



Preparation of solid lipid nanoparticles through various methods using different precursors

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ABSTRACT

Now a day there has been exponential increase in interest in developing nanoparticles for novel drug delivery system. Nanoparticles provide many advantages over conventional drug delivery system like improved pharmacokinetic property; enhance bioavailability, smaller drug dose required for the treatment. Recently solid lipid nanoparticles (SLN) materialized as novel approach to oral and parenteral drug delivery system. SLN possess a solid lipid core that can solubilise lipophilic drug. Lipid core was stabilised by using surfactant (emulsifier). SLN can be prepared by using various precursors like emulsion, micro emulsion, and SLM can be prepared by using lipid coated microcrystal. These precursors further proceed to obtain particles of desired size and shape by making use of various techniques and equipment's. Each precursor show benefits along with some limitations.

Keywords: solid lipid nanoparticles, SLN precursors, membrane contractor, spray dry and congealing, GAMA.

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INTRODUCTION

A solid lipid nanoparticle is typically spherical in shape or some time bicontinuous structure with an avg. Diameter b/w 10-1000 nm. In SLN drug is encapsulated in lipid matrix which is stabilised by using surfactant or co-surfactant or by using mixture of surfactant. Combination of surfactants prevents particles agglomeration more efficiently. Lipid used in SLN preparation are triglyceride i.e. Tristearin, Monoglyceride i.e. Glycerol Monostearate, steroids and wax's. There are various methods which uses different types of precursors for the preparation of solid nanoparticles. These precursors provide intermediates to the obtain nanoparticles of desired size. Precursor chosen for the preparation of SLN depends on size of particle which we want to obtain. Some precursors like emulsion, micro emulsion produce SLN whereas some precursors and methods produce SLM (solid lipid micro particles). Various solvents used during preparation of precursor which removed completely at final step of SLN formation which is important from toxicological point of view. Precursors used for SLN preparation are namely:-

1) Emulsion

It is mixture of two or more immiscible liquid which consist a fine dispersion of minute droplets of one liquid into

another with or without emulsifier. It is widely used as precursor for the synthesis of SLN.

Emulsion can be o/w or w/o type or either w/o/w or o/w/o. SLN can be prepared through emulsion by following techniques:-

1.1) By Hot Homogenisation

1.11) high pressure homogenisation (HPH):- various approaches are applied in hot homogenisation technique to obtain SLN. SLN can be prepared by hot homogenisation, which involve high shear and ultrasonic homogenisation. It is used for polymeric nanoparticles production by allowing production of colloidal suspension of SLN without solvent which is good from toxicological point of view. Size of obtained nanoparticles below 500nm by hot homogenisation and low micro particle content but major drawback is that it can't use for Thermosensitive drug substance due thermal exposure and for encapsulating hydrophilic drug. First problem can be overcome by using cold homogenisation techniques but its gives larger particles as compare to particles obtained by hot homogenisation. Second problem can resolve by LDC (lipid-drug conjugate) system. In this system drug conjugated with lipid either by covalent linking or by salt formation then formed LDC proceed for nanoparticle preparation.

1.12) high shear and ultrasound homogenisation: - these two methods are widely used and can easily handle. Both these method used to improve dispersion quality of micro

particles. SLN particles prepared by these methods consist suitable emulsifying agent which allows formation hot intermediates due to use of high shear for mixing.

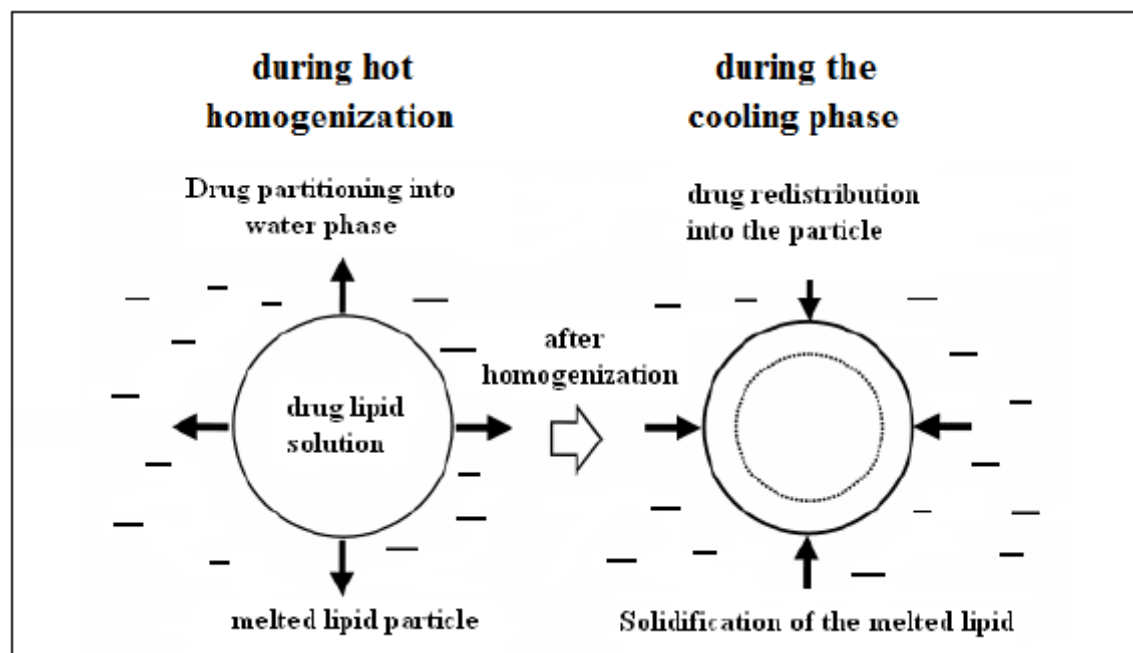


Figure 1: drug partitioning when hot homogenization technique used for SLN preparation. ¹

1.2) *Melt Dispersion Technique*:-by employing this technique micro particles obtained from emulsion. For lipophilic and hydrophilic drug o/w and w/o type emulsion used respectively. Lipophilic drug nanoparticles prepared by dissolving drug in melted lipid and then emulsified in hot surfactant solution using high shear for mixing, then obtain emulsion cooled at room temperature to get solid lipid micro particles². Whereas for preparing nanoparticles of hydrophilic drug, aqueous solution of drug emulsified with melted lipid and then put in external aqueous phase to obtain w/o/w emulsion then it cooled to room temperature to obtain solid micro particles of 1-250µm in diameter³.

1.3) *Supercritical Fluid Extraction Of Emulsion (SFEE)*:-this method based on extraction of solvent from emulsion by passing through extraction column with supercritical CO₂ in concurrent direction. Extraction efficiency depend on operating temperature and pressure. In this method drug in dissolved in melted lipid and emulsified with aqueous solution of surfactant and then homogenised to obtain fine emulsion. Then obtained o/w emulsion introduced in extraction column and simultaneously supercritical CO₂ introduced from bottom counter-currently at constant temperature (35°C) and pressure (80bar).

Solvent extraction occur when emulsion come in contact with supercritical CO₂ and expansion of organic phase occur due to inverse flux of supercritical CO₂ into emulsion droplet and leads to precipitation of lipid-drug material dissolved in organic phase⁴.

Advantage:-this method is high solvent extraction efficiency as compare to other conventional methods. This method ensures complete removal of solvent which is important from toxicological point of view. Particle obtained by this method have mean diameter b/w 20-90nm in diameter⁴.

1.4) *Phase Inversion Temperature (Pit)*:-this method uses the concept of ability of Polyethoxylated surfactants to change their affinity toward oil and water with temperature. In this method, surfactant used which leads to conversion of emulsion from o/w type to w/o when heated above pit and again converted back when temperature decreases below pit⁵.

Pit method used for preparation of nanoparticles and nanocapsules. Now days it is used for the preparation of SLN. In which it consist oil phase and aqueous phase. Oil phase consist solid lipid and non-ionic surfactant and aqueous phase consist NaCl. Both phases heated separately at equal temperature above pit i.e. approximately 90°C. Then aqueous phase added drop wise in oily phase under agitation and obtain w/o emulsion. Then it cool at room temp below pit and then o/w emulsion formed and SLN obtained of 30-100nm in diameter⁶.

2) Micro Emulsion as Precursor

Micro emulsion is also commonly used as precursor for SLN preparation. Particle size of droplet in micro emulsion varies from 10-80 nm. Particles shape of micro emulsion is not static its various from droplet like swollen micelle's to bicontinuous structure. Microemulsion has two unique properties one is it has low interface tension b/w oil and water interface and second one is highly flexible interface which is obtained by using suitable co-surfactant⁷.

Techniques used to prepare SLN from micro emulsion are:-

2.1) *Micro emulsion dilution technique (MDT)* - this method first used by Gasco (researcher) for the preparation of SLN. This method can used for both lipophilic as well as for hydrophilic drug because of great solubilisation property off micro emulsion^{8,9}. SLN prepared by this method consist

formation of o/w type micro emulsion which is prepared by using melted lipid and by aqueous solution of surfactant and co-surfactant under stirring. Then formed micro emulsion cooled by diluting with water volume 10-200 times of micro emulsion and get SLN with reduced particle size and small size distribution.

B) Micro emulsion cooling technique (*MCT*):-in this method SLN prepared from o/w emulsion by cooling at 4°C without diluting the emulsion. Emulsion obtained by melting emulsifying wax. This method operates at mild temp, less time consuming and high drug entrapment is obtainable¹⁰. Particle size of obtained nanoparticles varies from 50-300nm.

3) Soap Micellar Solution as Precursors

This method based on coacervation technique which produces particles of 200-1000nm size. In this method interaction b/w micellar solution of fatty acid alkaline solution and acid solution takes place. As proton exchange proceed b/w coacervation solution and soap solution, fatty acid get precipitates^{11,12}.

This method not uses drug incorporation in solvent and complex equipment's for SLN preparation. Drug incorporates in micellar solution which is obtained at Kraft point. Good solubilising property of micellar solution help in loading poorly soluble drug^{13,14} and give high drug loading in SLN. Particle size of SLN depends on micellar solution concentration and grade of polymer used for stabilisation.

4) Using Water Miscible Solvent System

This method is developed to encapsulate drug to get enhanced stability and bioavailability. This method operates at mild temperature which makes it useful for Thermolabile drug substance. Different method used for SLN using water miscible solvent system

4.1) *solvent injection method*: - in this method drug and lipid dissolved in water miscible solvent which is injected in water phase through syringe needle with continuous stirring. Then water is added which result into precipitation of lipid, encapsulating drug. Particle size of obtained SLN depends on type of lipid, surfactant, and solvent used in preparation and also depends on viscosity of external phase. This method produces nanoparticles of 100-500nm in diameter.

4.2) *solvent evaporation method*: - in this method o/w emulsion prepared for lipophilic drug which is dissolved in inner organic phase¹⁵ and w/o emulsion for hydrophilic drug that is dissolved in inner aqueous phase system^{16,17}.

In this method lipid matrix dissolved in water immiscible organic solvent which is emulsified aqueous phase then solvent is removed under reduced pressure which results into precipitation of lipid matrix and nanoparticles formed of 30-500nm in diameter^{16,18}. But this method become out dated because nanoparticles are formed by removal of solvent by evaporation and chances of solvent residue remain left which is not good from toxicological point of view.

Organic solvent and prepare emulsion of o/w type. When this emulsion poured in water, drug start to solidify which is

dissolved in organic solvent due to diffusion of solvent from droplet to continuous phase.

Solvent used like benzyl alcohol, methyl ethyl acetone, ethyl Formate in this method give good quality drug loaded PGLA microsphere¹⁹.

5) Coarse and Fine Suspension as Precursors

SLN prepared by this precursor requires one step process which convert particle of suspension directly into solid nanoparticles. This precursor used as feed solution which first atomised by various technique like pneumatic and ultrasonic atomisation to get spray foam, then it come in contact with hot gas, which results into formation solid dried particles due to evaporation solvent²⁰. Obtained dried particles separated by cyclone.

Advantage:-in this technique various parameter can be controlled like droplet size, solute concentration, relative humidity and temperature and which is helpful in characterisation of obtained nanoparticles²¹.

6) Solid Lipid Micro Particles as Precursor

SLM produced from ethanolic solution of lipid and drug. It can prepared by various method spray drying and spray congealing method. SLM prepared by spray drying method is smaller and more homogenous in nature. Shape of the particles influenced by:

- (i) Drying rate
- (ii) Viscosity of liquid which constitute feed
- (iii) Surface tension

Whereas in electrospray method, SLM and SLN prepared by forming alcoholic solution of lipid which is used for preparing particles of nearly 1µm in diameter. The solution contained in syringe which is connected with metallic capillary. Then solution passed through syringe under the influence of electric field and solvent get evaporated during travelling.

Particle size and shape depend on solvent and applied voltage^{22,23}.

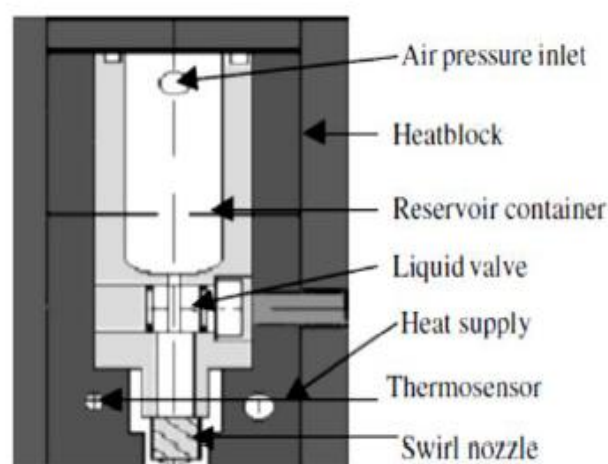


Figure 2: spray congealing equipment based on Buchi b-290 mini spray dryer²⁴

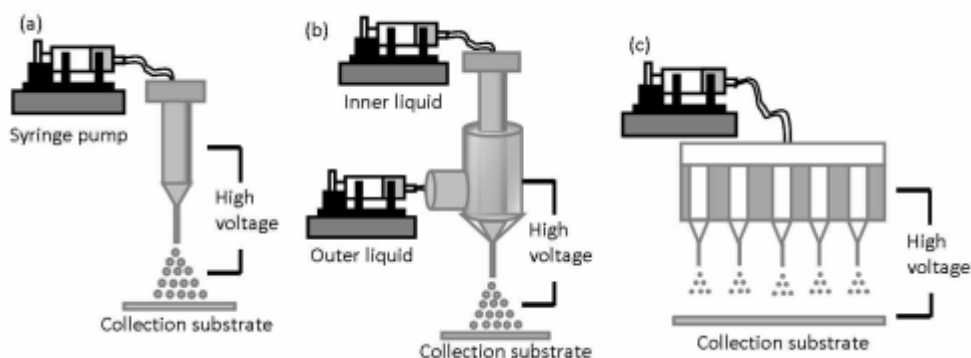


Figure 3: (a) standard electrospray. (b) Coaxial electrospray. (c) Multiplexed electrospray

7) Micronized Lipid Matrix (Mlm)

MLM prepared by cryogenic micro ionisation method. In this firstly lipid matrix prepared by melts dispersing or solvent stripping. In melt dispersion, drug dissolved in molten lipid whereas in solvent stripping, drug and lipid dissolved in mixture of solvent.

Obtained lipid matrix cooled in liquid nitrogen at -80°C . Then grind to obtain micronized lipid matrix. Obtained particles then sieved and get particles size varies from $1\text{-}500\mu\text{m}$ in diameter.

8) Coated Microcrystals as a Precursor

Coated microcrystal prepared by rapid expansion of supercritical solution (REES) also called supercritical fluid

nucleation. In this method matrix dissolve in supercritical fluid (SCF) and expanded passing through nozzle to get particles²⁵.

In modified REES method lipid coated BSA (bovine albumin serum)²⁶ used for SLN preparation. Coating is done by REES method. In which coating material and BSA microcrystal placed in autoclave hang rotating impeller, heated and pressurised with CO_2 (temperature range $35\text{-}40^{\circ}\text{C}$ and pressure about 200 bar). The system is left to achieve equilibrium at these conditions which results into solubilisation of coating material in SCF. Then autoclaved cooled which lead to decrease in pressure and phase change from SCF to liquid phase and coating material become insolubilize and get precipitate over BSA microcrystal and coated BSA particle's collected from bottom.

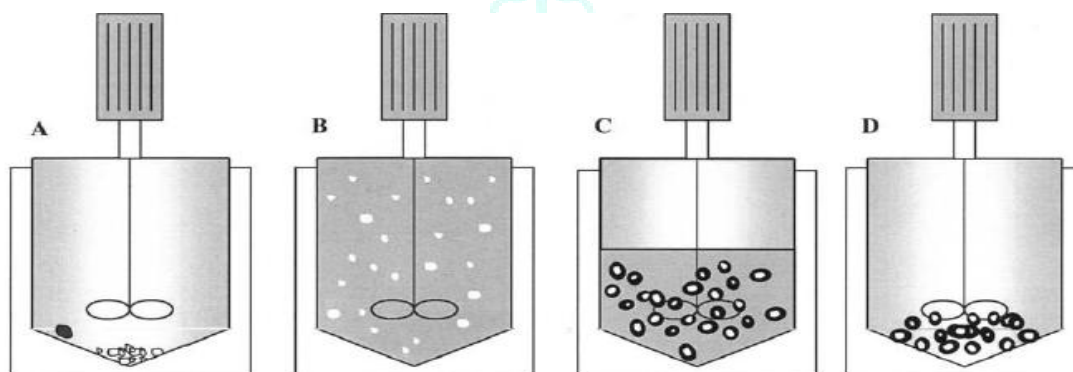


Figure 4: Schematic representation of coating process. (a) filling step: bsa particle represented in white and coating material represent in black. (b) solubilisation of coating material in scf CO_2 . (c) decompression phase: insolubilisation of coating material. (d) harvesting of coated particles²⁷.

9) Particles from Gas Saturated Solution/Suspension

Gas saturated solution/suspension expanded by using nozzle to prepare nanoparticles. Gas saturated solution can be prepared by gas assisted melting atomisation (GAMA) in which melted material mixed with SCF i.e. CO_2 under pressure and then expanded by passing through nozzle. During travelling of saturated solution, SCF get vaporize and dry fine particle are collected. Then these particles are used to prepare suspension by dispersing these particles in water. Prepared suspension further expanded by passing through nozzle to get nano sized particles.

10) Using Lipid and Water Phase as Separate Entities

SLN can be prepared by passing lipid and water phase as separately through membrane contractor made up of Kerasep ceramic membrane²⁸ [28]. In this lipid material heated in pressurised vessel and passed through membrane pores which results into formation of small articles which detached from membrane due to tangential flow of water. Then obtained water dispersion cooled to get SLN of $100\text{-}200\text{nm}$ in diameter. Particle size depends on type and concentration of surfactant used in formulation²⁹.

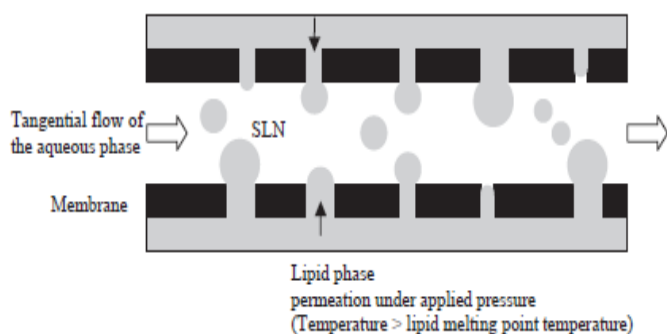


Figure 5: schematic diagram of membrane contractor for SLN preparation²⁷

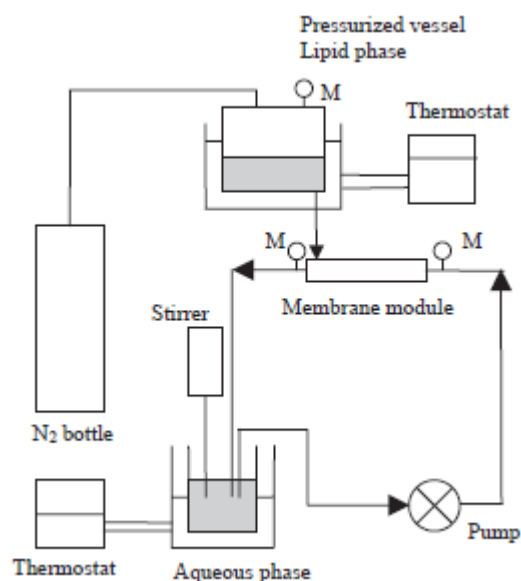


Figure 6: experimental setup for SLN preparation by membrane contractor²⁷

CONCLUSION

Various precursors are used to prepare SLN by employing different-2 type of techniques to obtain particles of different size and shape. Material used in SLN preparation should be safe and biocompatible. Solvent used in precursor formation should remove from final preparation because traces of solvent are not safe from toxicological point of view. Precursor chosen for SLN preparation depends on particle size and shape and to enhance drug entrapment and physiochemical parameter.

Each precursor leads to formation of particle with different size. Every precursors show advantage and some limitation. Selection of precursor for preparation of SLN depend on benefit to limitation ratio, size of particle which we want to obtain, safety from toxicological point of view, reproducibility, feasibility, and characteristics of drug encapsulated within particles.

REFERENCES

- [1] Müller R.H., Mäder K, Gohla S, Solid lipid nanoparticles (SLN) for controlled drug delivery-a review of the state of the art. *European journal of pharmaceuticals and biopharmaceutics*, 2000. 50(1):161-177.
- [2] Bodmeier R, Wang J, Bhagwatwatar H. Process and formulation variables in the preparation of wax microparticles by a melt dispersion technique. I. Oil-in-water technique for water-insoluble drugs. *J Microencapsul* 1992; 9:89-98
- [3] Bodmeier R, Wang J, Bhagwatwatar H. Process and formulation variables in the preparation of wax microparticles by a melt dispersion technique. 11. W/O/W multiple emulsion technique for water-soluble drugs. *J Microencapsul* 1992; 9:99-107
- [4] Chattopadhyay P, Shekunov B, Yim D, Cipolla D, Boyd B. Farr S. Production of solid lipid nanoparticle suspensions using supercritical fluid extraction of emulsions (SFEE) for pulmonary delivery using the AERx system. *Adv Drug Deliv Rev* 2007; 6:444-453
- [5] Shinoda K, Saito H. The stability of O/W type emulsions as a function of temperature and the HLB of emulsifiers: the emulsification by PIT-method. *J Colloid Interface Sci* 1969; 30:258-263
- [6] Montenegro L, Campisi A, Sarpietro M.G., Carbone C., Acquaviva R., Raciti G, Puglisi G. *In vitro* evaluation of idebenone-loaded solid lipid nanoparticles for drug delivery to the brain. *Drug Dev Ind Pharm* 2011; 37:737-746
- [7] Hoar T.P., Schulman J.H. Transparent water in oil dispersions: the oleopathic hydromicelle. *Nature* 1943; 152:102-103
- [8] Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. *Adv Drug Deliv Rev* 2002; 54:S77-S98
- [9] Gasco M.R. Method for producing solid lipid microspheres having a narrow size distribution. US5250236 (1993)
- [10] Koziara J.M., Lockman P.R., Allen D.D., Mumper R.J. Paclitaxel nanoparticles for the potential treatment of brain tumors. *J Control Release* 2004; 99:259-269
- [11] Battaglia L, Trotta M, Cavalli R. Method for the preparation of solid micro and nanoparticles. WO2008149215 (2008)
- [12] Battaglia L, Gallarate M, Cavalli R, Trotta M. Solid lipid nanoparticles produced through a coacervation method. *J Microencapsul* 2010; 27:78-85
- [13] Bianco M.A., Gallarate M, Trotta M, Battaglia L. Amphotericin B loaded SLN prepared with the coacervation technique. *J Drug Deliv Sci Tech*, 2010; 20:187-191
- [14] Chirio D, Gallarate M, Peira E, Battaglia L, Serpe L, Trotta M. Formulation of curcumin- loaded solid lipid nanoparticles produced by fatty acids coacervation technique. *J Microencapsul* 2011; 28:537-548
- [15] Trotta M, Debernardi F., Caputo O. Preparation of solid lipid nanoparticles by a solvent emulsification-diffusion technique. *Int J Pharm* 2003; 257:153-160
- [16] Garcia-Fuentes M, Torres D, Alonso M.J. Design of lipid nanoparticles for the oral delivery of hydrophilic macromolecules. *Coll Surf B: Biointerf* 2003; 27:159-168
- [17] Gallarate M, Trotta M, Battaglia L, Chirio D. Preparation of solid lipid nanoparticles from W/O/W emulsions: Preliminary studies on insulin encapsulation. *J Microencaps* 2009; 26:394-402
- [18] Siekmann B, Westesen K. Investigation on solid lipid nanoparticles prepared by precipitation in o/w emulsion. *Eur J Pharm Biopharm* 1996; 42:104-109
- [19] Sah, H., 2000. Ethyl formate—alternative dispersed solvent useful in preparing PLGA microspheres. *Int. J. Pharm.* 195:103-113.
- [20] Killeen M.J. Spray drying and spray congealing of pharmaceuticals. In *Encyclopedia of Pharmaceutical Technology*. Edited by Swarbrick J, Boylan JC 2000
- [21] Pilcer G, Amighi K. Formulation strategy and use of excipients in pulmonary drug delivery. *Int J Pharm* 2010; 392:1-19
- [22] Trotta M, Cavalli R, Trotta C, Bussano R, Costa L. Electrospray technique for solid lipid-based particle production. *Drug Dev Ind Pharm* 2010; 36:431-438
- [23] Bussano R, Chirio D, Costa L, Turci F, Trotta M. Preparation and characterization of insulin loaded lipid-based microspheres generated by electrospray. *J Disper Sci Technol* 2011; 32:1524-1530
- [24] A. Maschke, C. Becker, D. Eyrich, J. Kiermaier, T. Blunk, and A. Gopferich, Development of a spray congealing process for the preparation of insulin-loaded lipid microparticles and characterization thereof, *Eur. J. Pharm. Biopharm*, 2007, 65:175-187
- [25] Byrappa K, Ohara S, Adschiri T. Nanoparticles synthesis using supercritical fluid technology – towards biomedical applications. *Adv Drug Deliv Rev* 2008; 60 299-327
- [26] Ribeiro Dos Santos I, Richard J, Pech B, Thies C, Benoit J.P. Microencapsulation of protein particles within lipids using a novel supercritical fluid process *Int J Pharm* 2002; 242:69-78
- [27] Luigi Battaglia L, Gallarate M, Panciani P.P, Ugazio E, Sapino S, Peira E and Chirio D., Techniques for the preparation of solid lipid nano and microparticles, *Research gate*, 2015; 51-70
- [28] Charcosset C., Fessi H. Novel method for preparing solid lipid nanoparticles using a membrane reactor. WO2007000531 (2007)
- [29] El-Harati A.A., Charcosset C., Fessi H. Influence of the formulation for solid lipid nanoparticles prepared with a membrane contactor. *Pharm Dev Technol* 2006; 11:153-157