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ISSN: 0975-7538
Research Article

Formulation and evaluation of self-emulsification drug delivery system of Dronedarone

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ABSTRACT

The aim of the present study was to investigate the potential of nano-emulsion (thermodynamically stable, transparent, dispersion of oil and water having droplet size less than 200nm). Formulation of self-Emulsifying system of Dronedarone as a model drug, by using Myristic acid isopropyl ester, Tween80, Ethanol as oil phase, surfactant and co-surfactant respectively and water. Various o/w nano-emulsion formulations were prepared by spontaneous self- emulsification method. The area of nano emulsions were identified by constructing pseudo ternary phase-diagrams. The nano-emulsions that were prepared subjected to thermodynamic stability testing. The tests were characterized by using droplet size, Scanning electron Microscopy (SEM), viscosity, zeta potential and pH and in-vitro dissolution studies. The in-vitro dissolution studies of optimized formulation was compared with nanoemulsion. Thus these results suggested that nano-emulsions are the key vehicles for improved emulsification delivery of Dronedarone.

Keywords: Dronedarone, Myristic acid isopropyl ester; Ethanol; Nano-emulsion; SEM; Tween80.

INTRODUCTION

"Nano emulsion" is defined as thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by surfactant molecules. A nano emulsion is considered to be a stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant and co-surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm - 200 nm, and have very low oil/water interfacial tension. These are transparent. The nano emulsion that is formed readily and are sometimes spontaneously, generally without high-energy input. In many cases a co-solvent is used in addition to the surfactant, the oil phase and the water phase. (RK Chouksey *et al.*, Nano emulsion: A Review).

Anti-Arrhythmic drugs are one of the numerous drugs having the limitation of poor aqueous solubility and bioavailability. In addition thereto blurred vision and allergic reactions are the prime obstacles that led to commercial withdrawal of certain drugs of this class. Flecainide, Amiodarone, sotalol, Digoxin can be counted among these. Duration of action of can be increased by improving its release patterns from formulation and systemic anti-arrhythmic effects without major side effects. Dronedarone which was chemically known N-(2-butyl-3-{4-[3-(dibutylamino) propoxy]benzoyl}-1-benzofuran-5-yl)methanesulfonamide. It has Empirical formula $C_{31}H_{44}N_2O_5S$ and has Molecular Mass of 556.758 g/mol.

The antiarrhythmic effect of dronedarone may be due to at least two major actions. As it prolongs the duration of action potential and refractory period in myocardial tissue via inhibition of sodium and potassium channels and via inhibition of calcium channels and blockage of β1-adrenergic receptors, a decrease in AV conduction and sinus node function can be observed.

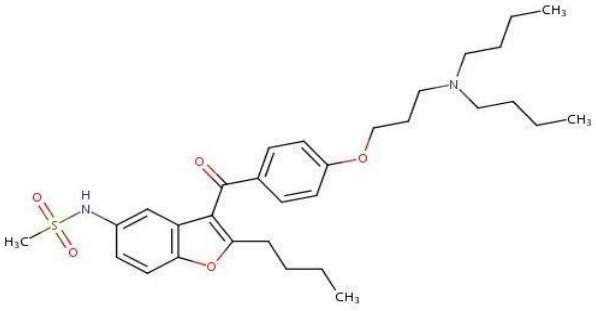

Figure 1: Molecular structure of dronedarone

Dronedarone can also cause an increase in blood pressure by inhibition of alpha1-adrenergic receptors (drugbank.ca). Now a day's Nano emulsions are the potential drug delivery systems for oral and parenteral administration of drugs like Anti-Arrhythmics. It was found that Nano emulsions could be a very good carrier for highly lipophilic drugs. The aim of the present studies was to formulate and evaluate self-emulsification drug delivery of Dronedarone.

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Received on: 23-06-2015
Revised on: 30-06-2015
Accepted on: 04-08-2015

MATERIALS AND METHODS

Dronedarone (MSN Laboratories, Rudraram, Medak, Telangana), Iso Propyl Myristate (Sisco Research Laboratories Pvt. Ltd., Mumbai), Almond Oil, Arachis Oil, Oleic Acid (S.D.Fine Chemicals, Mumbai), Tween 60, Tween 80, Span 60, Tween 20, Span 20 (Oxford Chemicals, Mumbai) and Ethanol(Merck laboratories, Mumbai). The other chemicals that are used were analytical grade.

Drug characterization

Determination of melting point

Melting point of pure Dronedarone was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Dronedarone individually by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 100°C min raise of temperature per minute. The raise in temperature was viewed through magnifying lens. The temperature at which the drug started melting was recorded. This was performed thrice and average value was calculated.

Determination of solubility of Dronedarone in different solvents

The solubility of the Drug in various solvents (Oils, Surfactants, Buffers, co-surfactants) were determined by shake flask method and sonication. An accurately measured 5ml of each solvent was taken in a vial separately. To each vial an excess amount of Drug was added. Vials were sealed properly and stirred using cyclomixer for 10min for proper mixing. They were then kept on probe sonicator for 12 hrs with little intermediate sessions of gaps. The solution was then allowed to equilibrate for 48 hrs. After 48 hrs, the solutions were transferred into centrifuge tubes and centrifuged at 2000 rpm for 10 minutes using a centrifuge (Mfd. Remi motors, Mumbai, India) and supernatant liquid was filtered through filter. Suitable dilutions were prepared from the aliquots and analyzed using UV spectroscopic (Lab India UV+3000) method at 290 nm. Amount of drug dissolved in each medium was calculated by using respective calibration curves.

Selection of excipients

Selection of oil

For proper development of a Nano emulsion, selection of appropriate oil having good solubilization capacity for Dronedarone is a prime requirement. Correlating the solubility of drug with loading of the drug in oil phase can affect the ability of the Nano-emulsion was to maintain the drug in the solubilized form. The solubility of the Dronedarone drug in various oils were determined by adding an excess amount of drug in 5ml of oils that were selected (Oleic Acid, Sunflower Oil, Sesame Oil, Isopropyl Myristate) was poured in stoppered vials and mixed using a magnetic stirrer for 24 hrs. The vials containing the mixtures were kept at 25 ± 1°C in isothermal shaker for 3 days to reach the state of equilibrium. After three days, the samples were centrifuged at 2000 rpm for 15 minutes (Remi motors, Mumbai, India). The supernatant was taken and filtered. The concentration of Dronedarone was determined in the oils using UV visible Spectrophotometer at 290 nm (Haritha *et al*., 2011)

Selection of surfactant

Emulsions are the formulations where two immiscible liquids phases are dispersed in one another by using a mechanical shear. It is an inherent tendency of dispersed liquid and continuous phase to attract the molecules of each other to form a successive phase. An interfacial - tension (σ) exists between the two liquids, which can be reduced by incorporati ng a suitable surfactant into the system. Hence, to select the best surfactant from a pool, the emulsification ability of the surfactants was screened. 300mg of surfactant and oily phase were added to each other, and the mixture is gently heated at 45-60° C for homogenizing the selected components. Then 50 mg of the homogenized mixture was diluted with distilled water to 50 ml to yield fine emulsion. The ability of the emulsion formation was monitored by noting the number of volumetric flask inversions required to give a uniform emulsion. The resulting emulsions are observed visually for the relative turbidity (Haritha *et al*., 2011). The emulsions were allowed to stand for 1-2 hours to check any change in turbidity, and their transmittance was assessed at 290 nm (λ_{max} of Drug) by colorimeter using distilled water as blank.

Selection of co-surfactants

Co-Surfactants are the excipients added to the emulsion for further stabilizing the interfacial film and prevent the coalescence of the droplets. 100 mg of co-surfactant was added to 200 mg of the surfactant that was selected previously, and surfactant mixture (Smix) was then added to the selected oil phase. Effect of co-surfactant in stability was checked in the identical way as screening of surfactant. As the ratio of Co-surfactants to surfactants was same and the turbidity of resulting Nano-emulsions will help in assessing the relative efficiency of the co-surfactants to improve the emulsification ability of the surfactants .

Drug - excipient interaction studies

The compatibility studies of the drug with the excipients were further assessed by using drug - excipient interaction studies. The drug was mixed with the excipients in 1:1 ratio in separate glass vials which were then properly sealed and kept undisturbed at different storage conditions like at room temperature, at 40°C, and in refrigerator for a period of one month. After every week vials were withdrawn and contents were observed for any changes in their physical appearance and colour.

Construction of pseudo ternary phase diagram

On the basis of the study of solubility, a combination of Isopropyl Myristate was selected as the oil phase, Smix (Tween 80, Ethanol were selected as surfactant and co-surfactant). Distilled water was used as an aqueous phase. Smix were mixed at different mass ratios (1:1, 1:2, 2:1, 1:3). These ratios were chosen in increasing concentration of surfactant with respect to surfactant for a detailed study of the phase diagrams. For each phase diagram, oil and Smix at a specific ratio was mixed thoroughly at different mass ratios from 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 in different glass vials. Pseudo ternary phase diagrams of Oil, Smix and aqueous phase were developed using the aqueous titration method. The physical state of the Nano emulsion was marked on a pseudo-three component phase diagram with one axis representing the aqueous phase, the second representing oil and the third representing a mixture of surfactant and co-surfactant at a fixed mass ratio.

Selection of formulations

Formulations were selected from Nano-emulsion region of the constructed phase diagram was to incorporate drug into oil phase. The formulation was chosen with the criteria of maximum oil being emulsified with the minimum amount of Smix. The constant amount of Dronedarone that is 1% w/w of Dronedarone, was selected for the formulations, dissolved in the oil phase of the emulsion. Selected formulations were subjected to various thermodynamic stability tests.

Determination of concentration range of the selected formulation components by construction of ternary phase diagrams

The main aim for construction of Ternary Phase diagram was to determine the concentration range of each factor as well as to identify the desired region of emulsification posse's clear emulsion characteristic.

A series of formulations were prepared with varying concentration ranges of Oil, Smix and water. Concentration of Isoproyl Myristate was varied from 4 -70% (w/w) as an oil phase, Smix from 40-8% (w/w) which includes both Tween 80 and Ethanol and water from 56-22% (w/w). Total Oil, Smix and water added up to 100% in each mixture. Each formulation was homogenized heating gently up to 45-50^{o}C. Accurately weighed 50mg of each mixture was then emulsified to 50 ml with distilled water, under the conditions of gentle shaking and the resultant emulsion was allowed to stand undisturbed for 15min for equilibration. The selection of emulsification range was done on the virtual clearance and % Transmittance. Only those compositions having % transmittance more than 70% and clear appearance were considered desirable and were used in plotting ternary phase diagram. Ternary phase diagrams were plotted using Chemix Software (version 3.60). Desirable emulsifying region and concentration range of each component were identified from phase diagram.

Formulation development

From the results of solubility, emulsifying ability, concentration ranges to be used from pseudo ternary phase diagram Isopropyl Myristis Acid as Oil phase, Tween 80 and Ethanol Surfactant and Co-Surfactant were weighed and mixed. The drug was accurately weighted to represent 1%w/w of the total weight of formulation and added to previous mixture and stirred by using magnetic bar on magnetic stirrer, at room temperature until the drug was completely dissolved in the formulation. The weighed amount of water then added drop wise with continuous stirring. Then droplet size was then further reduced by using method of sonication.

Formula optimization

From the diffusion profiles of the fi ve developed formulations in different buffers which indicated the ability of the system to self-emulsify with minimum contact of aqueous phase, the formulations having highest diffusion rate as % release of drug vs Time (hours) in buffers are selected as optimized formulations for final evaluations.

Characterization and evaluation of nano-emulsion

Thermodynamic stability studies

To overcome the problem regarding the thermodynamic stability study was performed, which are as follows:

Heating cooling cycle

Heating and cooling cycle was done in refrigerator ranging the temperature of 4^{o}C and 45^{o}C for 48 hours. The formulations which were stable at these temperatures were subjected for centrifugation test.

Centrifugation

Centrifugation study for the selected formulations was done at 3500 rpm about 30 minutes. Formulations did not show phase separation were processed further for the freeze thaw stress test.

Freeze thaw cycle

Three freeze thaw cycles were carried out between at a temperature of -21^{o}C and 25^{o}C where the formulation were stored for more than 48 hours at each temperature. Those formulations, which passed these tests, were selected and processed for further study.

Droplet size analysis

50 mg of the nano emulsified formulation was diluted to 50 ml with ethanol and was allowed to equilibrate for 15min. Droplet size of the resulting emulsion was then measured by using coulter counter particle size analyzer (Horiba SZ100, Particle size Analyzer, Ca). It measures the change in resistance as function to drop-

let size. Refractive indices of the formulation as well as dispersion medium and viscosity of the formulation were fed in the dispersion technology software and mean globule size (Z-Average) (Sav Ajay Kumar *et al*., 2014).

Zeta potential

Zeta Potential was of the optimized formulations were measured by the instrument Zeta-sizer (Horiba, Ca).

Refractive index

The Refractive Indices of the optimized formulations were measured by Abbe's refractometer. The refractive Index of the formulations was measured after one month once again. (Abdus Samad *et al*., 2012).

Viscosity determination

Brookfield DVE Viscometer (Brookfield Engineering Laboratories, Inc, Middleboro, MA) was used to determine the viscosity of the optimized formulations. About 0.5 g of sample was taken for analysis without dilution the sample by using spindle no. 63 at different rpm at 25±-0.5°C (Abdus Samad *et al*., 2012).

In-vitro drug release studies

An In-Vitro drug release study for the optimized formulations was performed using Franz diffusion cell method with an effective diffusional area of 3.14 cm^2 and 25 ml of the receiver's chamber capacity. Samples are collected periodically and replaced with fresh dissolution medium. Samples after filtration through syringe filter (Whattsman filter paper) were analyzed by using UV visible spectrophoto metric method at 290 nm for Dronedarone content. Cumulative % drug release data at various pH buffers with the marketed formulation.

pH

The apparent pH of the formulation was measured by using digital pH meter which is standardized previously (Ajay Thakur *et al*., 2013).

Scanning electron microscopy (SEM)

Structure of the Nano-emulsion were studied by using S.E.M report (Bruker S3700N, Germany). It was used to know the structure and size of Nano-emulsion droplets. Observations were performed, a drop of the Nano-emulsion was deposited directly on the holey film grid and observed after the sample was dried. (Sav Ajay Kumar *et al*., 2014).

RESULTS AND DISCUSSION

Melting point

Melting point of pure Dronedarone was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Dronedarone individually by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 100°C min raise of temperature per minute. The raise in temperature was viewed through magnifying lens. The temperature at which the drug started melting was recorded as 140 - 145°C. This was performed thrice and average value was calculated.

Solubility of dronedarone

The maximum solubility of dronedarone was found in Isopropylmyristate (0.353 ± 0.05 mg/ml) compared to other oils. Maximum solubility of dronedarone was found in tween 80 (1.069 ± 0.12 mg/ml) and ethanol (1.532±0.13) was selected as co-surfactant as it forms stable Nano-Emulsion, also acts as a permeation enhancer. Therefore, Tween 80 and Ethanol was selected as Smix (surfactant and co-surfactant), respectively for the phase study. The results are shown in Figure No 2.

Excipients selection

The physiochemical properties of Drug suggests it has good potential properties for the delivery of drug. The important criteria for selection of excipients of Nano-emulsion formulation. Maximum the solubility of the drug in oil phase was main criteria, as it will help the emulsion to maintain the drug in solubilized form. In this study, we selected Tween-80 as a surfactant which has an HLB value of 15. Thus, the co-surfactant selected for the study was Ethanol, which has an HLB value of 4.2. Dronedarone is a highly lipophilic drug and its physicochemical properties suggest that it has good potential for drug delivery. Therefore, in the present study different Nano- Emulsions were prepared for self-emulsifying drug delivery of Dronedarone.

Psuedo-ternary phase diagram

Psuedoternary phase diagrams were constructed for each Smix ratio, separately so that the o/w Nano emulsion regions could be identified and could be optimized. Pseudoternary phase diagrams were constructed for each Smix ratio separately as shown in Figure No 3 to Figure No 6 which represents the Smix Ratio 1:1, 1:2, 2:1, 1:3 respectively. The maximum was observed in 1:1 Smix (Figure No 3), when co-surfactant was added along with the surfactant, the interfacial film. The maximum amount of oil could be solubilized was 34% (m/m) with around 28% (m/m) of Smix. The surfactant concentration was increased in Smix ratio (1:1, Fig 4.4.2). The further increase in the surfactant concentration in the Smix to 2:1 (Figure No 4), the increased concentration of oil that could be solubilized by this ratio was 36% (m/m) with around 31% (m/m) of Smix. The maximum concentration of the oil that could be solubilized1by this ratio was 41% (m/m) with around 42% (m/m) of Smix. When the Smix ratio of 3:1 was studied (Figure No 6) the small area of the Nano-emulsion further decreased and the liquid crystalline area started to appear in the phase diagram. The maximum amount concentration of the oil that could be solubilized by this ratio was around 42% (m/m) with

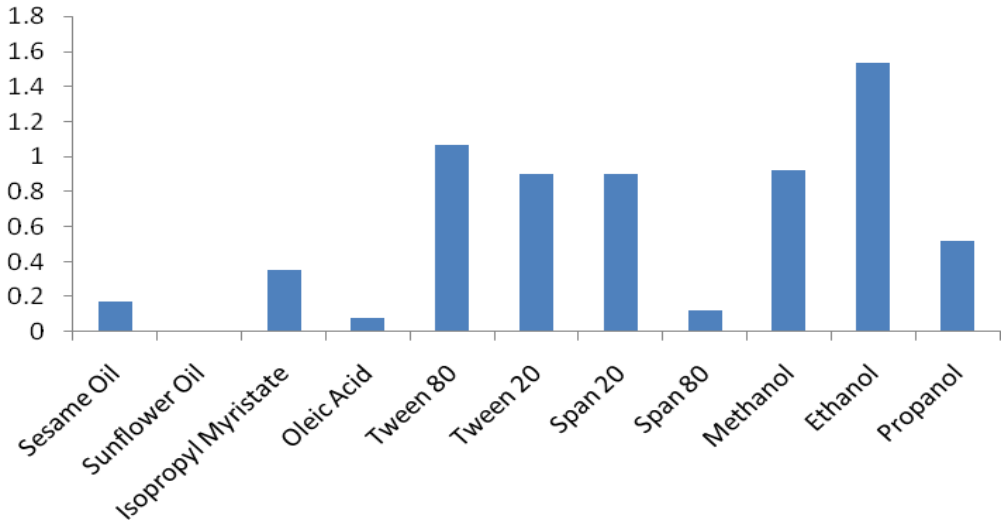

Figure 2: Solubility of dronedarone drug in oils, surfactants and co-surfactants

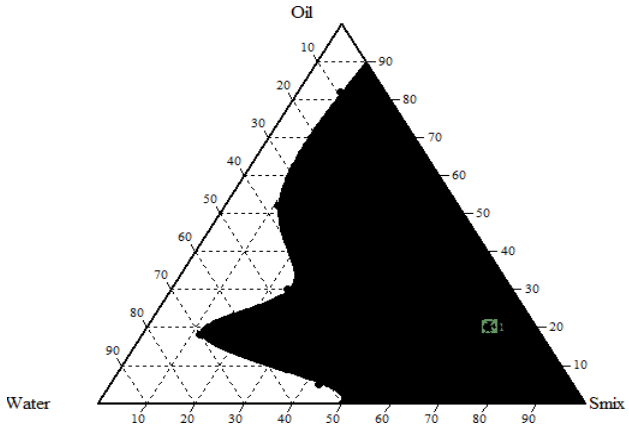

Figure 3: Psuedo ternary phase diagram showing the o/w nanoemulsion at smix ratio 1:1

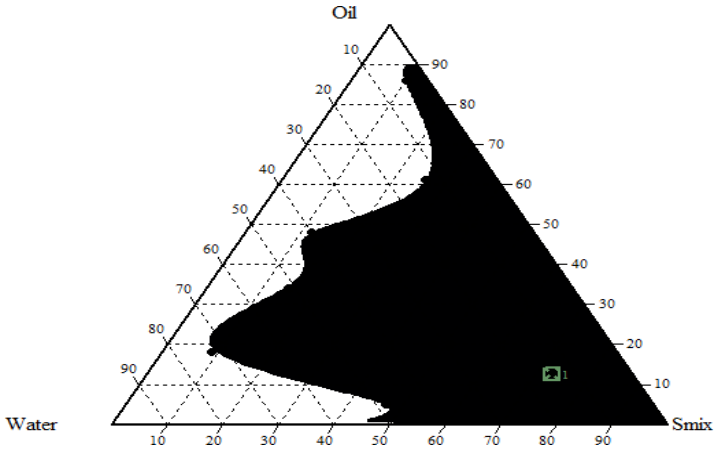

Figure 4: Psuedo Ternary phase diagram showing the o/w nanoemulsion at smix ratio 1:2

Table 1: Formulations of dronedarone

Sample	Ratio	Oil (mg)	Smix (mg)	Water (mg)
F1	1:1	4	40	56
F2	1:1	10	39	52
F3	1:1	16	36	48
F4	1:1	24	36	41
F5	1:1	32	32	36

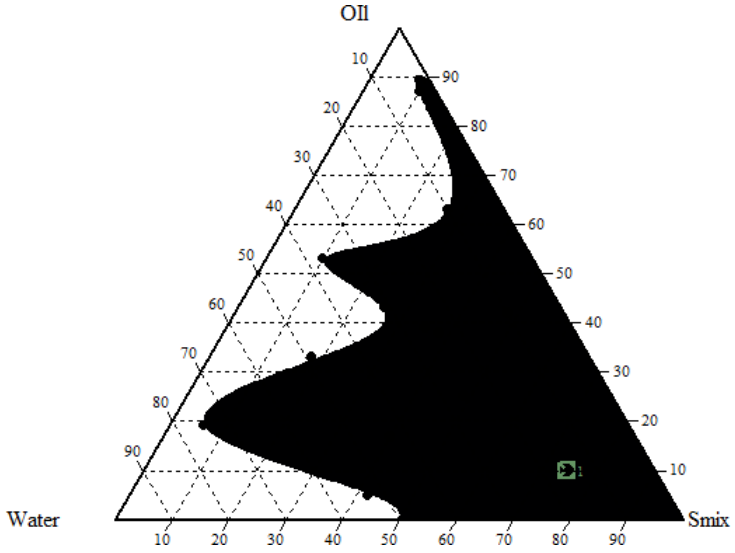

Figure 5: Psuedo ternary phase diagram showing the o/w nanoemulsion at smix ratio 2:1

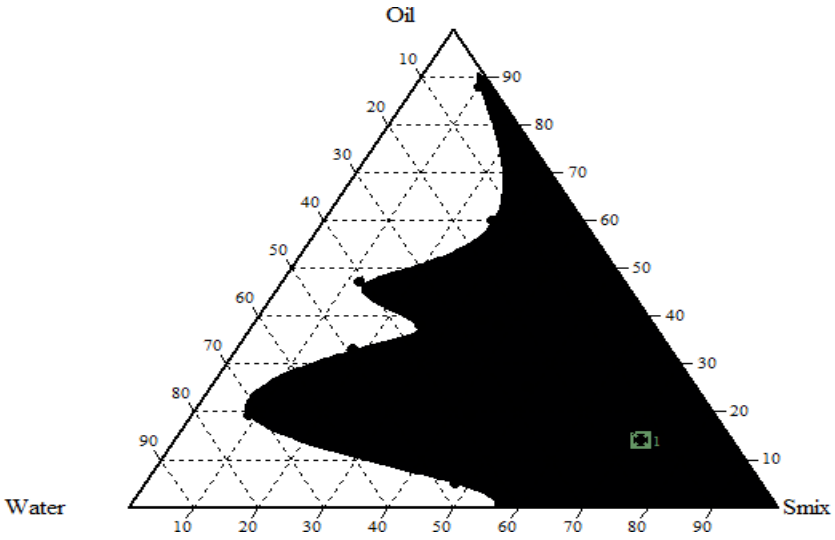

Figure 6: Psuedo ternary phase diagram showing the o/w nano-emulsion at smix ratio 1:3

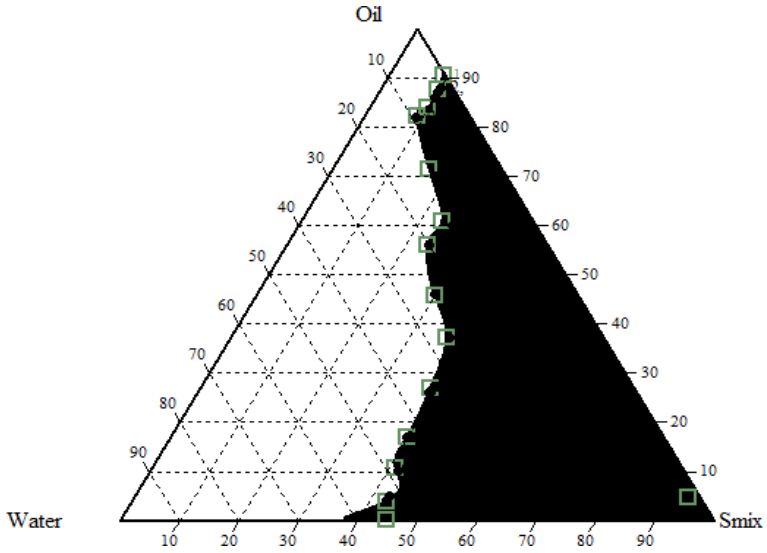

Figure 7: Ternary phase diagram showing the o/w nano-emulsion regions

Table 2: Stability studies of formulations

Sample code	Heating and cooling	Centrifugation	Freeze-thaw Cycle	Inference
F1	Pass	Pass	Pass	Pass
F2	Pass	Pass	Pass	Pass
F3	Pass	Pass	Pass	Pass
F4	Pass	Pass	Pass	Pass
F5	Pass	Pass	Pass	Pass

Table 3: Viscosity of nano-emulsion formulations

Sample code	Viscosity (cps)*
F1	34.52 ± 1.2
F2	31.21 ± 1
F3	37.13 ± 1.3
F4	45.55 ± 1.5
F5	41.32 ± 1.8

* Centipoise

Table 4: Refractive index of nano-emulsion formulations

Sample Code	Refractive Index of Formulation	Refractive Index of Placebo Formulation
F1	1.421	1.426
F2	1.622	1.626
F3	1.331	1.334
F4	1.439	1.443
F5	1.674	1.677

Table 5: pH of the formulations

Sample Code	pH
F1	6.8
F2	6.9
F3	6.3
F4	6.2
F5	6.6

Table 6: Cloud point of optimized formulations

S.No.	Sample Code	Cloud Point (°C)
1	F1	70 ± 1
2	F2	71 ± 2
3	F3	68 ± 1
4	F4	69 ± 2
5	F5	72 ± 3

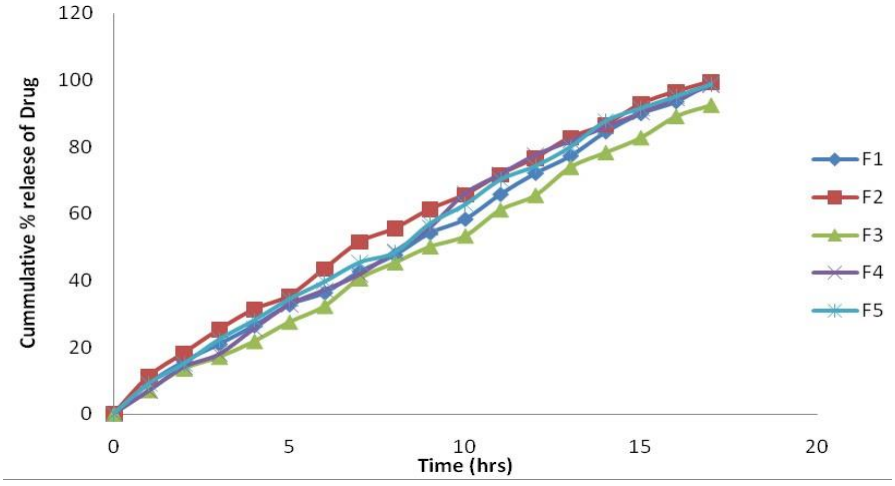

Figure 8: Cumulative % drug release v/s time(hrs) F1 to F5

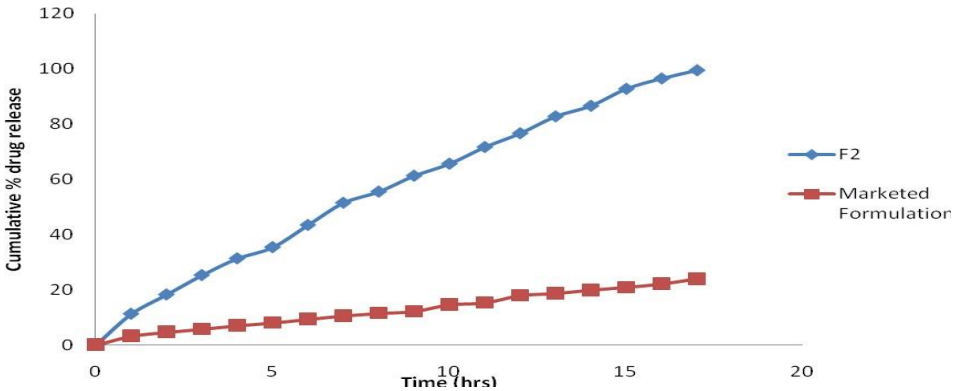

Figure 9: Cumulative % drug release v/s Time (hrs) F2 and marketed formulation

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Measurement Results

Date	:	Thursday, April 16, 2015 2:38:42 PM
Measurement Type	:	Particle Size
Sample Name	:	nano emulsion sample-1
Scattering Angle	:	173
Temperature of the holder	:	25.1 °C
T% before meas.	:	32
Viscosity of the dispersion medium	:	0.893 mPa·s
Form Of Distribution	:	Standard
Representation of result	:	Scattering Light Intensity
Count rate	:	1791 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	197.2 nm	459.5 nm	262.7 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	197.2 nm	459.5 nm	262.7 nm

Cumulant Operations

Z-Average	:	23.1 nm
PI	:	0.589

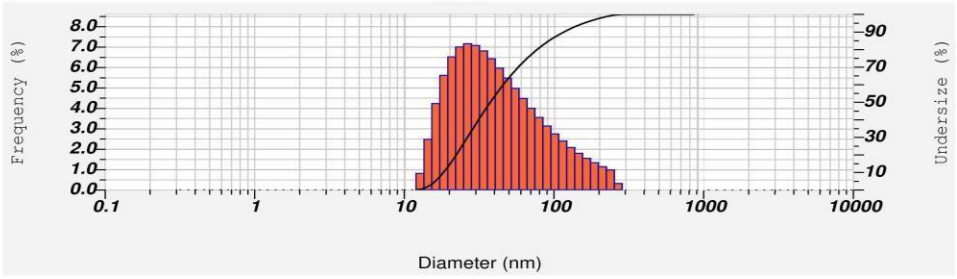

Figure 10: Graph indicating the mean particle size of formulation F1

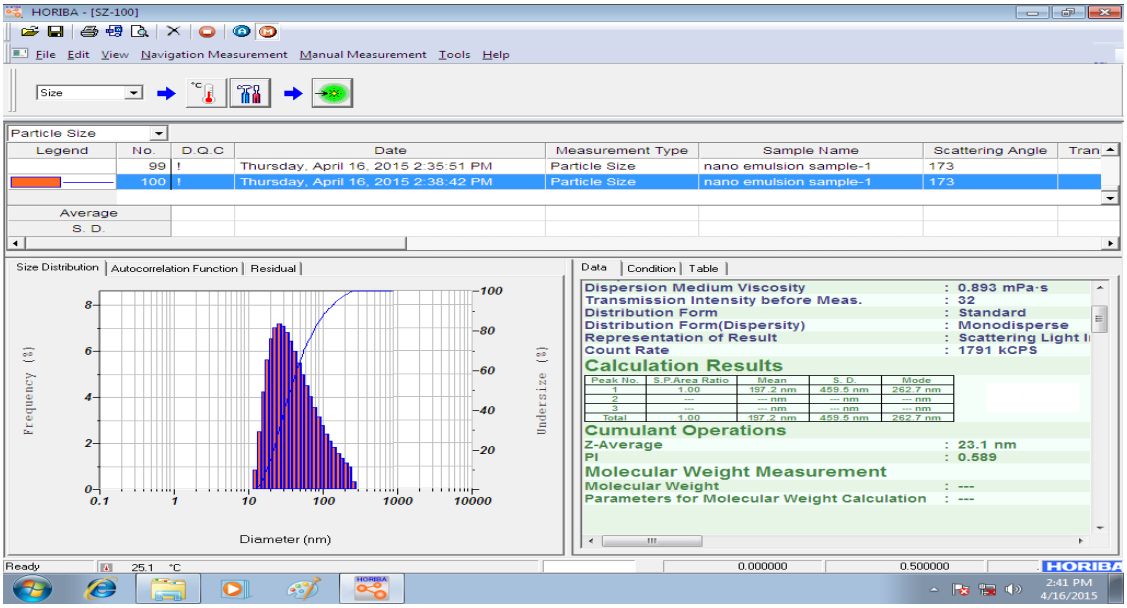

Figure 11: Graph indicating the mean particle size of formulation F1

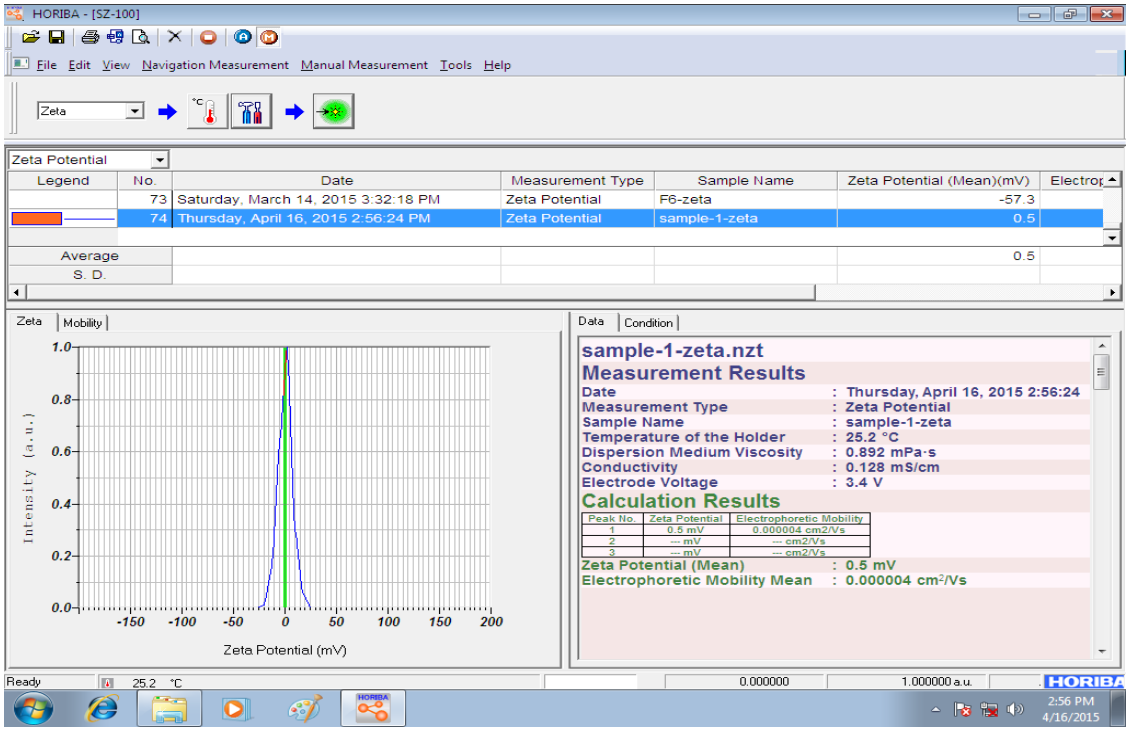

Figure 12: Graph indicating the zeta potential of the formulation F1

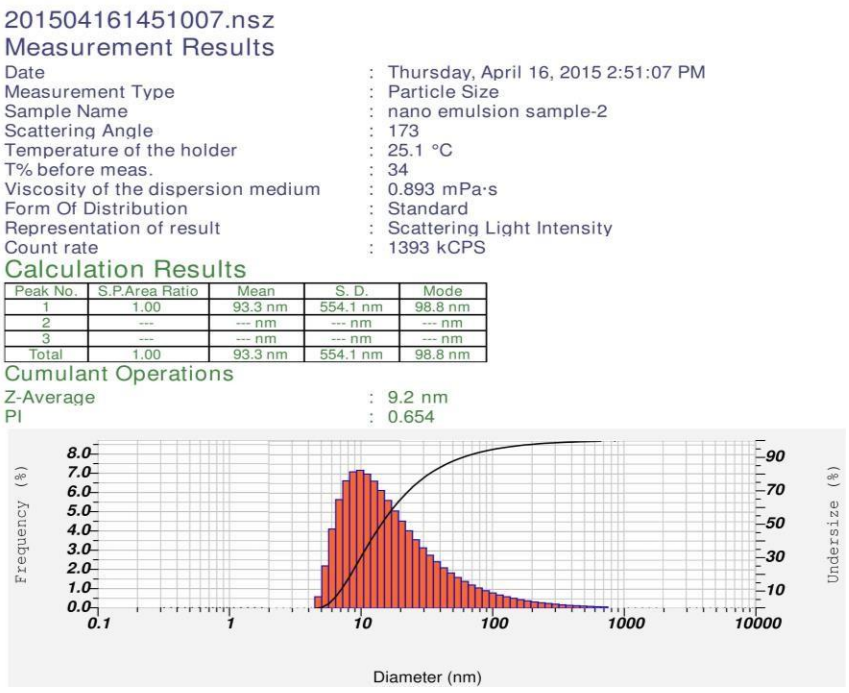

Figure 13: Graph indicating the mean particle size of formulation F2

around 34% (m/m) of Smix [4]. When the co-surfactant concentration was increased from the 1:1 to 1:2 compared to surfactant, the area was decreased. A total of 5 formulations were selected based on their ability to form oil in water.

Determination of concentration range of the selected formulation components by construction of ternary phase diagram

A series of emulsifying formulations were prepared with varying concentrations of Oil, Smix and water. Concentration of Isoproyl Myristate was varied from 4 - 70% (w/w) as an oil phase, Smix from 40-8% (w/w) which includes both Tween 80 and Ethanol and water concentration which is varied in a different concentration of 56-22% (w/w). Total Oil, Smix and water added up to 100% in each mixture. Each formulation was homogenized with the heat up to 45-50^{0}C. Those compositions having % transmittance more than 70%.As shown in Figure No 7.

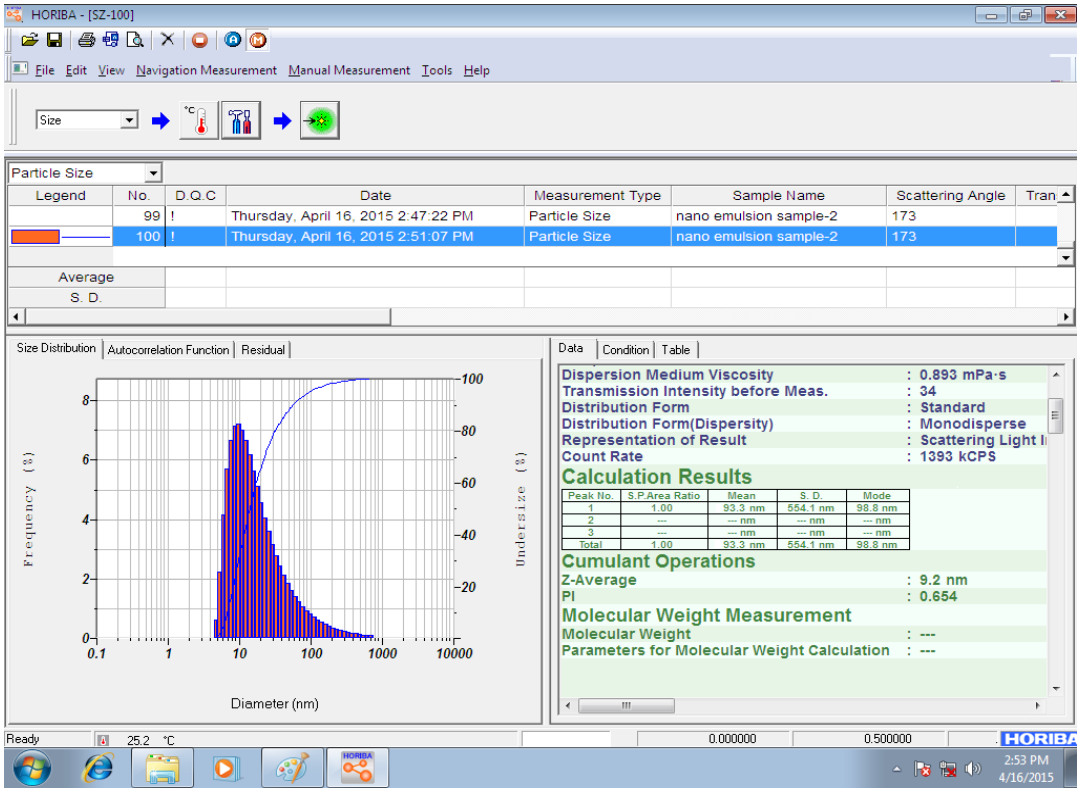

Figure 14: Graph indicating the mean particle size of formulation F2

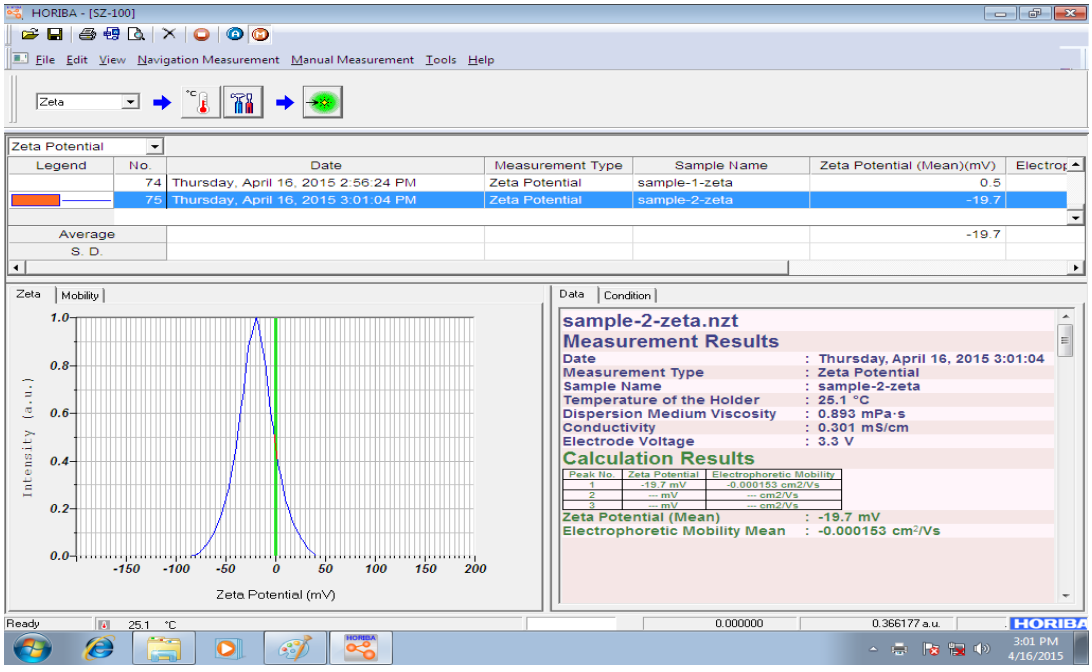

Figure 15: Graph indicating the zeta potential of the formulation F2

Dispersion stability studies

All the formulation were passed the stabili ty tests. The compositions of selected formulations are given in the Table 2.

Viscosity

Formulation F2 had the least viscosity (31.21 ± 1cps) compared to other formulations. This may be due to the lower oil content. Viscosity of optimized formulations was very low. As shown in Table 3.

Refractive index

The values of the refractive index of drug loaded formulations and placebo formulations are given in Table 4. The refractive index were compared with that of the placebo formulations were compared with those of the placebo, and found that there were no significant differences ($p < 0.05$) between the two values. Thus, there were no interactions between Nano-Emulsion excipients and drug.

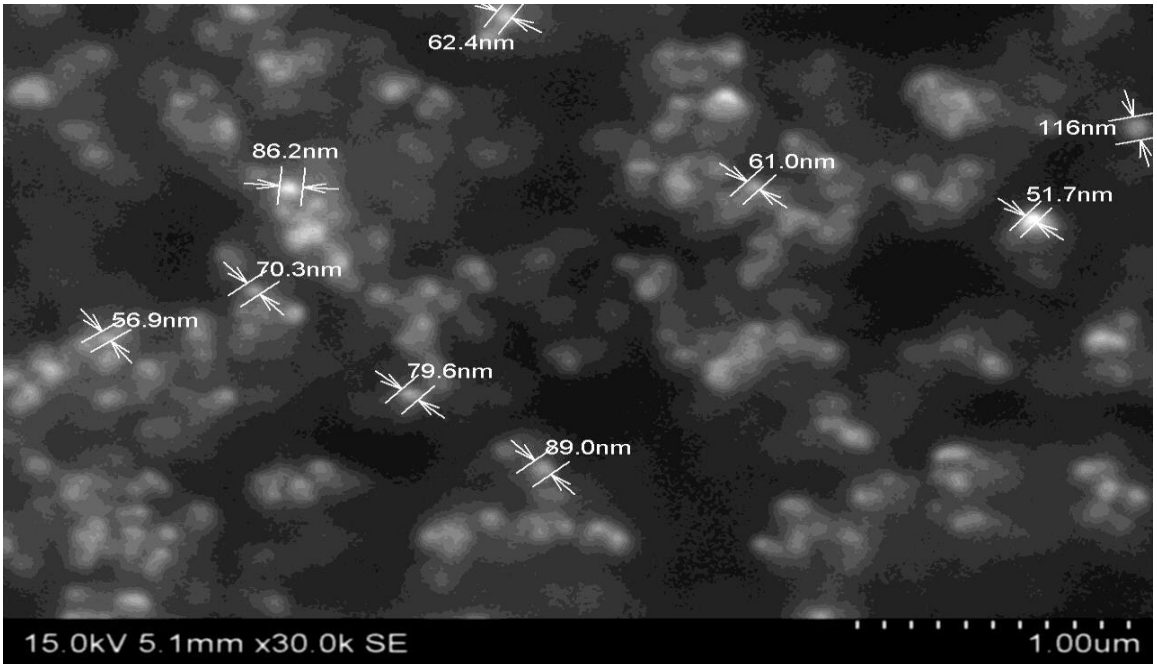

Figure 16: Scanning electron microscopy report of dronedarone formulation (F2)

pH

The pH value of all developed nano-emulsion formulations are in the range of 5.8 to 6.9, which is well within the limits. Hence, it can be concluded that all the formulations could not produce any difficulty. The results are shown in Table 5.

Cloud point

Cloud point indicates the temperature above which there is a change in the type of emulsion formed. The results of cloud point were calculated and reported in the Table 6.

***In-Vitro* diffusion studies**

In vitro diffusion studies were performed to compare the percent drug release from 5 different Nano Emulsions formulations (F1 - F5). The study was carried out using pH 7.4 Phosphate buffer in receiver component. In vitro diffusion was the highest in formulations F2 and lowest in formulation F3 and the lowest for normal Marketed Drug. The maximum release in F1and F2 could be due to the smallest droplet size and lowest viscosity compared to other Nano emulsions. The results are shown in the Figure No 8 and the comparative release of best and marketed formulation was shown in Figure No 9.

Droplet size analysis measurements

All the formulations had small droplet diameter between 10 - 200 nm. Polydisperesity index (PI) is a measure of particle homogeneity and it varies from 0.0 to 1.0. The closer to zero the polydispersity value the more homogenous are the particles. Formulations showed their PI in between 0. 310 to 0. 654 that indicates acceptable homogenicity. Zeta Potential of all Nano emulsion formulations was found between -19.7 to 0. 5 mV in the 100 times diluted. The results shown in the Figure No 10 to 15. The SEM analysis report was shown in Figure No 16.

CONCLUSION

Preformulation studies of Dronedarone were performed and it was found to be a poorly water soluble. Components were selected in which the solubility of Dronedarone was highest and the components used forms a rapid emulsion on contact with Aqueous medium. 5 formulations of SEDDS were developed based on miscibility zones obtained from pseudo ternary phase diagrams and concentration ranges obtained from ternary phase diagrams. The marketed Multaq tablet showed just 24.06% release in 17 hrs in pH 7.4 phosphate buffer where the optimized formulations F2 showed 99.52% release of drug in 17hrs time. This indicated the tremendous change in increase contrast of dissolution profile of Dronedarone from its conventional Multaq Tablet.

ACKNOWLEDGEMENT

The authors thank to principal and management of Malla Reddy College of Pharmacy, Secunderabad, for providing facilities to complete my research work and my deep greatness to MSN laboratories, Rudraram, for providing Dronedarone as gift sample.

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