Research Article

Evaluation of Non Micronized Piroxicam SEDDS Formulation

***Surya N. Singh[1,2], U. K. Patil[2,3]**

1. Product Development Lab, ACG-Associated Capsules Pvt. Ltd., Kandivli (west), Mumbai-400067 Maharashtra, India.
2. Institute of Pharmaceutical Sciences and Research Center, Bhagwant University, Ajmer-305004, India.
3. People's Institute of Pharmacy and Research Center, Bhopal-462037, Madhya Pradesh, India.

ABSTRACT

Piroxicam is a nonsteroidal anti-inflammatory drug that is characterized by low solubility-high permeability and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal. The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry there are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compacts is a promising technique towards such a novel aim. The present study was designed to improve the dissolution rate of non micronized piroxicam at the physiological pH's through its increased solubility by preparing liquid-solid dispersions of drug using triethyl citrate(TEC): acconon : polysorbate-80. The dissolution tests of the preparations were performed 1.2 pH simulating gastric using USP dissolution apparatus II. The concentration of the dissolved drug in the medium was determined by direct or first-derivative UV spectroscopy. The dissolution rates of the formulations were dependent on the nature and ratio of drug to carriers in SEDDS and the corresponding physical mixtures as well as the pH of the medium. Hence in the present study, it was attempted to evaluate non micronized Piroxicam formulation in the form of self emulsifying drug delivery system(SEDDS) technique. Formulation studies were performed to check the In Vitro study, Particle size analysis, Zeta potential, were performed. Hence it was concluded that SEDDS of Non Micronized piroxicam could be formulated.

Keywords: Invitro study, non micronized piroxicam, particle size analysis, zeta potential

Received 08 July 2014 Received in revised form 30 July 2014 Accepted 02 August 2014

***Address for correspondence:**
Surya N. Singh,
Product Development Lab, ACG-Associated Capsules Pvt. Ltd., Kandivli (west), Mumbai-400067 Maharashtra, India.
E-mail: isurya1981@gmail.com

INTRODUCTION

It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. Many potential drug candidates are characterized by a low oral bioavailability. Often, poor drug dissolution and solubility rather than limited permeation through the epithelia of the gastrointestinal tract are responsible for low bioavailability of orally taken drugs. Therefore, together with permeability, the solubility and dissolution behaviour of a drug are key determinants of its bioavailability when administered orally. There are several methods for enhancing the dissolution rate of poorly water-soluble drugs including reducing particle size to increase surface area, thus increasing the dissolution rate of drug (1); solubilisation in surfactant systems (2,3); formation of water soluble complexes (4); drug derivatization such as strong electrolyte salt forms that usually have a higher dissolution rate (5); producing liquisolid formulations (6–10), manipulation of the solid state of a drug substance to improve drug dissolution i.e. by decreasing crystallinity of the drug substance through formation of solid solutions (11), and solid dispersion formulations (12–16). The most common method is to increase the surface area of the drug by micronization. But, in practice the effect of micronization is often disappointing, especially when the drugs

are encapsulated or tableted (17–19). Micronised drugs also have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area (18). Among the techniques to increase the aqueous solubility/dissolution rate, the formulation of solid dispersions is one of the most popular (12, 20–22), although few marketed products rely on this concept. This approach frequently improves bioavailability as well as therapeutic effects (13, 23, 24) that are limited or rate controlled by dissolution. Different polymers and sugars have frequently been used as a carrier in solid dispersion formulations (25–30). Mechanisms suggested as being responsible for the improved aqueous solubility/ dissolution properties of solid dispersions include reduction of the particle size of the incorporated drug, partial transformation of the crystalline drug to the amorphous state, formation of solid solutions, formation of complexes, reduction of aggregation and agglomeration, improved wetting of the drug and solubilisation of the drug by the carrier at the diffusion layer (21,31–33). It is highly acceptable, that often more than one of these phenomena determine the rate and extent of dissolution. It has been shown that the methods for the preparation of solid dispersions are simple and less expensive than other techniques (31,34–39).

Cogrinding is environmentally desirable as unlike other techniques it does not require toxic solvents and sophisticated equipment. In this research work an attempt was made to use the cogrinding technique as a promising technique to enhance the dissolution rate of a poorly water-soluble drug, piroxicam.

MATERIALS AND METHODS

Materials:

Piroxicam was provided by Ramdev Chemical Pvt Ltd (Boisar Thana), Sodium Choloride, Potassium Di-hydrogen phosphate, Hydrochloric acid were used are AR grade of S.D.Fine. Triethyl Citrate was purchased from Alfa Aesar a johnson matthey company, Acconon was obtained from Abitec and Tween -80 was purchase from Mohini Organics Pvt. Ltd (mumbai).

Apparatus:

The analysis was performed by using the analytical balance GR-200 (AND), pH meter PHAN (Lab India), Dissolution Tester USP of Electrolab-TDT-08L, Ultraviolet spectrophotometer UV-1601-Shimadzu, Particle size determine by Malvern Mastersizer Hydro 2000mu, Zeta potential determine by Malvern Zetasizer Ver.6.12.

Preparation of Piroxicam(Non Micronized) Dispersion:

Accurately weighed amounts of Triethyl Citrate were placed in an glass beaker and an accurately weighed amount of Piroxicam (Non Micronized) was incorporated into the same carrier with stirring than add accurate weighted amounts of Acconon and Tween -80 to ensure homogeneity. The mixture was stirring until a clear homogeneous liquid was obtained, if required heat the liquid at 60°C to get clear homogeneous liquid.

Table 1: Composition of SEDDS Formulation

Vehicle	Composition of SEDDS Formulation(mg)					
	A	B	C	D	E	F
Piroxicam	10	10	10	10	10	10
Triethyl citrate		440	220	240	240	100
Polysorbate-80			220	100	100	190
Cremophor RH				100		
Cremophor EL					100	
Acconon						190

Manufacture of the Capsule Formulation:

The above process was followed to the point of agitation and the mixture form liquid was filled into the bodies of size 1 capsules using medicine droppers. These were then allowed to capped and then give banding. The fill weight of the capsules was 410 mg, containing 10 mg Piroxicam. The

filled capsules were stored at room temperature until testing; homogeneity was indicated by the excellent clear solution of capsule. Following preparation of the dispersion, the chemical stability of Piroxicam was determined by HPLC to ensure that the drug had not undergone chemical decomposition during the preparation or in the stability. It was noted that there is no leakage or visible change in appearance was apparent during the time of storage under ambient temperature.

Dissolution Studies:

Dissolution studies were carried out in triplicate (one capsule per vessel, each contain 10mg Piroxicam) with an Electrolab TDT-08L dissolution test (USP) in 900 mL simulated gastric fluid prepared without pepsin maintained at 37 ± 0.5°C using the basket apparatus fixed at a rotation speed of 50 rpm. Samples of 10 mL were withdrawn at various time intervals and filtered through Whatman filter paper (41, Ashless, circles 125mm, cat No-1441-125 GE Health care UK Limited) in ther-mostatic test tubs. The volume in the vessel was immediately replaced with fresh dissolution medium maintained at the same temperature. The formulations were assessed visually according to the final appearance of the emulsion formed. The corresponding concentration of Piroxicam was determined from the calibration curve made from standards of known concentration. The Concentration of Piroxicam in each aliquot was determined by using an ultraviolet spectrophotometer UV-1601(Shimadzu) at 242 nm with reference to a suitable constructed standard curve and wthout interference from Acconon, Triethyl Citrate and Tween-80. Dissolution tests were carried out for 45 min. The results presented are mean values of three determinations.

Particle size:

There are two main reasons why many industries routinely employ particle characterization within their businesses.

1. Better control of product quality

In an increasingly competitive global economy, better control of product quality delivers real economic benefits such as:

- Ability to charge a higher premium for your product
- Reduce customer rejection rates and lost orders
- Demonstrate compliance in regulated markets.

2. Better understanding of products, ingredients and processes

In addition to controlling product quality, a better understanding of how particle properties affect your products, ingredients and processes will allow you to:

- Improve product performance
- Troubleshoot manufacturing and supply issues
- Optimize the efficiency of manufacturing processes
- Increase output or improve yield
- Stay ahead of the competition.

By far the most important physical property of particulate samples is particle size. Particle size measurement is routinely carried out across a wide range of industries and is often a critical parameter in the manufacture of many products. Particle size has a direct influence on material properties such as:

- Reactivity or dissolution rate e.g. catalysts, tablets
- Stability in suspension e.g. sediments, paints
- Efficacy of delivery e.g. asthma inhalers
- Texture and feel e.g. food ingredients
- Appearance e.g. powder coatings and inks
- Flowability and handling e.g. granules
- Viscosity e.g. nasal sprays
- Packing density and porosity e.g. ceramics.

Measuring particle size and understanding how it affects your products and processes can be critical to the success of many manufacturing businesses.

In order to simplify the interpretation of particle size distribution data, a range of statistical parameters can be calculated and reported. The choice of the most appropriate statistical parameter for any given sample will

depend upon how that data will be used and what it will be compared with. For example, if you wanted to report the most common particle size in your sample you could choose between the following parameters:

- Mean – 'average' size of a population
- Median – size where 50% of the

population is below/above

- Mode – size with highest frequency.

If the shape of the particle size distribution is asymmetric, as is often the case in many samples, you would not expect these three values to be exactly equivalent, as illustrated below.

Zeta Potential:

Zeta potential is a physical property which is exhibited by any particle in suspension. It can be used to optimize the formulations of suspensions and emulsions. Knowledge of the zeta potential can reduce the time needed to produce trial formulations. It is also an aid in predicting long-term stability.

Zeta potential is a measure of the magnitude of the electrostatic or charge repulsion or attraction between particles in a liquid suspension. It is one of the fundamental parameters known to affect dispersion stability. Its measurement brings detailed insight into the causes of dispersion, aggregation or flocculation, and can be applied to improve the formulation of dispersions, emulsions and suspensions.

The speed with which new formulations can be introduced is the key to product success. Measuring zeta potential is one of the ways to shorten stability testing, by reducing the number of candidate formulations and hence minimizing the time and cost of testing as well as improving shelf life.

The liquid layer surrounding the particle exists as two parts; an inner region (Stern layer) where the ions are strongly bound and an outer (diffuse) region where they are less firmly associated. Within the diffuse layer there is a notional boundary inside which the ions and particles form a stable entity. When a particle moves (e.g. due to gravity), ions within the boundary move it. Those ions beyond the boundary stay with the bulk dispersant. The potential at this boundary (surface of hydrodynamic shear) is the zeta potential.

The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles in suspension have a large negative or positive zeta potential then they will tend to repel each other and there will be no tendency for the particles to come together. However, if the particles have low zeta potential values then there will be no force to prevent the particles coming together and flocculating.

The general dividing line between stable and unstable suspensions is generally taken at either +30 or -30 mV. Particles with zeta potentials more positive than +30 mV or more negative than -30 mV are normally considered stable. However, if the particles have a density different form the dispersant, they will eventually sediment forming a close packed bed (i.e. a hard cake).

Factors Affecting Zeta Potential

1. pH

In aqueous media, the pH of the sample is one of the most important factors that affect its zeta potential. A zeta potential value on its own without defining the solution conditions is a virtually meaningless number. Imagine a particle in suspension with a negative zeta potential. If more alkali is added to this suspension then the particles tend to acquire more negative charge. If acid is added to this suspension then a point will be reached where the charge will be neutralised. Further addition of acid will cause a buildup of positive charge. Therefore a zeta potential versus pH curve will be positive at low pH and lower or negative at high pH. There may be a point where the plot passes through zero zeta potential. This point is called the isoelectric point and is very important from a practical consideration. It is normally the point where the colloidal system is least stable.

A typical plot of zeta potential versus pH is shown in (**figure 3**). In this example, the isoelectric point of the sample is at approximately pH 5.5. In addition, the plot can be used to predict that the sample should be stable at pH values less than 4 (sufficient positive charge is present) and greater than pH 7.5 (sufficient negative charge is present). Problems with dispersion stability would be expected at pH values between 4 and 7.5 as the zeta potential values are between +30 and -30mV.

2. Conductivity

The thickness of the double layer (κ^{-1}) depends upon the concentration of ions in solution and can be calculated from the ionic strength of the medium. The higher the ionic strength, the more compressed the double layer becomes. The valency of the

ions will also influence double layer thickness.

A trivalent ion such as Al will compress the double layer to a greater extent in comparison with a monovalent ion such as Na+.Inorganic ions can interact with charged surfaces in one of two distinct ways (i) non-specific ion adsorption where they have no effect on the isoelectric point. (ii) specific ion adsorption, which will lead to a change in the value of the isoelectric point. The specific adsorption of ions onto a particle surface, even at low concentrations, can have a dramatic effect on the zeta potential of the particle dispersion. In some cases, specific ion adsorption can lead to charge reversal of the surface.

3. Concentration of a formulation component

The effect of the concentration of a formulation component on the zeta potential can give information to assist in formulating a product to give maximum stability. The influence of known contaminants on the zeta potential of a sample can be a powerful tool in formulating the product to resist flocculation for example.

RESULTS AND DISCUSSION:

Dissolution Studies:

Triethyl citrate(TEC), Acconon and Polysorbate-80 were chosen as the hydrophilic polymers for the present studies as these highly water soluble and non-toxic solvent are known to enhance dissolution rate of insoluble drugs. Piroxicam dispersion containing a unit dose of 10mg non micronized piroxicam in a solubilizing matrix comprising either triethyl citrate(TEC), acconon and polysorbate-80 or combination thereof were prepared for in vitro evaluation. The dissolution studies were conducted in an acidic (0.1 NHCL) solution to encompass the pH values encountered in the GIT. The solubility of piroxicam in purified water is 0.086mg/mL, and this level was not achieved within 45 min. In acidic media, the dissolution of piroxicam from the powder alone was incomplete during 45 min. All the binary systems with either triethyl citrate(TEC), acconon and polysorbate-80 displayed better dissolution properties with respect to piroxicam alone. Piroxicam being a weakly acidic drug having pKa of 5.1, all preparation showed higher concentration of dissolution in gastric fluid when compared with the gastric fluid. The increase in solubility of non micronized piroxicam by triethyl citrate(TEC), acconon and polysorbate-80can be probably be explained by increased wettability and micellar solubilization seems more logical as both carriers being surfactants cause a decrease in the interfacial tension between piroxicam and the dissolving solution. A similar increase in the solubility of other drugs by either triethyl citrate(TEC) has been reported (Dordunoo et al.,1991). The results of the dissolution efficiencies at 45min (DE45) and MDT of various piroxicam dispersion formulations are collected in (**Table 3**).

All the dispersion exhibited significant faster gastric fluid dissolution rate than the pure drug. Increasing the proportion of solubilzing carrier to drug and hence the self-emulsifying efficiency of the formulation, resulted in an improvement in the drug solubilization and in the visual grading of the emulsions formed. In these studies, Triethyl citrate(TEC appeared to have slightly better solubilzing properties than acconon and polysorbate-80. For example, at all ratios of piroxicam: TEC, formation of clear microemulsion in acidic medium was obtained, whereas piroxicam: Acconon formulations required higher proportion of carrier to produce similar results. The mixture of piroxicam: triethyl citrate(TEC): acconon: polysorbate-80 provided faster release than individual lipid material in dissolution media. Not less than 90% of piroxicam was released within 10 min. MDT was less than 10 min for all formulation, the dissolution efficiency after 45 min (DE45, %) were ranged from 95.4–97 in dissolution medium.

In vitro release of non micronized piroxicam from liquid-solid dispersion system of various batches prepared by physical mixture method.

Table 2: Dissolution Profile of Piroxicam

Name of the drug	Piroxicam
Loding dose in mg	10
Total No. Of reading including zero time reading	06
Dissolution medium	0.1NHCL
RPM	50
Volume of dissolution medium (ml)	900
Volume of sample removed (ml)	10
Volume of dissolution medium replaced (ml)	10

Table 3: Cumulative Percentage drug Release of Non Micronized Piroxicam SEDDS

S.No	Time	Cumulative Percentage drug Release of Piroxicam SEDDS Formulation					
		A	B	C	D	E	F
1	05	5.20	22.61	6.25	9.34	12.26	83.13
2	10	5.47	28.62	11.80	18.11	29.69	88.53
3	15	6.72	38.07	19.56	24.83	49.43	92.46
4	30	11.30	52.78	50.49	70.32	67.69	96.13
5	45	12.54	63.32	59.97	77.12	80.66	100.17

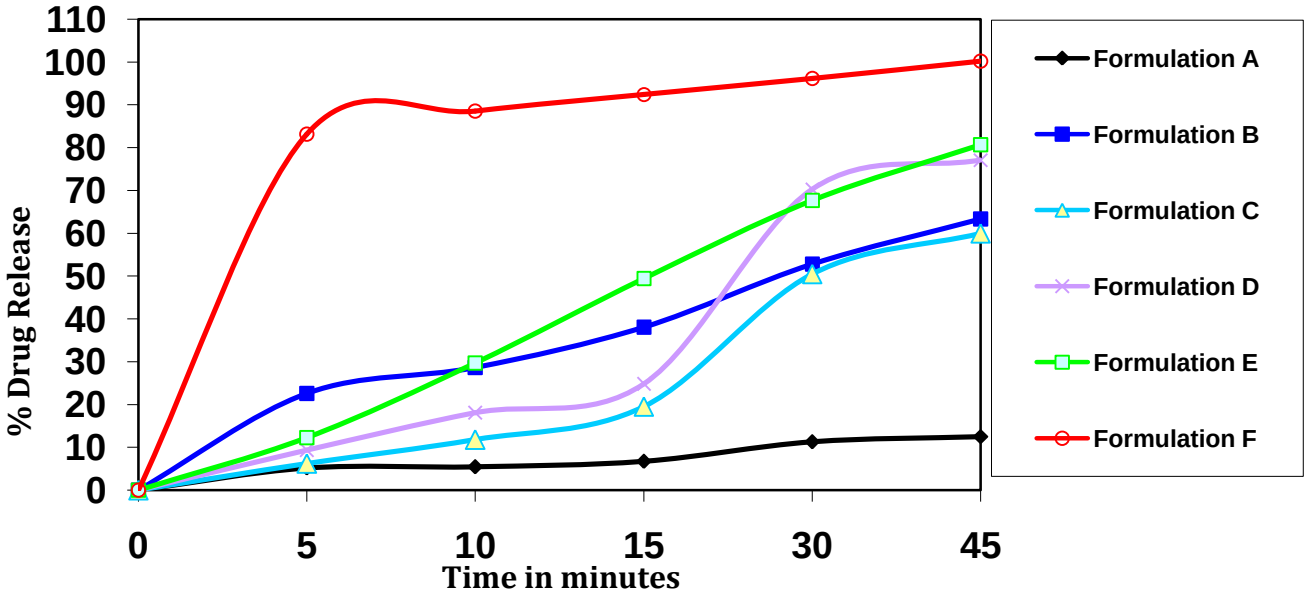

Figure1: Cumulative Percentage drug Release of Non Micronized Piroxicam SEDDS 10mg in 0.1N HCL

Particle Size:

Equivalent weight of one capsule dosage of formulation was diluted with water (900ml) in volumetric flask and gently mixed by inverting the flask. The particle size was determined by Malvern Mastersizer 2000 (United Kingdom). SEDSS formulation form opaque dispersion with globule size > 100nm whereas SEDSS disperse to give optically clear or slightly opalescent dispersions with globule sizes <100nm.

The formulation of the SEDDS containing Piroxicam, TEC, Polysorbate-80 as surfactant and Acconon as co-surfactant. Based on the formulation of a suitable micro emulsion upon expose to water, the optimized formulations were developed and there bioavailabilities were compare with conventional capsule formulation. Each type of sample material has its own ideal range of sample concentration, if the sample concentration is too low than there may not be enough light scattered to make a measurement and if the concentration is high than light scattered by own particle will itself scatted by another, this is called

multiple scattering. If the sample concentration is larger than 1% by volume than particle interaction will influence the results.

Particle size is important factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. It is measured by dynamic light scattered techniques. This employs the fluctuation in scattered light intensity to measure the velocity of the Brownian diffusion and consequently the dispersed droplets.

The droplet size of the emulsions is determined by photon correlation spectroscopy(which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 1000nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even10 after 100 times dilution with water which proves the system's compatibility with excess water.

Zeta potential:

Equivalent weight of one capsule dosage of formulation was diluted with water (900ml) in volumetric flask and gently mixed by inverting the flask. The Zeta potential was determine by Malvern Zetasizer Ver.6.12 (United Kingdom).

Zeta potential is not a size dependent parameter using the approximation of the Smoluchowski theory. Zeta potential measurement in the zetasizer nano series means that the concentration requirement is not as strict as those used for the size and molecular weight measurement. If the sample is too concentrated a low sample count rate error will be displayed and if too low than generated results being variable. Many samples will require dilution and this procedure is absolutely critical in determining the fine value measured. The zeta potential is as dependent on the composition of the disperse phase as it is on the nature of particle surface.

The sample preparation is to preserve the existing state of the surface during the process of dilution. There is only one way to ensure this is the case. This is by filtering or centrifuging some clear liquid from the original sample and using this to dilute the original concentration sample. In this way equilibrium between surface and liquid is perfectly maintained.

Another method is to imitate the original medium as closely as possible. This should be done with regard to pH, Total ionic concentration of the system, Concentration of any surfactant or polymers present.

The non polar dispersant to suppress the zeta potential, the actual value measured can seem very high as much 200 to 250mv. In such non polar system equilibration of the sample offer dilution is the time dependent step, equilibration can take in excess of 24hrs.

Laser Doppler Micro-electrophoresis is used to measure zeta potential. An electric field is applied to a solution of molecules or a dispersion of particles, which then move with a velocity related to their zeta potential. This velocity is measured using a patented laser interferometric technique called M3-PALS (Phase analysis Light Scattering). This enables the calculation of electrophoresis mobility, and from this, the zeta potential and zeta potential distribution.

CONCLUSION

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDS, which have been shown to substantially improve oral bioavailability. Their efficiency is case specific, thus their proper characterization is of utmost importance. Lipid base formulation is still not very widespread as commercial formulations, despite their great success in bioavailability enhancement of poorly soluble drugs. The can be attributed to lack of proper understanding of development and manufacturing process to physical and chemical stability issues. Effective in vitro tests should be utilized which can predict in vivo performance of the fascinating and diverse group of formulations.

Future focus should be on understanding of the role of individual lipids and surfactants in the formulation of SEDDS with regard to dispersion process, the structure of the formed emulsion particle and drug

solubilisation.

The present results of investigation show the suitability of triethyl citrate(TEC), acconon and polysorbate-80 as the carrier for preparation of non micronized piroxicam liquid-solid dispersion filled into hard gelatine capsules. As mentioned above, these substances are widely used as pharmaceutical excipients. The non micronized piroxicam: triethyl citrate(TEC): acconon: polysorbate-80 dispersion were formed at different ratios. The dissolution rates of piroxicam dispersions were higher than that of pure drug; this was possibly caused by the increase in drug wettability.

Sample Details

Sample Name: Non Micronized Piroxicam SEDDS in 900ml
SOP Name: mansettings.nano
General Notes:

File Name:	sedds.dts	**Dispersant Name:**	Water
Record Number:	7	**Dispersant RI:**	1.330
Material RI:	1.59	**Viscosity (cP):**	0.8872
Material Absorbtion:	0.01	**Measurement Date and Time:**	Tuesday, March 19, 2013 ...

System

Temperature (℃):	25.0	**Duration Used (s):**	140
Count Rate (kcps):	21.4	**Measurement Position (mm):**	4.65
Cell Description:	Disposable sizing cuvette	**Attenuator:**	11

Results

Z-Average (r.nm): 199.0
PdI: 0.671
Intercept: 1.03
Result quality Good

	Size (r.nm):	% Intensity	Width (r.nm):
Peak 1:	127.7	81.5	34.25
Peak 2:	45.57	18.5	9.451
Peak 3:	0.000	0.0	0.000

D(10): 90.9 D(50): 235 D(90): 344 D(100): 459

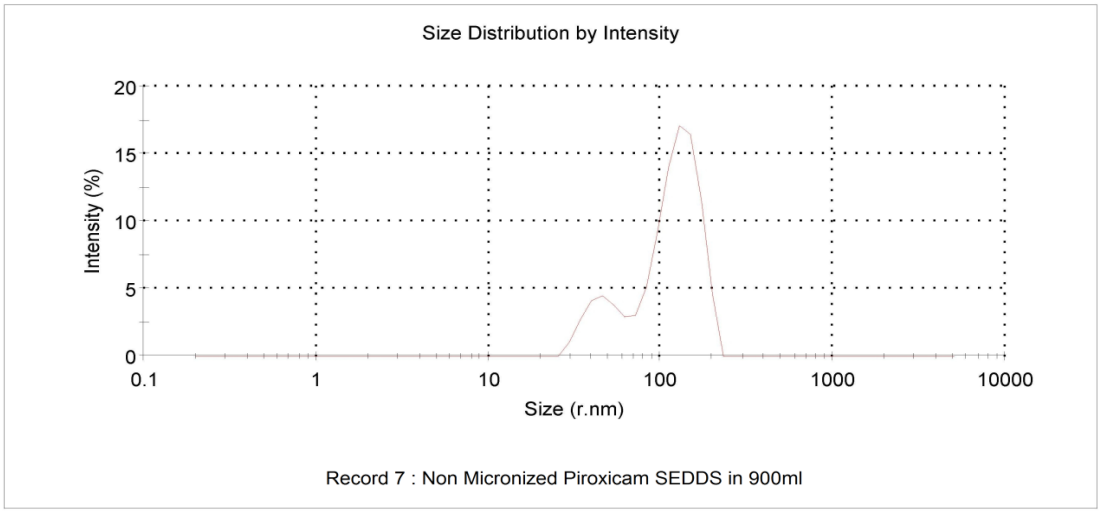

Figure 2: Particle Size Distribution of Non Micronized Piroxicam SEDDS in 900ml

Sample Details

Sample Name:	Non Micronized Piroxicam SEDDS in 900ml		
SOP Name:	mansettings.nano		
General Notes:			
File Name:	sedds. dts	**Dispersant Name:**	Water
Record Number:	4	**Dispersant RI:**	1.330
Date and Time:	Tuesday, March 19, 2013 3:01...	**Viscosity (cP):**	0.8872
		Dispersant Dielectric Constant:	78.5

System

Temperature (℃):	25.0	**Zeta Runs:**	12
Count Rate (kcps):	78.5	**Measurement Position (mm):**	2.00
Cell Description:	Clear disposable zeta cell	**Attenuator:**	11

Results

			Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV):	-17.9	**Peak 1:**	-17.9	100.0	3.56
Zeta Deviation (mV):	3.56	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm):	1.65e-4	**Peak 3:**	0.00	0.0	0.00
Result quality	Good				

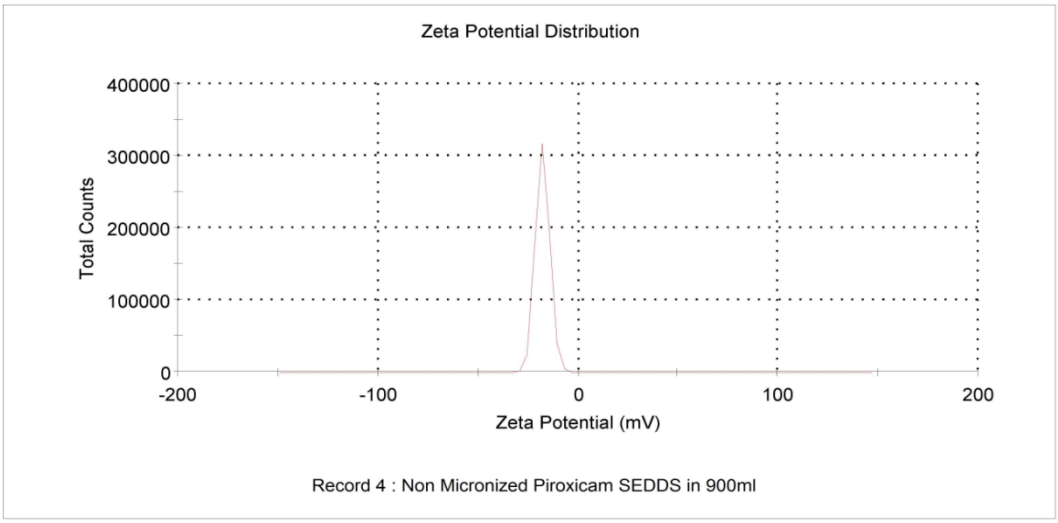

Figure 3: Zeta Potential of Non Micronized Piroxicam SEDDS in 900ml

ACKNOWLEDGMENT

The authors are grateful to the ACPL for providing the necessary infrastructure facilities to carry out the studies. We would like to thank Dr. Avinash R. Tekade for his guidance in the publication of article.

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