AMERICAN JOURNAL OF PHARMTECH RESEARCH

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Scale Up of Doxycycline Hydrochloride Lipomer By Nanoprecipitation Using An Air Atomization Technique

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ABSTRACT

The present study discusses scale up of asymmetric doxycycline hydrochloride (DH) LIPOMER (lipid polymer nanostructures) by nanoprecipitation. A solution of Doxycycline hydrochloride , Glyceryl monostearate and Gantrez AN119 in tetrahydrofuran was added to a non solvent phase comprising Isopropyl alcohol and water, under stirring to obtain doxycycline hydrochloride LIPOMER. At the 1X (400mg solids) scale the process was optimized to increase solute concentration and solvent to non solvent ratio while decreasing total solvent volume. At 10X scale varying the agitator speed, agitator type and number of baffles, at a maximum addition rate of 4mL/min, particles with an average size of ~455 nm were obtained with a 45° pitched six blade turbine agitator and baffles. Using the principle of geometric similarity the 10X batch, gradually scaled up to 240X (96 gm solids), revealed average particle size in the range 454 to 510 nm with >80% entrapment efficiency (EE).Using air atomization introducing small globules of the solvent phase (100 mL/min), in to the non solvent phase enabled a size of ~340 nm with 84% EE at 120X and 240X. DH LIPOMER exhibited good stability and asymmetric shape. More importantly LIPOMER in the desired size range (~300-600nm) for RES uptake was optimized. Air atomization presents a simple and practical approach for scaleup of nanoparticles by nanoprecipitation.

Keywords: Doxycycline hydrochloride, LIPOMER, scale up, Air atomization, nanoprecipitation, nanoparticles

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Received 08 July 2013, Accepted 16 July 2013

Please cite this article in press as: Devarajan PV. *et al.*, Scale Up of Doxycycline Hydrochloride Lipomer By Nanoprecipitation Using An Air Atomization Technique . American Journal of PharmTech Research 2013.

INTRODUCTION

Our group has recently reported splenotropic behavior of asymmetric lipid polymer nanostructures (LIPOMER) of doxycycline hydrochloride (DH) [1, 2]. The LIPOMER comprised Gantrez AN 119 as polymer, and glyceryl monostearate (GMS) as the lipid. Splenotropy was confirmed in various animal models including rat, rabbit, and dogs. Further, DH LIPOMER revealed promise in dogs suffering from E.canis infection (Unpublished data). Such splenotropic nanoparticles can have immense application in the treatment of spleen resident infections including ehlriochiosis, and brucellosis[3, 4]. Scale up of DH LIPOMER was therefore considered as important step for translation of this important finding from laboratory to the clinic. Interestingly, asymmetric DH LIPOMER was prepared by a modified nanoprecipitation method wherein the aqueous phase was modified by inclusion of a less polar solvent IPA[2]. Hence scale up was attempted using the same approach.

Nanoprecipitation entails fine and rapid distribution of an organic solvent phase containing drug and polymer, into an aqueous non solvent phase. A number of approaches have been evaluated to achieve this fine and rapid distribution. Using a microfludic system, PLGA nanoparticles were obtained by hydrodynamic flow focusing. The polymer solution was focused as a thin stream in between two water streams with the water streams maintained at higher flow rates. Rapid precipitation and mixing occurred due to the thin width of the solvent stream, enabling nano size (10-50 nm) [5]. In another approach SLN of less than 250 nm average diameter with a narrow size distribution have been reported by mixing of co-flowing organic solvent and aqueous non solvent in micro channels formed by concentric capillaries of about 110 nm diameter[6]. A confined impingement jet mixer comprising of a small internal mix chamber, which allowed the two phases to impinge on each other at high velocity, is reported for the fabrication of beta carotene nanoparticles of average 55 nm size [7]. A modification of the same is the multi jet vortex mixer where inlet jets are tangentially introduced in to the cylindrical chamber leading to micro mixing enabling nanoprecipitation[8]. As an alternative, static mixers which comprised of tortuous elements which were motion less and assembled in to a column or tube are reported [9]. The advantage claimed includes continuous manufacture with lower requirement of energy and space, and low cost. Nevertheless, the need for special fabrication processes and the possibility of clogging of the micro devices are possible limitations of the above approaches [10]. An attempt to overcome these limitations is the development of fluidic nanoprecipitation system. In this system, the aqueous phase was allowed to flow through a dispersing channel and the organic

phase introduced in to this hydrodynamic fluid. Nanoparticles in the size range of 140-500 nm are reported using this method [11]. Although the above methods have been proposed for scale up of nanoprecipiatation the same has not been actually demonstrated.

Ibuprofen loaded eudragit nanoparticles of size 105 nm, were prepared allowing controlled mixing of the solvent and non solvent phases through a T mixer device. The two solutions were allowed to flow from two separate stirred tanks through T mixer in to third tank which held the raw nanoparticles dispersion. Using such a system a 20 fold scale up of nanoparticles by nanoprecipitation is reported [12].

Intensified mixing and mixing of titrated volumes of organic and aqueous phase has been the thrust to obtain nano size and also monodisperse particles with low polydispersity index [11]. Nevertheless all the reported methods rely on dilute solutions to achieve nanosize. The need for design of complicated devices could also be an additional limiting factor.

On the small scale, the stirred tank approach is the common process for nanoprecipitation, wherein the organic solvent containing the drug and polymer is added under stirring to the aqueous phase held in a vessel. Relatively slow mixing with the possibility of non uniformity is cited as a limitation of this method on the large scale [9]. Using an ultrasonic transducer attached with a frequency generator to introduce the solvent in the atomized state, microparticles were readily obtained using the stirred tank approach [13]. The micron size could be attributed to inefficient mixing due to large volumes dictated by the need for dilute solutions.

It was our contention that nanoprecipitation in concentrated solutions could be optimized to enable uniform dispersion in the conventional tank approach, due to smaller volumes. Accordingly in the present study the objective included first increasing solute concentration in the organic solvent and the solvent to non solvent ratio while decreasing total solvent volumes. The second objective was to increase the laboratory batch size to 240 fold from an initial solid content of 400 mg(X) to 96 gm (240X).

MATERIAL AND METHODS

Materials

Doxycycline Hydrochloride was a gift from Alembic, India. Gantrez AN 119 [poly(methylvinyletherco-maleic anhydride)] (ISP) was gift by Anshul Agencies India. Geleol (Glyceryl Monosterate) (GMS) of Gateffose was a gift from Colorcon Asia. All other chemicals or solvents were of spectroscopic or analytical grade. Water was obtained by double distilled glass assembly.

Preparation of lipomer (laboratory scale)

DH-LIPOMER was prepared by modified nano-precipitation as reported earlier [1, 2]. DH (100mg), Gantrez AN119 (200 mg) and GMS (100mg) were dissolved in tetrahydrofuran (10 ml). The solvent phase was added at a rate of 4 mL/min (drop wise) under constant magnetic stirring to a non solvent phase (30 ml) comprising IPA and water in equal ratio and tween 80 (1% w/v) as the surfactant. This was followed by addition of aqueous magnesium acetate solution (5% w/v, 3ml) as stabilizer. The dispersion was kept stirred at 28±5°C till complete evaporation of solvent followed by centrifuging at 15000 rpm for 15 min and the pellet was separated. The LIPOMER pellet was redispersed in 5 ml water by probe sonication for 5 min (10s on/off cycle) in an ice bath. Trehalose (10% w/v) was added as cryoprotectant, and the dispersion freeze dried in a Labconco freeze dryer.

The above formula [1X - total solid content 400 mg] was optimized by changing one variable at a time (OVAT method) to maximize solid content, minimize solvent volume and decrease process time. Accordingly volume of solvent, volume of non solvent, IPA:water ratio in the non solvent and surfactant concentration were systematically varied and their effect on LIPOMER size and entrapment efficiency were evaluated. Selected LIPOMER formulation was scaleup up to 10X level (total solid content 4 gm). DH (1 gm), Gantrez AN119 (2 gm) and GMS (1 gm), were dissolved in tetrahydrofuran (20 ml). The rate of addition of the solvent was maintained at 4 ml/min under constant stirring using an over head stirrer (3 blade propeller) to a non solvent phase (150 ml) comprising IPA: water (30:70) with tween 80 (1% w/v) as a surfactant. The agitator speed, agitator type (Propeller, Turbine and 45^{o} pitched turbine agitator) and number of baffles was varied.

Scale up (10X to 240X)

Scale up from 10X to 240X scale was attempted using the principle of geometric similarity. Based on the result at 10X scale, the condition selected were 45° pitched turbine stirrer with 6 blades, stirring speed 1000 RPM, number of baffles 4 and solvent addition rate 4 ml/min. The various system parameters and relevant ratios are indicated in Table 1 & 2 respectively.

Table 1. System Parameters and dimensions for scaleup of LIPOMER

Ratio	Scale of operation				
	10X	**30X**	**60X**	**120X**	**240 X**
Vessel diameter	6.2 cm	9 cm	12 cm	14 cm	17cm
Liquid depth	6 cm	9.1 cm	10.6 cm	14.36 cm	14.60 cm
Agitator Diameter	2 cm	3 cm	4.1 cm	4.5 cm	5.5 cm
Baffle Diameter	0.55 cm	0.80 cm	1.05 cm	1.2 cm	1.5 cm
Agitator bottom clearance	2cm	3 cm	4 cm	4.5 cm	5.5 cm

Table 2. System Ratios for scale up of LIPOMER

	Ideal ratio	Scale of operation					Average ratio ± SD
		10X	30X	60X	120X	240X	
Vessel diameter to agitator diameter	3	3.10	3.00	2.93	3.11	3.09	3.05±0.073
Vessel diameter to liquid depth	1	1.03	0.989	1.13	0.974	1.16	1.06±0.079
Vessel diameter to baffle diameter	10-12	11.27	11.25	11.42	11.66	11.33	11.39±0.157
Vessel diameter to agitator bottom clearance	-	3.1	3.0	3.0	3.11	3.09	3.06±0.052
Agitation blade width to agitator diameter	-	0.200	0.183	0.189	0.183	0.194	0.19±0.006

Air atomization technique

An external mix two fluid nozzle (Figure-1A) was used for atomization as depicted in Figure-1B. Solvent phase was fed at a constant rate in to the nozzle with a 0.2 mm diameter using a peristaltic pump. This approach was evaluated at 120X scale using a 3^2 factorial design. The variables evaluated were air pressure and solvent addition rate. Particle size and % EE were retained as the parameters for evaluation. The optimum solvent addition rate and atomization pressure 30 lb/cm^2 arrived at using 3^2 factorial design was evaluated at 240X scale. Atomizer distance from non solvent phase surface was adjusted to give maximum distribution of solvent phase on to non solvent phase when atomized. Ratio of the vessel diameter to atomizer distance from the initial non solvent level was maintained constant at both the scales. (120X and 240X)

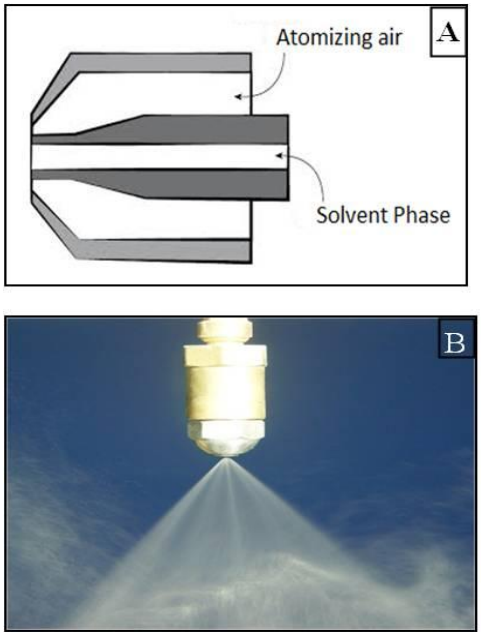

Figure 1: Schematic representation of external mix two fluid nozzle (A) and Air atomization technique (B)

CHARACTERIZATION OF NANOPARTICLES

Entrapment efficiency

Entrapment efficiency was determined by analysis (15,000 RPM for 30 min) of the nanoparticulate dispersion during the preparation of nanoparticles. Supernatant was diluted100 times with water and analyzed by UV spectrophotometry (Shimadzu, Japan) at λmax 275 nm. The % entrapment efficiency was calculated using Eq. (1),

$$\% \text{ Entrapment efficiency} = ([DH]_{total} - [DH]_{supernatant})/ [DH]_{total} \times 100 \quad (1)$$

Particle Size Determination

The particle size was measured by Photon Correlation Spectroscopy using Coulter N4 plus submicron particle size analyzer (Beckman Coulter) by scattering light at 90° at 25°C. The nanoparticle dispersion was diluted appropriately with water, filtered through 0.45 μm, to obtain final counts per second (Intensity), 5×10^4 to 1×10^6.

Transmission Electron Microscopy (TEM)

Copper grids (Cu 200, EM Sciences) were immersed in dispersions of DH LIPOMER and left undisturbed overnight at 4°C to allow their deposition on the grid. The grids were then washed thrice with distilled water. Freshly prepared aqueous phosphotungstanic acid solution (10 mg ml−1) was used as negative staining agent. Grids were treated with phosphotungstanic acid solution for 30 seconds and washed five times with distilled water. Stained samples were finally vacuum dried. The TEM images of stained DH LIPOMER were recorded on Techni G2 TEM (FEI, Eindohoven, Netherlands).

Differential scanning calorimetry (DSC)

Thermal behaviour of the formulations was determined by differential scanning calorimetry. Powdered samples were accurately weighed (5 mg) in aluminium pans, sealed and subjected to differential scanning calorimetry under nitrogen flow using a Perkin Elmer Pyris 6 DSC thermal analysis instrument. Thermograms were recorded by heating samples from 35°C to 250°C at a heating rate of 10°C min−1 with empty aluminium pan as the reference.

Stability evaluation

Stability of LIPOMER was evaluated as per ICH guidelines at 30±2°C/65±5%RH and 40±2°C/75±5% RH.

Data analysis

All data in the tables and the figures are expressed as mean ± standard deviation. Statistical analysis was performed using the one-way ANOVA with Tukey-Kramer HSD and Student's *t*

tests. P <0.05 was the criterion for statistical significance

RESULTS AND DISCUSSION

A detailed understanding of product and process parameters is crucial for successful scale up. Systematic knowledge of formulation boundaries helps to develop optimized formulations with desired properties. Nanoprecipitation based on Marangoni effect, influenced by interfacial turbulence among two solvents which is the result of the complex and cumulated phenomena of diffusion, flow and surface tension variations. Size of nanoparticles is significantly influenced by rate of precipitation, with smaller size related to rapid precipitation. The affinity of solutes to the non solvent phase favors delayed precipitation and hence larger size [14]. This is reflected in Figure.2 as a decrease in particle size with decrease in IPA concentration. Both GMS and Gantrez exhibit high affinity to IPA. Decrease in IPA concentration therefore resulted in more rapid precipitation and lower size. However the corresponding increase in water concentration influence entrapment efficiency adversely (Figure.2) due to the high water solubility of DH, which favored partitioning in to non solvent phase. Nevertheless the entrapment efficiency was still high (approx 80%). Further reduction in IPA concentration was not considered as earlier studies in our laboratory, confirmed the minimum concentration of IPA in the non solvent phase, as 30% v/v for the design of asymmetric LIPOMER (unpublished data). Hence the non solvent composition was further maintained constant at Water:IPA – 70:30. Reducing the solvent phase volume from 10 ml to 2 ml did not influence the entrapment efficiency (p>0.05) (Figure.3).

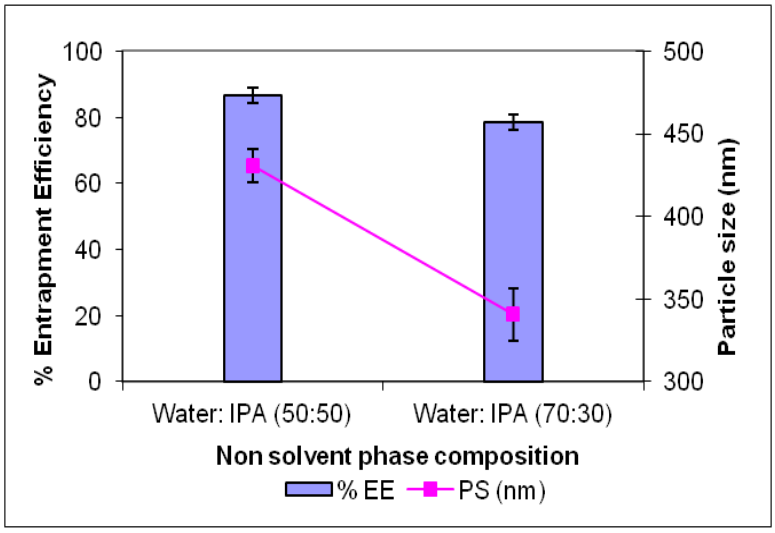

Figure 2: Effect of Water: IPA ratio in the non solvent Phase on particle size (PS) and entrapment efficiency(EE). Each value represents mean ± SD, n=3

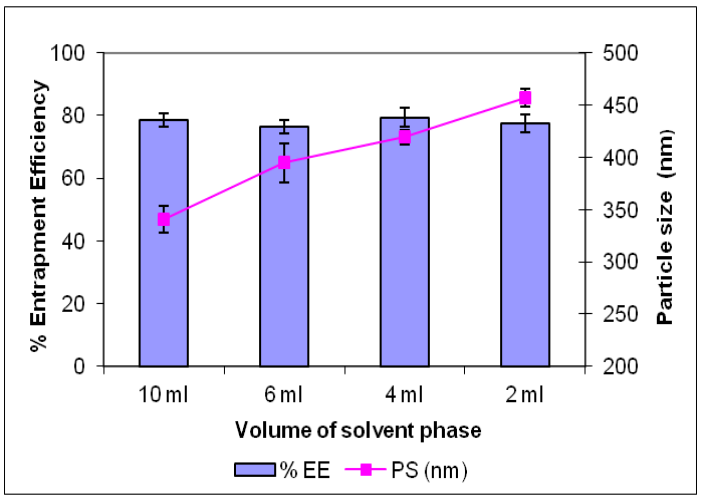

Figure 3: Effect of solvent phase volume on particle size (PS) and entrapment efficiency (EE) at (IPA:water)- 30:70, Each value represents mean ± SD, n=3

Increase in the viscosity of the solvent phase at lower volumes, hindered diffusion of the solvent phase in to non solvent phase resulting in slower mass transfer, slower precipitation and thereby larger LIPOMER formation ($p<0.05$) [14, 15, 16]. An inverse relationship was seen between particle size and non solvent phase volume (Figure.4) [16]. Similarly reduction in surfactant level due to hydrodynamic in-stabilization resulted in increase in size [14, 15, 16]. It is therefore easy to appreciate the increase in size with decrease in tween 80 concentrations (Figure.5). Despite a significant reduction in the organic solvent used in the process particle size obtained was in the range of 500-550 nm which is considered suitable for the LIPOMER under consideration. The solvent addition rate was maintained constant at 4ml/min at the larger scales as at higher rates significant agglomeration was evident.

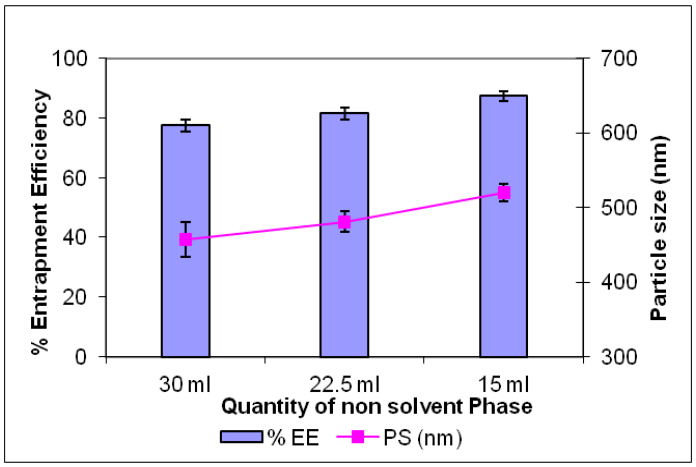

Figure 4: Effect of non solvent phase volume on particle size (PS) and entrapment efficiency (EE) at (IPA: water)-30:70 and Solvent phase-2ml, Each value represents mean ± SD, n=3

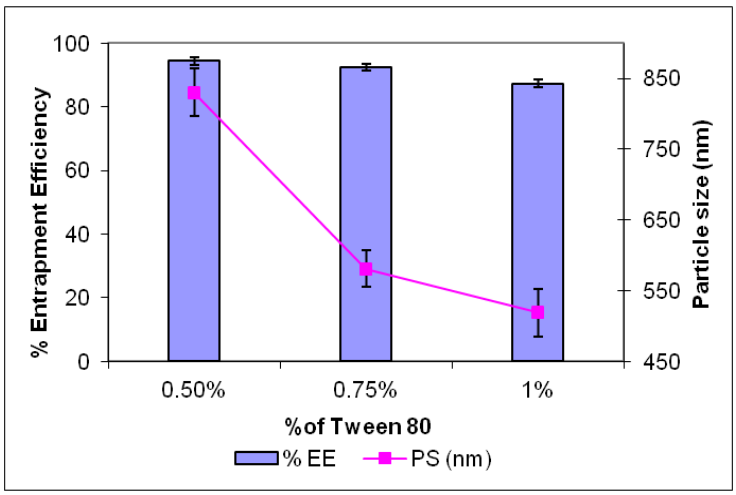

Figure 5: Effect of Tween 80 on particle size (PS) and entrapment efficiency (EE) at (IPA: water) – 30:70, Solvent – 2ml and non solvent-15ml, Each value represents mean ± SD, n=3

Scale up of LIPOMER (10X-240X)

At the 10X scale it was observed that entrapment efficiency remained relatively constant (approx 80%) while particle size exhibited high sensitivity to the variables evaluated. The degree of turbulence in the non solvent phase proportionally increases with increase in agitation rate resulting in greater average turbulent energy dissipation per unit mass. This greater turbulent energy result in greater drop breakage rate and/or smaller coalescence rates. Accordingly increase in agitator speed enabled smaller size (Figure.6). Speed of >1000 RPM using axial impeller were not feasible due air entrapment. In an attempt to increase the turbulence maintaining RPM at 1000, a turbine agitator was evaluated. Axial flow impellers (propeller) produce a constant pumping action toward the bottom of the tank followed by circulation to the top with a relatively rapid return to the impeller zone [17]. The circulation produced by the axial flow impellers increases the frequency of exposure to the high intensity shear in the impeller zone, where turbulent energy dissipation rates are much larger than in the bulk zone but the amount of shear provided to the product is relatively lower than the radial impeller. In contrast the radial flow agitators (turbine) create fluid flow directed radially outward from the impeller that circulates in the region above the agitator. These re-circulated fluid parcels then slowly return to the agitator zone by sedimentation. Turbine agitators compared to propeller provide high shear to the product at same RPM because of their geometry. Changing the angle of the turbine agitator from 90° to 45° can produce flow which is a combination of axial and radial patterns directed downward 45° from the vertical axis to provide greater shear along with more frequent exposure to the high intensity shear impeller zone [18].

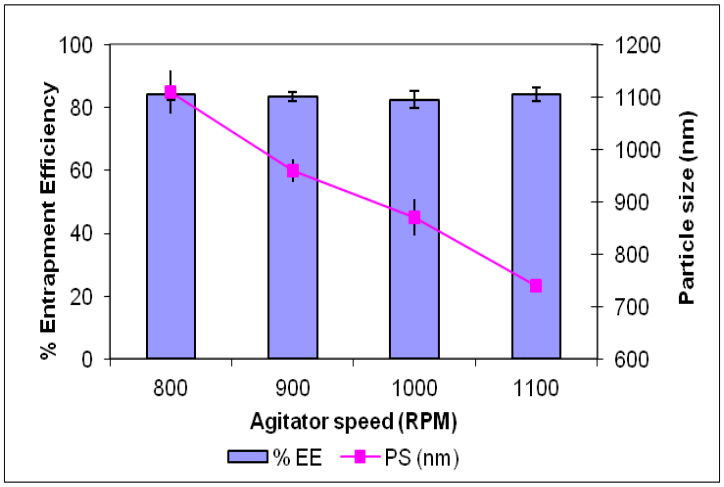

Figure 6: Effect of agitator RPM on particle size (PS) and entrapment efficiency (EE) (10X), Each value represents mean ± SD, n=3

Figure.7 depicts a significant decrease in particle size as suggested by the shear behavior of agitators with the smallest size exhibited by the 45° pitched turbine agitator. 45° turbine agitator comprising 3 blades was further explored to increase shear and turbulence (Figure.7). The number of blades on 45° turbine agitator was increased to enhance turbulence and maximize reduction in particle size ($p<0.05$) (Figure.8). Increasing the number of blades on the turbine agitator results in greater power numbers [19, 20] and hence maximize turbulent energy dissipation per unit mass of dispersion [21] to generate smaller drop distribution [22]. Accordingly a six blade turbine stirrer enabled formation of LIPOMER of the lowest average size < 550 nm (Figure.8). Introducing baffles in the system comprising the turbine agitator with six blades, revealed a further decrease in ($p<0.05$) in particle size, (Figure.9) as baffles also enabled an increase in agitator power [23]. The principle of geometric similarity used in scaleup ensured that all important ratios like vessel to agitator diameter, vessel diameter to liquid depth, vessel to baffle diameter, vessel diameter to agitator bottom clearance, agitation blade width to agitator diameter were maintained nearly constant at all scales (Table-2). Further the solvent phase addition rate of 4 ml/min was maintained constant. This provided similar hydrodynamics at each different scale and resulted in comparable particle size ($p>0.05$) and %EE ($p>0.05$) (Table-3). However, the solvent addition rate of 4ml/min was slow and impractical for scaleup as it took nearly 120 minutes at 240X scale. A number of other methods have been disclosed using a vibrating nozzle [15] and mixing intensified devices for scale up [12]. In the present study, we conceived a simple air atomization approach for introduction of the solvent phase in to the non solvent. Air atomization enables introduction of an atomized spray of small globule into the non solvent phase, at

relatively high rates. These globules rapidly break down to finer droplets. The air atomization solvent addition process was optimized using a 3^2 factorial design (Table-4). The quadratic model was significant ($p<0.001$) and chosen for further analysis. The predicted R square value (0.9747) is in reasonable agreement with adjusted R-square (0.9945) for the selected model. Based on the ANOVA for response surface quadratic model solvent addition rate (A), atomization pressure (B) the terms A^2 and B^2 were found to be significant. ($p<0.0001$) Based on the experimental design (Table-4) following equation was derived

(Particle size) = +515.65+136.20* A-136.7 * B+5.00 * A * B+85.97* A^2-22.53* B^2.....Eq.1

Where A= Solvent addition rate (ml/min) , B= Atomization pressure (lb/cm^2)

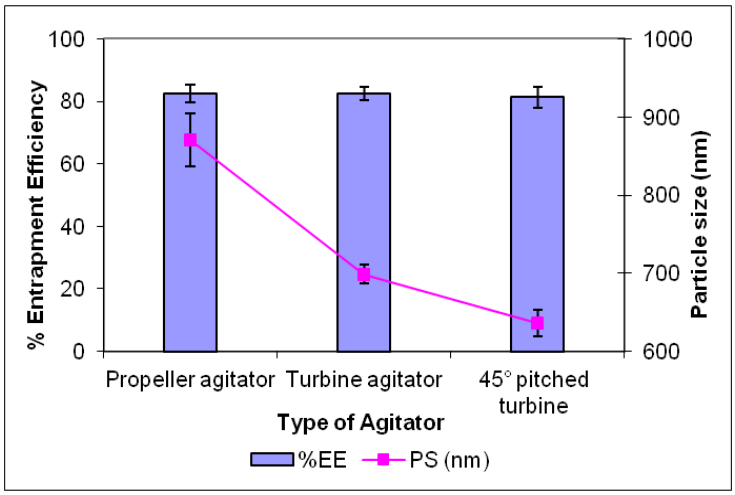

Figure 7: Effect of type of agitator on particle size (PS) and entrapment efficiency (EE) (10X), Each value represents mean ± SD, n=3

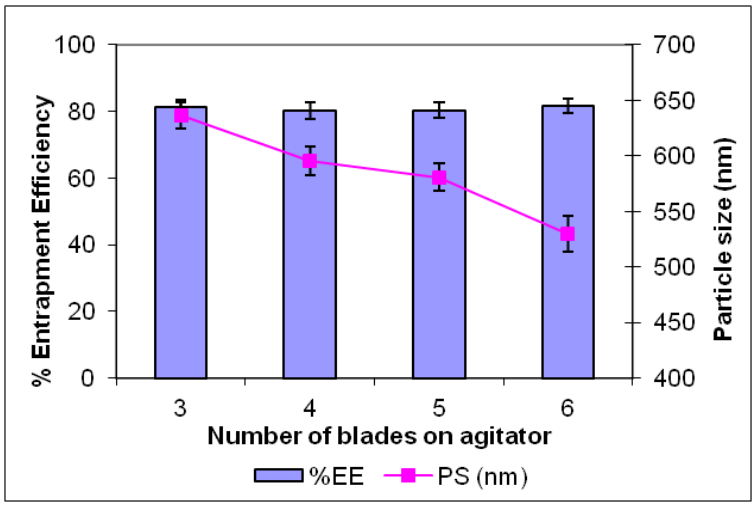

Figure 8: Effect of number of agitator blade on particle size (PS) and entrapment efficiency (EE) (10X), Each value represents mean ± SD, n=3

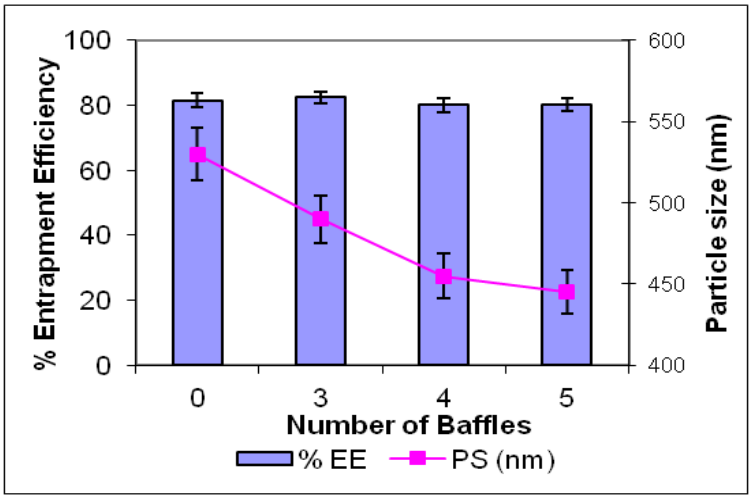

Figure-9: Effect of number of Baffles on particle size (PS) and entrapment efficiency (EE) (10X), Each value represents mean ± SD, n=3

Table 3.The entrapment efficiency and particle size of scale up batches

Solvent Addition	Scale up	Particle size	%EE
Drop wise solvent addition (4 ml/min)	1X	454 ± 28 (PI:0.4±0.03)	83.73
	10X	455 ± 23 (PI:0.4±0.04)	80.87
	30X	478 ± 36 (PI:0.6±0.07)	82.73
	60X	460± 14 (PI:0.4± 0.03)	81.63
	120X	510 ± 32 (PI:0.4±0.03)	83.54
	240X	480 ± 20 (PI:0.5±0.03)	82.23

Table 4. Experimental design (3^2 factorial) for variable affecting air atomization

Run	Flow rate (ml/ min)	Atomization pressure (lb/cm^2)	Particle size (nm)	% Entrapment Efficiency
1	100	30	340.6± 22 (PI: 0.3 ± 0.04)	84.637
2	100	20	513.6± 48 (PI: 0.6 ± 0.08)	82.74
3	70	30	310.2± 14 (PI: 0.3 ± 0.04)	83.43
4	70	10	580.4± 30 (PI: 0.6 ± 0.07)	84.61
5	130	30	590.4± 34 (PI: 0.3 ± 0.06)	82.53
6	70	20	460.6± 20 (PI: 0.4 ± 0.03)	83.22
7	130	10	840.6 ± 45 (PI: 0.8 ± 0.07)	82.31
8	100	10	640.4± 60 (PI: 0.7 ± 0.06)	82.17
9	130	20	737.4± 38 (PI: 0.6 ± 0.05)	83.32

The response surface diagram for the above model was generated using Design Expert 7 as shown in Figure.10. It is evident from the Figure.10 that particle size of DH-LIPOMER decrease with increase in atomization pressure at a constant flow rate. This could be due to finer droplets produced at high pressure as increase in air pressure results in a high ratio of air flow rate to liquid flow rate causing finer droplets. Smaller droplets carry smaller amounts of dissolved polymer which subsequently precipitate out as smaller size LIPOMER. Additionally the low

polydispersity index is smaller reflected good uniformity in size. Increasing the rate of addition at constant pressure, resulted in increased particle size of the LIPOMER, which was more prominent as the rate increased from 100 ml/min to 130 ml/min. Higher rate of addition due to decrease in effective turbulence could enable coalescence of droplets prior to precipitation and hence larger size. A flow rate of 100 ml/min and atomization pressure 30 lb/cm^2 which resulted in particle size of 340.6± 22 (PI: 0.3 ± 0.04) and entrapment efficiency of 84.63% was considered as optimal for evaluation at 240X scale. A particle size of 370 ± 29 nm (PI: 0.4±0.04) and % EE of 83.89 obtained at 240X scale confirmed the scaleup feasibility of air atomization in LIPOMER preparation. More importantly at the end of one year at 30±2°C/65±5%RH although an increase in average size to 536 nm was observed, all the particles were in the size range of ~300-600nm, considered desirable for RES uptake (Figure.11).

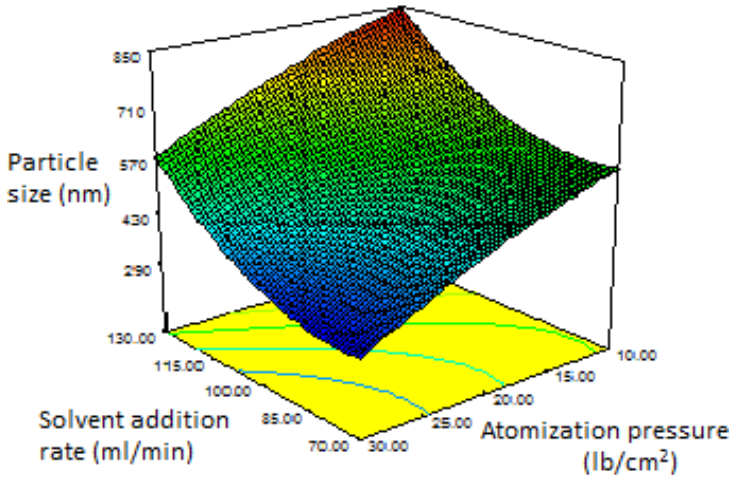

Figure 10: Response surface diagram for quadratic model at 120X scale

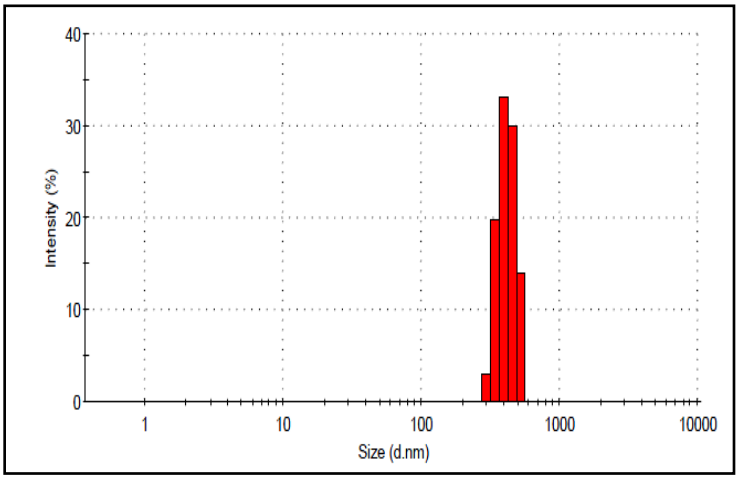

Figure 11: Particle size distribution of doxycycline hydrochloride LIPOMER after 12 months at 30±2°C/65±5%RH

Our study demonstrates the feasibility of the conventional stirred tank approach for scale up of nanoprecipitation. It is pertinent to note that desired size range of DH LIPOMER designed for RES uptake was obtained through conventional addition methods. Nevertheless air atomization enabled 25 times enhancement in solvent addition rate from 4 ml/min to 100 ml/min thereby enabling a significant decrease in process time, a crucial parameter for scale up. We present air atomization as a new approach in the preparation of polymer lipid hybrid nanoparticles by nanoprecipitation. Nanoparticle dispersion even at larger scale were readily freeze dried using 10% w/v trehlose as a cryoprotectant to obtain average LIPOMER size of 440 ± 26 nm (PI: 0.4±0.07) which reflect particle size after freeze drying (sf)/ particle size before freeze drying (si) ratio < 1.3. This average size achieved is considered suitable for the LIPOMER. Further TEM and SEM images (Figure.12A & 12B) revealed irregular shape as desired suggesting that the components and composition and not the method influenced shape. DSC (Figure.13) and XRD (Figure.14) study of LIPOMER revealed amorphous nature of Doxycycline Hydrochloride in LIPOMER. DH LIPOMER revealed good stability at 30±2°C/65±5% RH (12 Months) where as particle size increased significantly ($p<0.05$) at 40±2°C/75±5% RH. This could be because of lipid excipient present in the LIPOMER. However no drug content > 90% at all storage conditions.

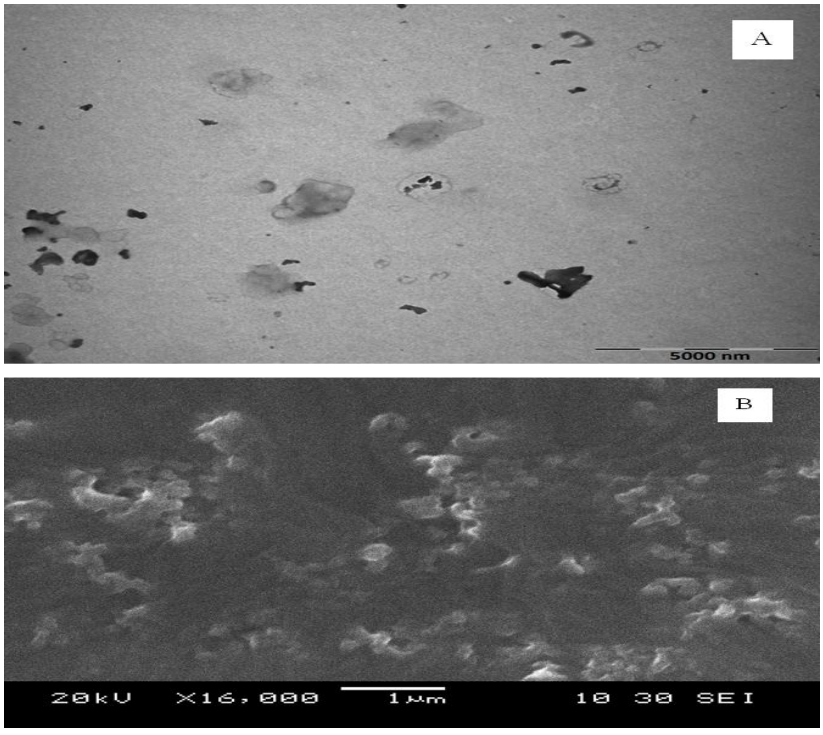

Figure 12: TEM (A) & SEM (B) image of asymmetric shape LIPOMER

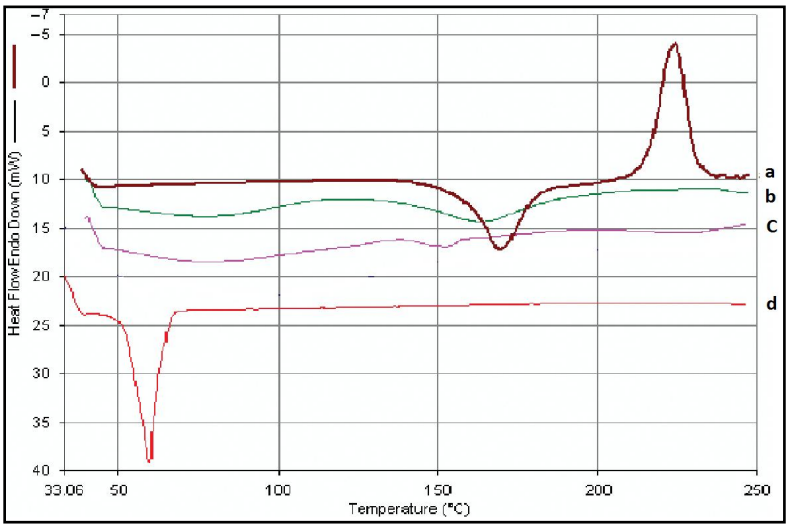

Figure 13: Comparative DSC thermograms of (a) DH (b) poly(methylvinylether-co-maleic anhydride) (c) LIPOMER (d) Glyceryl monostearate

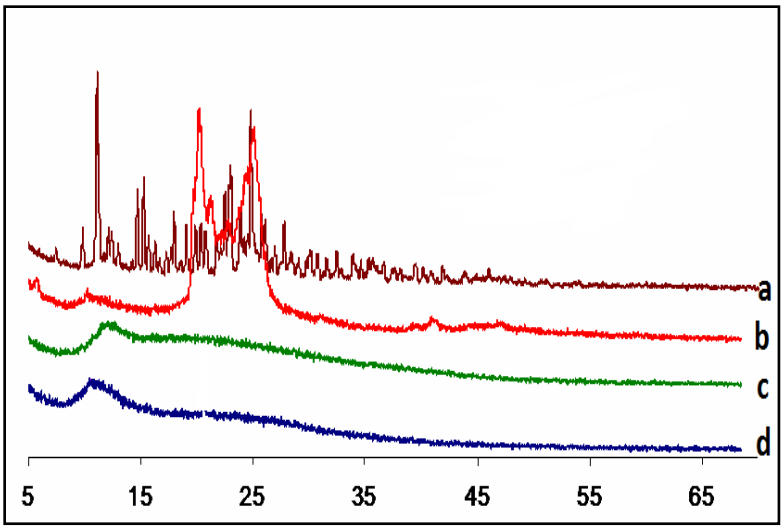

Figure.14: XRD of (a) DH (b) poly(methylvinylether-co-maleic anhydride) (c) Glyceryl monostearate (d) LIPOMER

CONCLUSION

The present study demonstrates scale up of LIPOMER up to a solid content of approx 100 gm. More importantly we propose a simple conventional stirred tank approach, coupled with air atomization to achieve scaleup by nanoprecipitation using well established principle of geometric similarity. It is expected that the approach could be readily extrapolated to even larger scales as it is based on use of conventional equipments and standard chemical engineering principles. While this approach looks promising for nanoparticles of relatively narrow size range above 300nm, adaptability of the same to prepare finer nanoparticles <100nm needs to be established.

ACKNOWLEDGEMENT

Author is thankful to Phoenix Pharmaceutical LLC, Ohio, USA for providing senior research fellowship. Tata Institute of Fundamental Research, Mumbai, India for powder X-ray diffraction study and Sophisticated Analytical Instrument Facility (SAIF) of Indian Institute of Technology (IIT), Mumbai, India for transmission electron microscopy study.

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