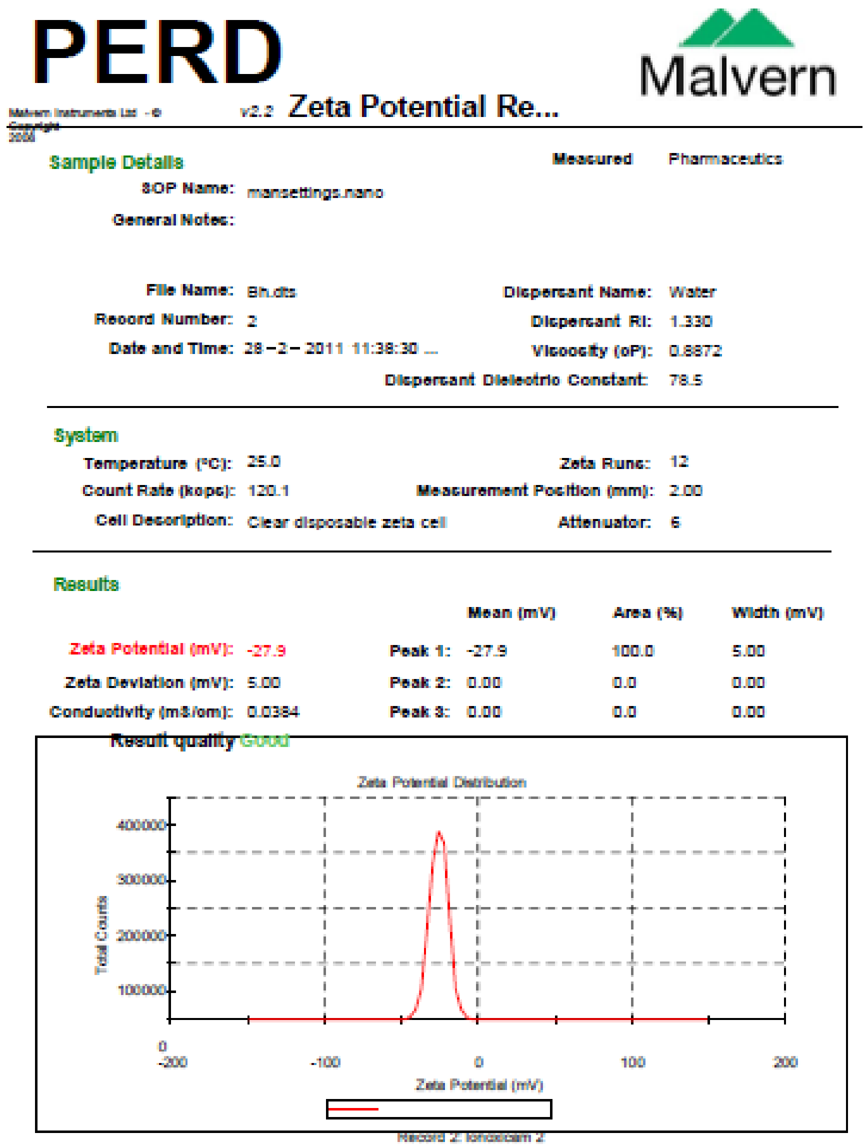
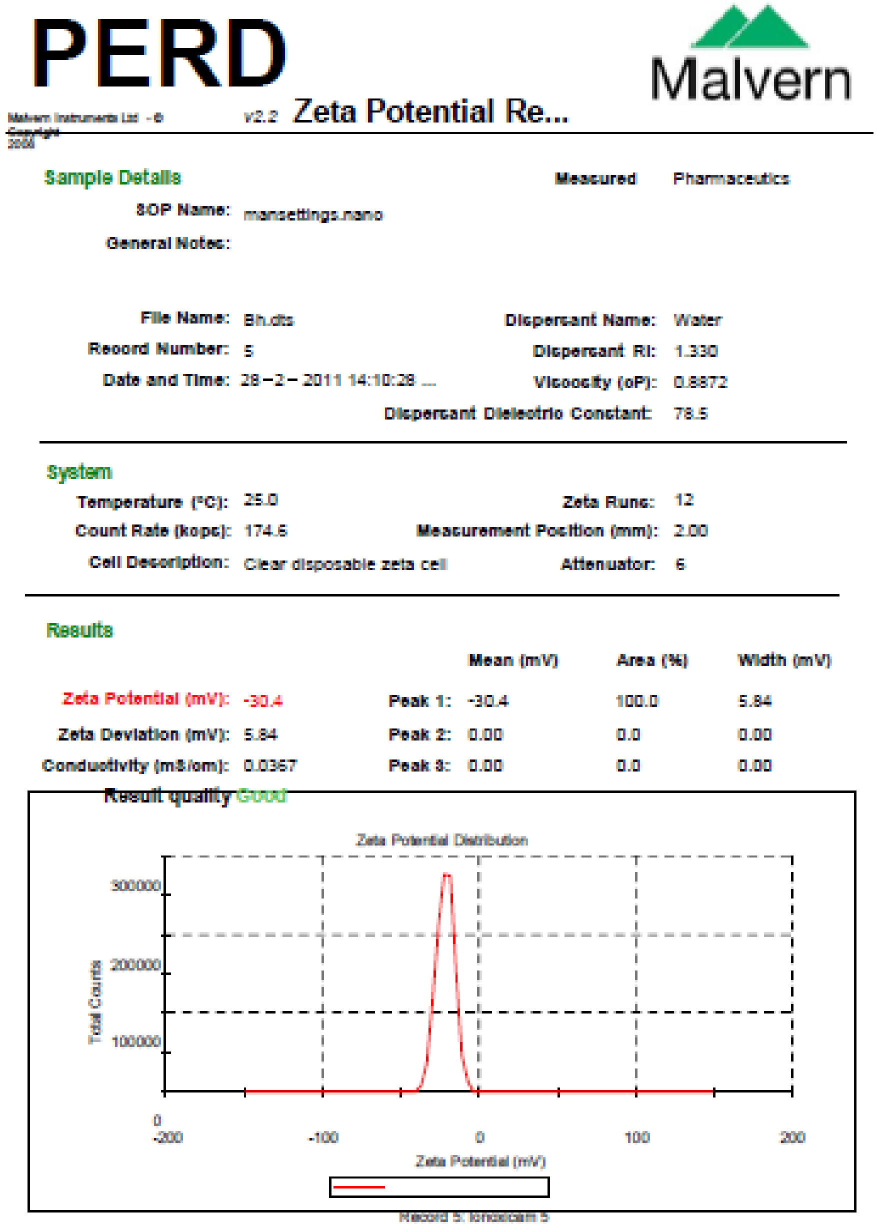


Figure 14: Zeta Potential of F6B

Scanning electron microscopy (SEM):

This was carried out to study the surface morphology of particles. It was found that Erythromycin stearate nanoparticles revealed a smooth texture. The SEM picture of pure drug particles was abundantly found with larger particle size when compared to F6C formulation. Thus, poloxamer 188 produced better surface characteristics. The surface structure of nanosuspension in the SEM of F6C appeared good in shape (Figure 16 to 18).



PERD

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Malvern Instruments Ltd - © Copyright 2008 v2.2 Zeta Potential Re...

Sample Details

SOP Name:	mansettings.nano	Measured	Pharmaceutics
General Notes:			
File Name:	8h.dts	Dispersant Name:	Water
Record Number:	5	Dispersant RI:	1.330
Date and Time:	28-2-2011 14:10:28 ...	Viscosity (cP):	0.8872
		Dispersant Dielectric Constant:	78.5

System

Temperature (°C):	25.0	Zeta Runs:	12
Count Rate (kcps):	174.6	Measurement Position (mm):	2.00
Cell Description:	Clear disposable zeta cell	Attenuator:	6

Results

			Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV):	-30.4	Peak 1:	-30.4	100.0	5.84
Zeta Deviation (mV):	5.84	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm):	0.0367	Peak 3:	0.00	0.0	0.00

Result quality Good

Figure 15: Zeta Potential of F6C

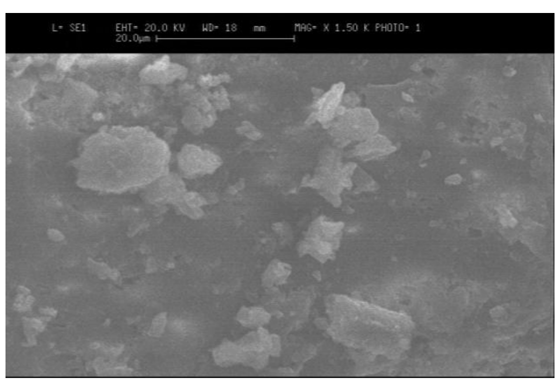

Figure 16: SEM photograph of pure drug Erythromycin stearate

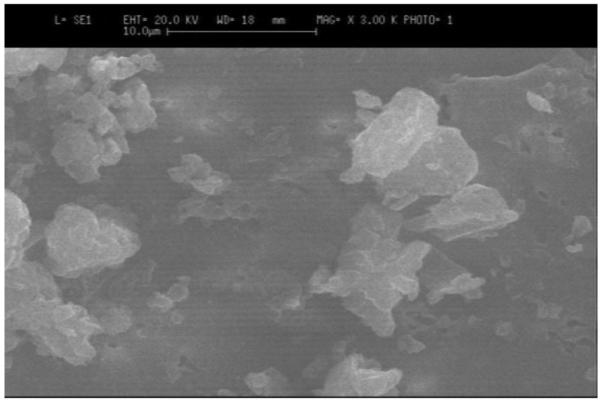

Figure 17: SEM photograph of formulation F6

Figure18: SEM Photograph of one particle of F6 Formulation

Drug content:

Drug content of nanosuspension was carried out by UV spectroscopy method. Drug content of formulation F6C was found to be 96.54%.(Table 6)

Table 6: Determination of Drug Content

Sr No.	Formulation codes	Stirring speed(rpm)	Duration of rotation(minutes)	Drug content (%)
1	F6A	15000	15	97.23
2	F6B	20000	20	95.44
3	F6C	25000	25	96.54

***Invitro* dissolution studies:**

In-vitro drug release data from the nanosuspension were carried out for 60 min and graphically represented as % CDR v/s Time profile (Figure 19 and 20). The cumulative percent drug release curve of all formulations such as F1 to F6, pure drug showed the desired rate in 0.1 N HCl up to 60 mins. The release of Erythromycin stearate nanosuspension of pure drug, F1, F2, F3, F4, F5 & F6 was found to be respectively 25.78%, 62.20%, 67.34%, 76.80%, 80.87%, 89.29%, 95.85%. Thus from the above results it was found that as the particle size is decreased, drug release is increased. When the % CDR v/s Time profiles of all 6 formulations were compared, the rate of

Erythromycin stearate released from the formulation with pure drug was significantly increased. (Table 7& 8)

Table 7: *In vitro* dissolution profile

Time in min.	Formulation code(n=3)						
	Pure Drug	F1	F2	F3	F4	F5	F6
5	5.98	5.63	6.03	7.64	7.84	8.24	10.45
10	9.33	11.09	13.10	15.72	16.33	18.34	20.76
15	12.71	19.39	19.81	27.27	31.30	36.55	39.98
30	17.34	31.57	37.41	38.08	40.72	49.61	59.31
45	21.92	54.26	59.94	54.58	57.43	66.57	78.13
60	25.78	62.20	67.34	76.80	80.87	89.29	95.85

Table 8: *In-vitro* dissolution profile of Optimized Erythromycin stearate Nanosuspension

Time in min.	Formulation code(n=3)			
	Pure Drug	F6A	F6B	F6C
5	5.98	10.45	8.98	9.57
10	9.33	20.76	19.32	19.87
15	12.71	39.98	40.79	41.05
30	17.34	59.31	57.99	58.76
45	21.92	78.13	79.08	80.61
60	25.78	95.85	96.19	95.59

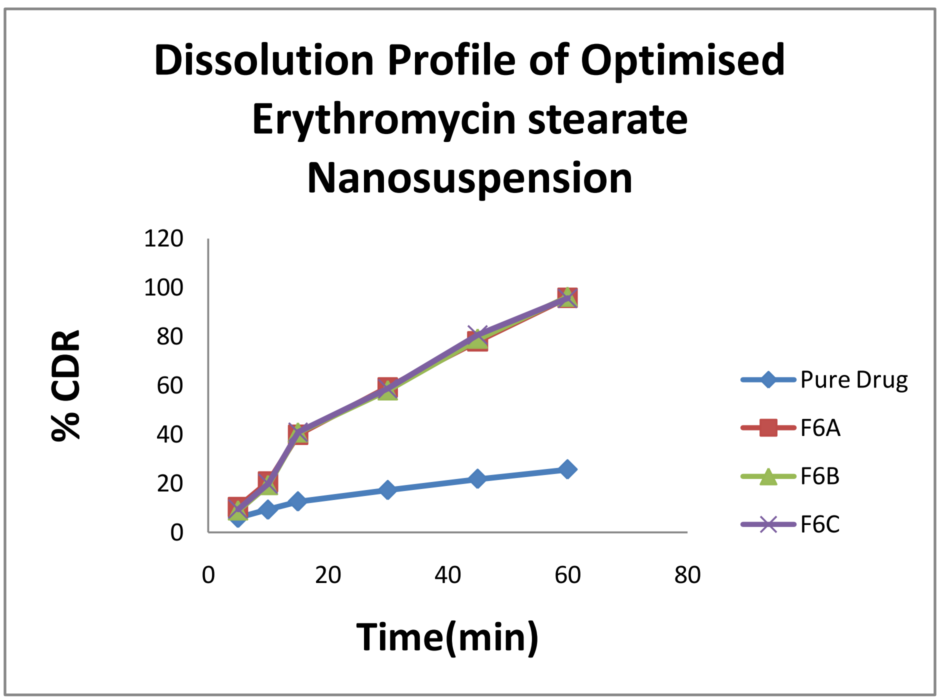

Figure 19: *In vitro* drug release profile of Optimized Erythromycin stearate nanosuspension

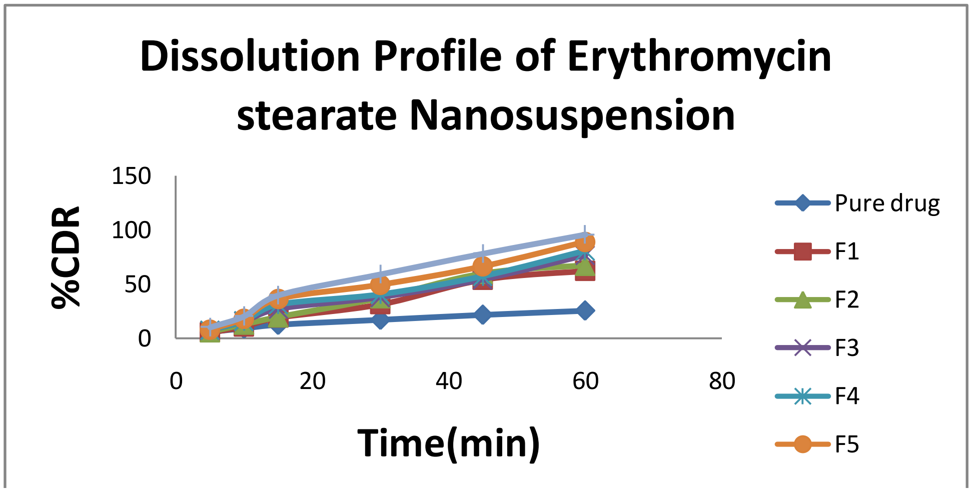

Figure 20: *In vitro* drug release profile of Erythromycin stearate Nanosuspension

CONCLUSION

Nanosuspensions can be successfully formulated from High Pressure Homogenization method, to enhance the dissolution rate of drug thus improving its solubility. All formulation was prepared using Poloxamer 188 and Tween 20 surfactant. Studies showed that the changeing the concentration of surfactants, stirring rate and duration of rotation influenced the particle size, zeta potential, drug content, drug release. From the results in can be concluded that formulated nanosuspension of Erythromycin stearate showed particle size 415.5 nm with 25000 rpm (25 mins) with good surface characters. Acceptable drug content was found in these formulations. Drug release profile of Erythromycin stearate of F6C showed good drug release when compared to other formulation such as F6A & F6B with respect to stability. The dissolution rate proved to be higher for smaller drug particles. Hence it has been proved that formulated Erythromycin stearate as nonosuspension is highly successful in enhancing dissolution rate. Thus, the objective of formulated nanosuspension of Erythromycin stearate by using high pressure homogenization method has been achieved with success. The developed formulation appears promising for other drugs which have poor solubility and bioavailability.

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