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A REVIEW ON SOLID LIPID NANO PARTICLES (SLNs)

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Abstract: Solid Lipid Nanoparticles(SLNs) is recently developed technique, in which the size ranges from 1 to 1000 nm particles can use for drug delivery system .It is basically a colloidal carrier .In this review the latest research and development of SLNs according to the modern literature are cited . The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could use for drug targeting. The proposed mechanism of drug release from SLNs is also mentioned in this review. The preparation techniques for production of SLNs are discussed with schismatic representation. Appropriate analytical techniques for the characterization of SLNs like photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry are highlighted. Aspects of SLN route of administration and the *in vivo* fate of the carriers are also discussed. Farther more the various applications with suitable example are also discussed.

Keywords: Colloidal drug carriers, Homogenization, TEM, PCS, Solid lipid nanoparticles, Production techniques, Targeting.

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INTRODUCTION

The new frontiers like liposome, solid lipid nano particles have shown improve drug delivery. Nano particles are 10-1000 nm ranges solid colloidal drug carriers in which the active moiety dissolved, entrapped or adsorbed–attached towards its surface[1]. In recent years small molecular weight drugs, macromolecules (protein, peptide, gens) was formulated in nano particular range, to provide them good enzymatic stability[2]. Solid lipid nano particles (SLNs) enhance the bioavailability of drugs like eg: cyclosporine A[3]. Due its bio degradable property its is less cytotoxicity. SLNs formulated in various application roots like parental, oral, dermal, ocular, rectal[4].

Advantages:

1**.** Excellent biocompatible with high target specific action.

2. Easily scale up is possible and stability is good.

3. Protection of chemically liable drugs from bio degradation in gut and sensitive molecule from outer environment.

4. Better control over release kinetics of encapsulated compound.

5. Compare to other bio polymeric molecule SLNs is very easy to produce .The raw materials are alike of emulsions.

6. With grafting monoclonal antibody it could act like a multifunctional dosage form.

7. Lyophilisation is possible.

Disadvantages:

1. It has very poor drug loading capacity.

2. Uncertain gelation tendency.

3. Uneven kinetics for polymeric transition.

4. Particle growth is observed during storage.

5. Relatively higher water content of the dispersion (70-99.9%) [5]

2. METHODS OF PREPARATION:

SLNs made up of solid lipid emulsions. Where Lipids such as ;Triglycerides, Tristearin, Glycerol monostearate (GMS), Waxes (cetylpalmitate),Steroids(cholesterol), Tripalmitin, Cocao butter, Monostearin, Lecithin, Tribehenate, Trimyristin are used. Poloxamer 188, Tween 80, PVA also can be used as a surfactant. Emulsifiers such as Pluronics F68, 127 can prevent particle agglomeration.

SLNs are prepared from lipid, emulsifier and water/solvent by using different methods and are discussed below.

1. High pressure homogenization

A. Hot homogenization

B. Cold homogenization

2. Ultrasonication /high speed homogenization

A. Probe ultrasonication

B. Bath ultrasonication

3. Solvent evaporation method

4. Solvent emulsification-diffusion method

5. Supercritical fluid method

6. Micro emulsion based method

7. Spray drying method

8. Double emulsion method

9. Precipitation technique

10. Film-ultrasound dispersion.

11. Membrane contactor technique.

12. Solvent injection technique

2.1. High pressure homogenization:

It pushes the liquid with high pressure (100-200bar) through a hollow gap of some few microns. With nearly 100Km/h rate and with high viscosity the fluid accelerates to a very short distance. Very high pressure stress and cavitations force interrupt the particle down to submicron size range with 5-40% lipid content. In HPH two different approaches with same principle were established[6].

A. Hot homogenization: Homogenization of an emulsion can be carried out in above the melting point of the liquid. With the help of high –share mixing device, a pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained. The HPH of pre emulsion can be carried out above the liquid melting point. Due to decrease viscosity of inner phase of emulsion in high temperature, particle size would be lower[7]. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles. The potential disadvantages of this

method are, high temperature shell may doctorate drug content. Occasionally 3-5 homogenization cycle at pressure of 500-1500bar are used[8,9] .

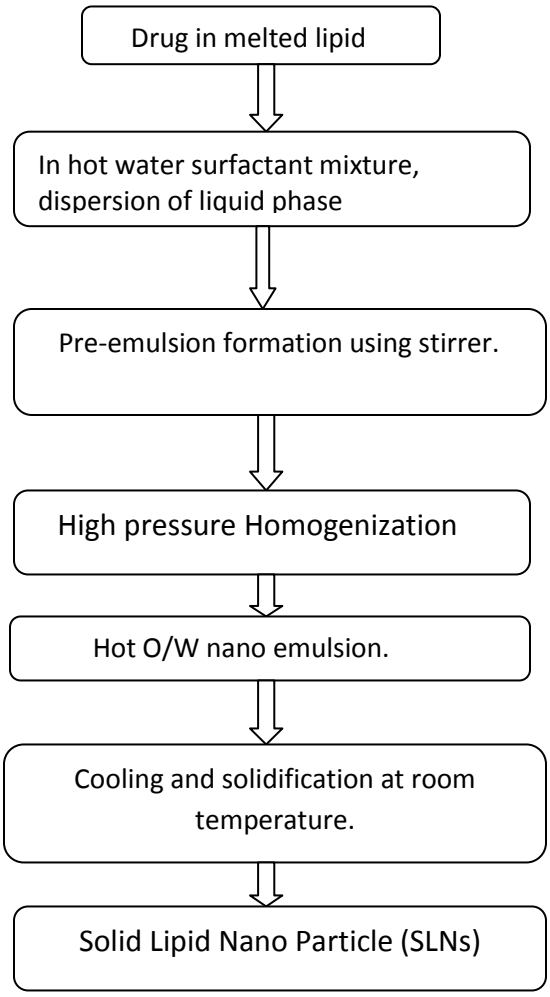


Fig1: Solid lipid nanoparticles preparation by hot homogenization process.

B. Cold homogenization:

Cold homogenization has been developed to over-come the temperature related degradation problems, loss of drug into the aqueous phase and partitioning associated with hot homogenization method. Unpredictable polymeric transitions of the lipid due to complexity of the crystallization step of the nano emulsion resulting in several modifications and/or super cooled melts. Here, drug is incorporated into melted lipid and the lipid melt is cooled rapidly using dry ice or liquid nitrogen. The solid material is ground by a mortar mill. The prepared lipid microparticles are then dispersed in a cold emulsifier solution at or below room temperature. The temperature should be regulated effectively to ensure the solid state of the lipid during homogenization. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenization samples[9,10]

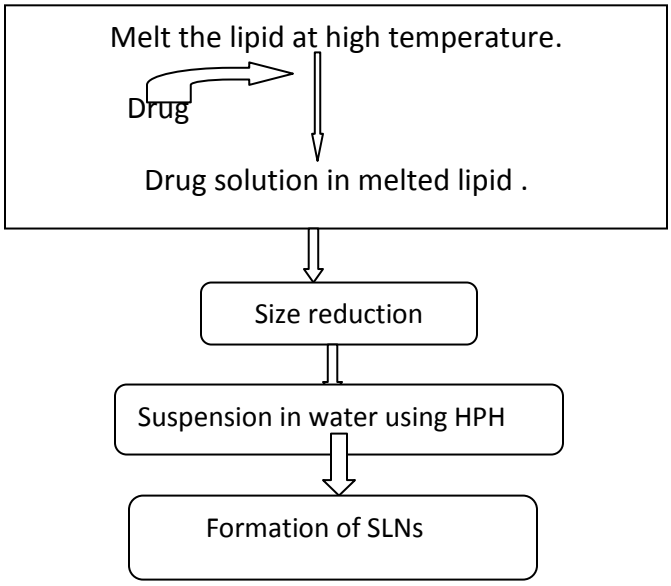


Fig. 2: Solid lipid nanoparticles preparation by cold homogenization process.

2.2. Ultrasonication /high speed homogenization: The promising advantages in these methods is that the equipments used is commonly available in lab scale**.** Broader size distribution ranging in micron range is the main disadvantages. Potential metal contamination and improper stability during storage like particle growth, accumulation of particle are major drawback[11.]

2.3. Solvent evaporation: Solvent evaporation method is also used to prepare SLNs. The lipophilic material is dissolve in a water miscible organic solvent (eg; cyclohexane) and emulsified in aqueous phase. Upon evaporation nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar). The main advantages of this system is it's a continuous process [7]

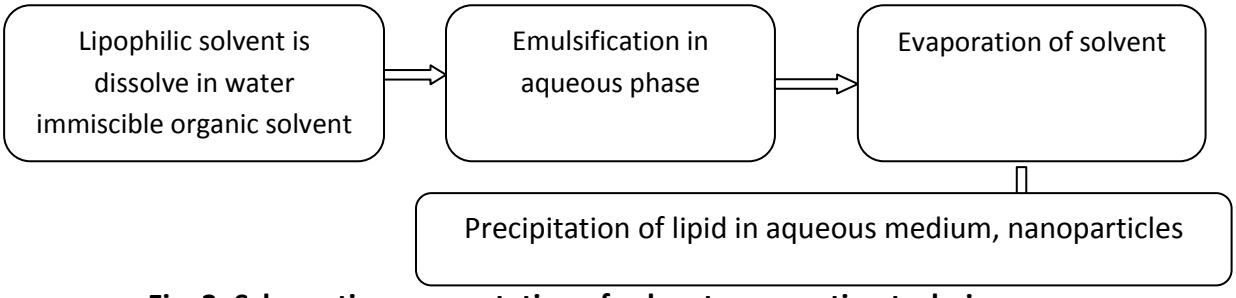


Fig. 3: Schematic representation of solvent evaporation technique

2. 4. Solvent emulsification-diffusion method:

Avoidance of heat is the most significance advantages of this method .Based upon the emulsion used and lipid concentration, the mean particle is dependable. SLNs with 30-100nm size range, could be possible to formulate in this method. In this technique lipid matrix is dissolve in water –immiscible organic solvent, and emulsification is took place in aqueous phase[12]. Nano particular dispersion formed by precipitation of lipid in aqueous media while maintaining low pressure & evaporation[13].

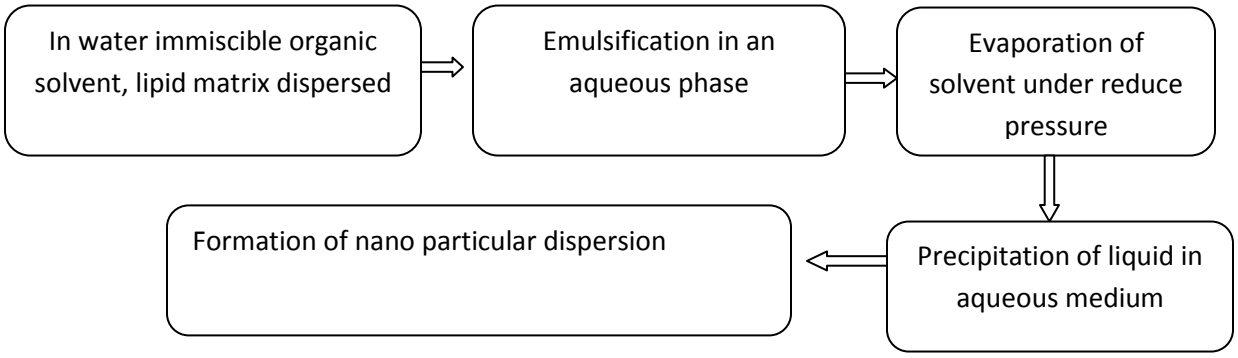


Fig. 4: Schematic representation Solvent emulsification-diffusion method

2.5. Supercritical fluid method: A fluid is termed super critical when its pressure and temperature exceed their respective critical value, by which the ability of the fluid to dissolve compounds increases. The rapid expansion of supercritical solution (RESS), particle gas saturated solutions (PGSS), aerosol solvent extraction solvent (ASES), supercritical fluid extraction of emulsions (SFEE) are the various technique used to formulate SLNs in this technique .In this technique avoidance of the solvent ,dry power particles ,instead of suspension , little pressure and temperature condition are the potential advantages . Carbon dioxide solution is an excellent choice as a solvent for this method [14, 15].

2.6 Micro emulsion based method: Gasco and company (1997) developed SLNs based on dilution of micro emulsion. Micro emulsion was an optically transparent mixture at 65-70°c or a slightly bluish solution which is typically composed of low melting lipid, emulsifier(s), Co-emulsifier and water.

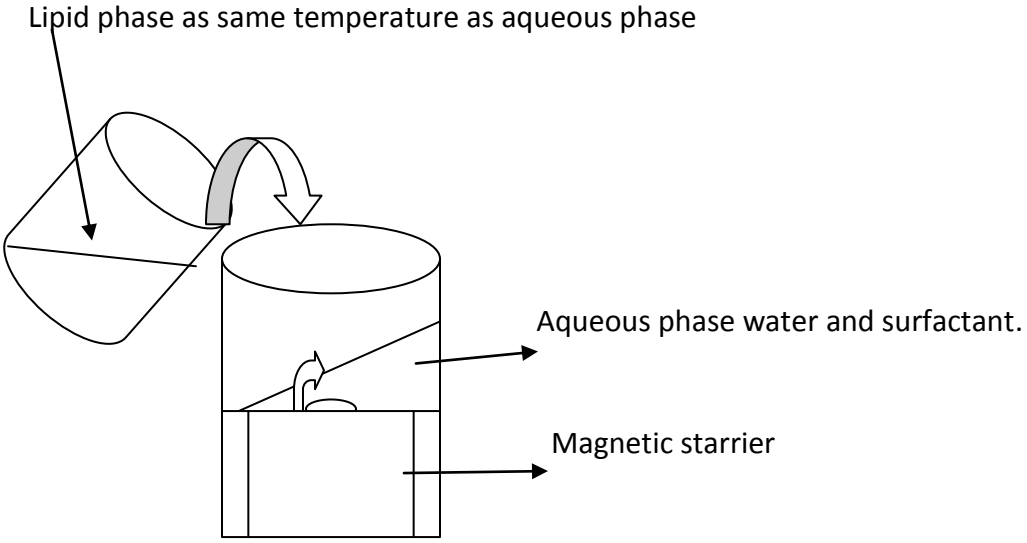
Fatty acid: stearic acid,

Emulsifier: polysorbate 60, polysorbate 20, soyaphosphatydylcholine and taurodeoxycholic acid sodium salt,

Co-emulsifiers: butanol, sodium monooctylphosphate, and water were used to prepare SLNs. The hot micro emulsion is dispersed in cold water (2-3ºC) under stirring. 1:25 to 1:50 is the typical volume ratio of the hot micro emulsion to the cold water .The dilution process is optimised by the composition of the micro emulsion[16,17,18] .The SLNs dispersion can be used as a

granulating fluid for transferring into solid product like tablets and pellets by granulation process .Too much of water need to be remove to obtain low particles content .The solvent which have the susceptibility to distribute with in aqueous phase (eg.acetone) were more preferable for SLNs formulation .More lipid solvent produce larger particle size . Considering micro emulsions, the temperature gradient and pH value fix the product quality in addition to the composition of the micro emulsion. High temperature gradients facilitate rapid lipid crystallization and prevent aggregation [19,20].

Step1



Step 2:

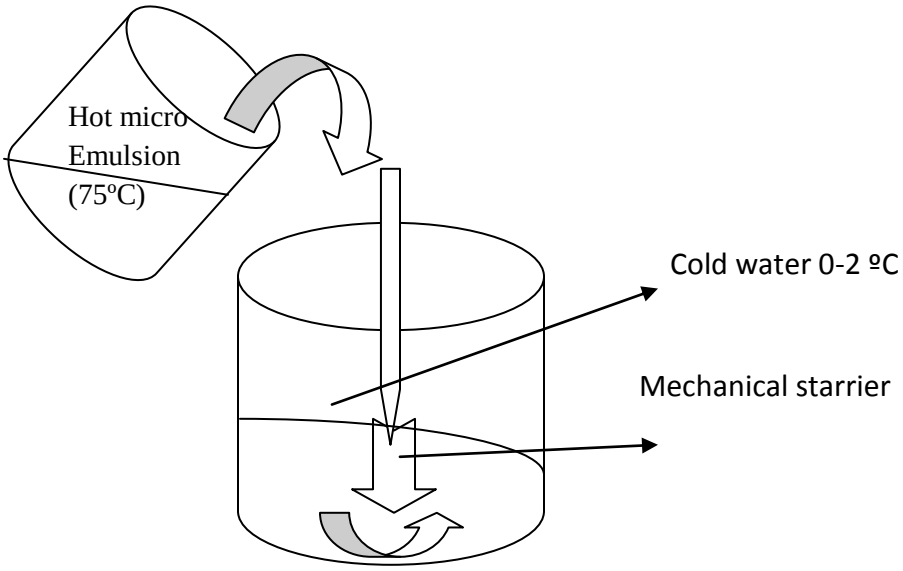


Fig. 5: Micro emulsion method

2.7. Spray drying method: This is conceder to be the best alternative technique for lyophilisation technique. Lipid with melting point above 70ºC were best suitable for this method [19]. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture[19].

2.8. Double emulsion method: In this technique drug is at first dissolve in aqueous phase and then emulsified in melted lipid phase. The primary emulsion was stabilised by upon addition of stabilizer eg: gelatine, poloxamer-407. Then this stabilized primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier[21]. Thereafter, the double emulsion was stirred and was isolated by filtration. The zidovudine loaded SLNs were prepared with stearic acid by process of w/o/w double-emulsion solvent evaporation method using 3^2 factorial design and different triglycerides alone and in different combinations, with/without stearic acid. Two operating variables, amount of lipid and polyvinyl alcohol concentration were found to have significant effect on the particle size and entrapment efficiency of the SLN [22]. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of the incorporation of a lipid/-PEG derivative. Sterical stabilization significantly improved the resistance of these colloidal systems in the gastrointestinal fluids [23].

2.9. Precipitation technique: In organic solvent (eg: chloroform, dichloromethane) glycerides are dissolved . The solution further emulsified in aqueous phase. After evaporation the lipid would be precipitated out as a SLNs [7].

2.10. Film-ultrasound dispersion:

After decompression, rotation and evaporation of the organic solutions consisting of lipid and drug, a lipid film is formed, in that add aqueous solution which includes the emulsions. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.

2.11. Membrane contactor technique: In this technique the liquid phase was pressed at a temperature above the melting point of the lipid through the membrane pores allowing the formation of small droplets. The aqueous phase was stirred continuously and circulates peripherally inside the membrane module, and sweeps away the droplets being formed at the pore outlets. SLNs were formed by the cooling of the preparation at the room temperature. Vitamin E loaded SLN are prepared using a membrane contactor technique to allow large scale production and their stability is promising[24].

2.12. Solvent injection technique: It is based on lipid precipitation from the dissolved lipid in solution. In ethanol, acetone, isopropano the solid lipids were dissolve .The lipid mixture were then add to the aqueous phase drop by drop using injection needle containing with or without surfactant .Dispersion was then filtered to separate excess lipid .Surfactant in aqueous phase

produce good SLNs**,** farther its provides extensive stability to the system. Solvent injection lyophilization method was used to prepare cinnarizine SLNs, a lipophilic drug. SLNs bearing oxybenzone was also prepared by ethanol injection method to improve its effectiveness as sunscreen and were characterized for particle size, polydispersity index, zeta potential and surface morphology[25,26,27] **.** The schematic representation of solvent injection method was shown in figure 6.

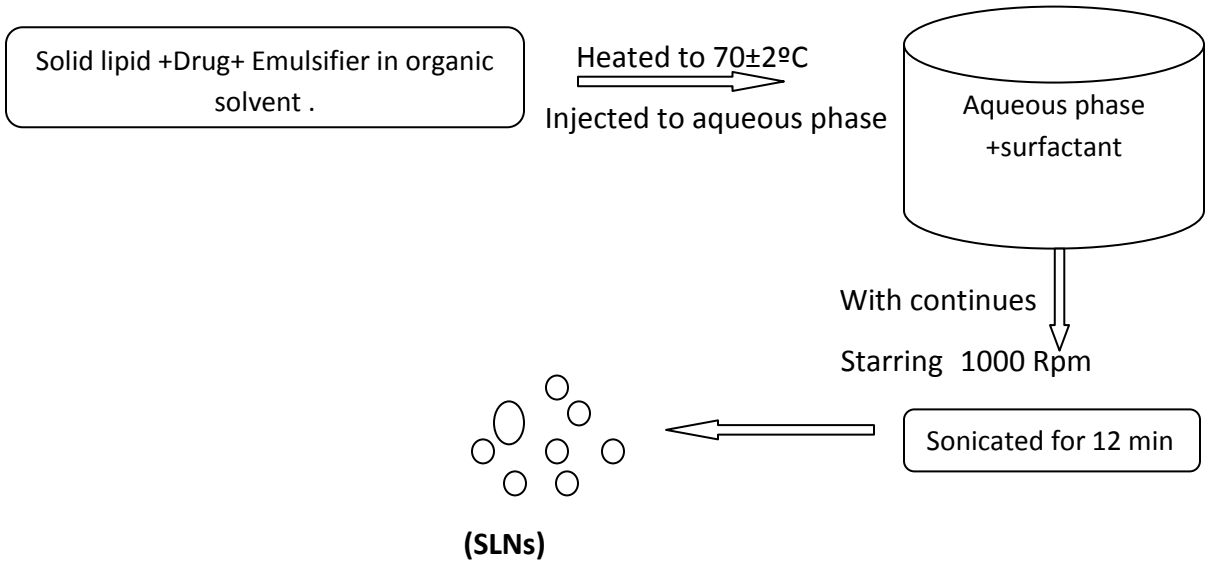


Fig 6: Solvent injection technique

Table1: Different methods for preparation of SLNs

Method	Drug	Lipid	Reference
Hot homogenization	Flurbiprofen	Trimyristin	28
Modified coacervation	Gatifloxacin	Tristearin	29
Ultrasonication or high speed homogenization	Cryptotanshinone	Compritol 888 ATO	30
Double emulsion technique	Zidovudine	Tripalmitin	31
Supercritical fluid technology	Indomethacin	Tripalmitin	32
Cold homogenization	vinorelbine itartrate	Glyceryl monostearate	33
Solvent emulsification-evaporation technique	Oridonin	Stearic acid	34

Secondary Production approaches:

Freeze drying:

The nano suspension was lyophilized to dry powder to prevent its degradation. The cryoprotectants are the substances added with the formulation to prevent structural damages that may be caused by sudden and quick process of freezing. The conditions of the freeze drying process and the removal of water promote the aggregation among SLNs. Bhoga Bhagya et al. Studied the effect of fructose and trehalose as cryoprotectant in different formulation of SLNs of methotrexate. Cryoprotectants were taken in 2% and 15% added in the cold aqueous medium. Suitability of the cryoprotectants was determined by the reconstitution behaviour with distilled water.

3. Types Drug incorporation models of SLNs : Based upon the solubility ,miscibility of the drug in lipid melt, the drug loading is dependable on SLNs . furthermore chemical and physical structure of the solid matrix , polymeric phase of the lipid material also influence the drug release .

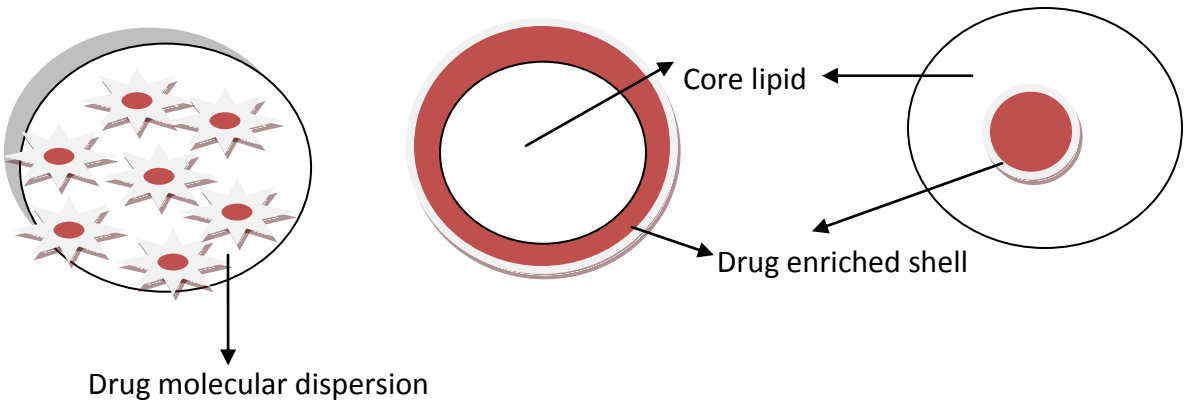


Figure 7: Diagrammatic representation for drug incorporation models.

Drug is molecularly dispersed in lipid matrix when SLN is prepared by cold homogenization. In Drug-enriched shell model the solid lipid core forms upon recrystalization. Drug-enriched core model: Cooling the nanoemulsion leads to a super saturation of the drug which is dissolved in the lipid melt leads to recrystalization of the lipid [35, 36].

3.1.Drug incorporation and loading capacity: Lipids like triglyceride, fatty acids, steroids, waxes, emulsifier (anionic and cationic) are responsible for varying of the particle size , drug loading capacity ,and size distribution of SLNs. The various factors of determining the loading capacity of the drug in the lipids depend upon following factors[37].

- Chemical and physical structure of the solid matrix of lipid.
- Proper solubility of the melted lipids.

- Proper mixing of the drug in melted lipid.
- Polymorphic stage of lipid materials.

To enhance the solubility in lipid melt of the drug one must can use some good solubilises. The presence of mono and diglycerides lipids used to promote drug solubilisation[38].

3. 2. Determinations of entrapment efficiency:

Drug entrapment efficiency did influence the release characteristic of drug molecule .After separation of entrapped drug from the SLNs, the amount of the drug which is encapsulate per unit weight of nano particle is determined . The separation of drugs from SLNs can be carried out by using technique called ultracentrifugation, centrifugation, filtration or gel permeation chromatography[39].

$$\% \text{ Drug entrapment efficiency} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of drug used in formulation}} \times 100$$

3. 2. 1 Centrifugation filtration:

With modern centrifugation technique, filters like ultra free used in this method .The degree of encapsulation can be determined by finding out the amount of drug remaining in the supernatant of SLNs suspensions after ultra/centrifugation. Dissolution and HPLC assays could be the possible way to determine the drug content.

4. Principles of drug release from SLNs[40,41] :

The drug release from the nanoparticles is as follows.

1. Drug release and partition co-efficient is reversely proportional.

2. Optimum surface area due to nano meter size rang of the particles gives higher drug release.

3. Formation of lipid matrix by homogeneously disperses technique leads to slow drug release.

4. Formation of lipid –drug crystals decreases the drug release.

4.1. Stability:

Gelation phenomena, increase in particle sizes and drug expulsion from the lipid carrier are the major problems of storage stability. The transformation of the lipid melt to lipid crystals results in an increase of particle surfaces, a decrease of the loading capacity of the lipid and therefore, it leads to increased stability problems.

5. Measurement of drug release from SLNs:

The various method popularly used *in vitro* release of the drug are:

1. Diffusion with artificial or biological membrane.

2. Dialysis bag diffusion technique.

3. Reverse dialysis bag technique.

4. Centrifugal ultra filtration.

5.1. *Ex vivo* model to determining permeability across the gut:

Ahlin et.al, did research on the activity of enalaprilat SLNs across the rate jejunum .20-30cm distal from pyloric sphincter was taken for the particular studies .similar studies has carried out by zhilu et at; by taking 10 cm long segments of duodenum.

6. Analytical characterization of SLN[42,43,44]:

6.1. Measurement of particle size and zeta potential: The physical stability of SLNs depends on their particle size .Photon correlation spectroscopy (PCS) and Laser diffraction(LD) are most significant technique used to determine particle size .PCS or dynamic light scattering , measure the fluctuation of intensity of scattered light which is caused by particle movement. In this technique one can estimate few nano meter to 3 micron size range of particles.PCS is very good tool to detected and characterise nano particle, however large particles is hardly detected by this method .Electron microscope attached with PCS and LD ,to estimate direct information of particles . Zeta potential allows to predict the stability of the formulation during storage. Zeta potential analyser or Zetameter used to estimate the zeta potential of suspended SLNs. Before measuring ZP, the SLNs dispersion is diluted 50-fold with original dispersion medium. Higher value of zeta potential may lead to deaggregation in the absence of steric acid (stabilizer) or hydrophilic appendages.

6.2Electrone microscope: Transmission electron microscope (TEM), and Scanning electron microscope (SEM) provides way to directly observed nano particles. SEM is widely used for morphological examination.

6.3. Atomic force microscopy: In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (non contact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. That ultra-high resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool (Mukherjee *et al.*, 2009).

6.4. Dynamic light scattering (DLS): Browniar motion is a effective feature of colloidal dispersion (SLNs). In Browniar motion lights get started scattering. The method called quasi-

elastic light scattering (QELS) or Dynamic light scattering (DLS), the intensity of the scattered light of nano particle were measured in microsecond time scale .At last it produce an auto correction factor . The potential advantages of this method are that it is very tedious and has its sensitivity to submicron particles.

6.5. Static light scatterings (SLS)/Fraunhofer difference: The light scattered from a solution of particles is collected and cited into an electromagnetic equations, in which particle size is the primary variable .This method need more cleanliness then DLS.

6.6Differential scanning calorimetric (DSC): The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature. The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature.

6.7. Acoustic methods: Another ensemble approach, acoustic spectroscopy, measures the attenuation of sound waves as a means of determining size through the fitting of physically relevant equations. In addition, the oscillating electric field generated by the movement of charged particles under the influence of acoustic energy can be detected to provide information on surface charge.

6.8. Nuclear magnetic resonance (NMR):

Both size and quantitative nature of the nano particles can be measure by NMR.

7. Application of SLNs:

7.1. SLNs for parental applications : Due to its good drug storage capability after freeze drying and consisting physiologically well tolerable ingredients SLNs are very suitable in parental use .Best approach is its size , it can easily circulate in micro vascular system and prevent macrophage uptake (in case of hydrophilic coating)[45].In viral and non viral gene genes delivery it is extensively used .In the treatment of cancer cationic SLNs have potential benefit in targeting cancerous cells . Treatment of central nervous system diseases such as brain tumors, AIDS, neurological and psychiatric disorders is often constrained by the inability of potent drugs to pass blood brain barrier (BBB). Hydrophilic coating of colloids improves the transport of these through BBB and tissue distribu-tion (Kreuter 2001; Wang *et al.*, 2002). Fundaro et al, 2000, prepared doxorubicin loaded stealth and non-stealth SLN and observed that the stealth nanopar-ticles were present in blood at higher concentrations than non-stealth SLN after 24 h following intraven-ous administration[46].

7.2. Solid lipid nanoparticles in cancer chemotherapy: In recent time chemotherapeutic drugs are vastly encapsulate in SLNs. Lili Qian et al. (2013) developed cationic core-shell nanoparticles with carmustine cantined with o^6–Benzylguanine shell for glioma therapy. On the other side. Xin-Hua Tian et al. (2011)[47] did research on enhanced brain targeting of temozolomide[52] in polysorbate-80 coated polybutylcyanoacrylate nanoparticles. In both the cases enhancement of bioavailability and less cyto toxicity was observed for chemothaputic agents. The rapid removal of colloidal particles by the macrophages of the RES is a major obstacle to targeting tissues elsewhere in the body, such as bone marrow and solid tumors. Improved stability of drugs, encapsulation of chemotherapeutic agents of diversified physicochemical properties, enhanced drug efficacy, improved pharmacokinetics and less *in-vitro* toxicity are the important features of SLN which make them a suitable carrier for delivering chemotherapeutic drugs[51].

7.2.1. SLN as targeted carrier for anticancer drug to solid tumour: Tamoxifen is an anticancer drug incorporated in SLN to prolong the release of drug after IV administration in breast cancer. Tumour targeting has been achieved with SLN loaded with drugs like methotrexate and camptothecin[49, 50].

7.2.2. SLN in breast cancer and lymph node metastases: Mitoxantrone SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of the drug[48].

7.3 Solid lipid nanoparticles for targeted brain drug delivery:

Particle size range of less than 50nm could be produce beneficial effect on brain targeting. Smaller size usually helps for uptake in RE system. As far as brain uptake is concern, most likely mechanism is endocytosis, by the endothelial cells lining of blood capillaries. SLNs-mediated drug transport to the brain depends on the over coating of the particles with polysorbate 80. Over coating with these materials seems lead to the adsorption of apolipoprotein E from blood plasma on to the nanoparticles surface. The particles then seem to mimic low density lipoprotein (LDL. Particles then interact with the LDL receptor leading to their uptake by the endothelial cells of brain. In a study to overcome the limited access of the drug 5-fluoro-2'-deoxyuridine (FUdR) to the brain, 3',5'-dioctanoyl-5- fluoro-2'-deoxyuridine (DO-FUdR) was synthesized and incorporated into solid lipid nanoparticles (DOFUdR- SLN)[53]. The surfactant coated poly (alkylcyanoacrylate) nanoparticles specifically designed for brain targeting is given by emphasizing the transfer of this technology to solid lipid matrices[51].

7. 4. **SLN applications for improved delivery of antiretroviral drugs to the brain**:

Current antiretroviral drugs (ARVs) often fail to effectively reduce the HIV viral: load in the brain. This, in part, is due to the poor transport of many ARVs, in particular protease inhibitors, across the blood brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSBF). Studies have shown that nanocarriers including polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLN) and micelles can increase the local drug concentration gradients, facilitate drug transport

into the brain via endocytotic pathways and inhibit the ATP-binding cassette (ABC) transporters expressed at the barrier sites. By delivering ARVs with nanocarriers, significant increase in the drug bioavailability to the brain is expected to be achieved.

7.5. SLNs for Nasal application[54,55]: In non invasive technique the nasal rout is a best alternative. Prodrug derivatization loading with drug and peptides and proteins can be formulated in SLNs dosage forms. In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers (Vila *et al.*, 2004). The role of PEG coating of polylactic acid nanoparticles in improving the transmucosal transport of the encapsulated bioactive molecule reported to be successful by Tobio et al, 1998. This concept can be useful for solid lipid nanoparticles.

7.6.SLNs for respiratory applications: Since walls of the alveoli in deep lungs are extremely thin rapid drug absorption by aerosolization of drugs (1-3 micrometer) occurs .In lung cancer treatment SLNs plays an affective role .Radio–labelled SLNs plays a significant role in lymphatic uptake by inhalation. In recent development, rafampicin, isoniazid, pyrazinamide , was prepared in SLNs in size range of 1.1-2.1 micrometer , was nebulized into guinea pig for direct pulmonary delivery .It was observed that SLNs loaded anti tubercular drug improves drug bioavailability and dosage frequency [56,57].

7.7. SLNs for ocular application: Biocompatibility, mucoadhesive ness, Iso ophthalmic pH, prolongs corneal resident time of SLNs improvise ocular targeting. Cavalli et al; 2002 developed tobramycine SLNs for targeting rabbit eyes. Cavalli et al; 2005 again develop SLNs of pilocarpine, a drug used in glaucoma .Both the cases he found good bioavailability in aqueous humor[58].

7.8 SLNs for topical application[58,59,60]: Researchers have reported intensively on the topical application of SLN. During the last few years, SLN and NLC have been studied with active compounds such as Vitamin E (Dingler *et al.*, 1999), tocopherol acetate (Wissing and Muller 2001), retinol (Jenning *et al.*, 2000), ascorbyl palmitate (Uner *et al.*, 2005a and 2005b), clotrimazole (Souto *et al.*, 2004), triptolide (Mei *et al.*, 2003), phodphyllotoxin (Chen *et al.*, 2006) and a nonsteroidal antiandrogen RU 58841 (Munster *et al.*, 2005) for topical application. A completely new, recently discovered area of application is the use of SLN in sun-protective creams (Waghmare *et al.*, 2012).

7.9. Stealth nanoparticles : The main advantages of this system is high clearance from immune system .Anti body labelled stealth nanoparticles have good drug delivery property in affected site .Stealth nanoparticle is tested on animals .

7.10. SLNs as cosmeceuticals: SLNs are effective in preparing sun screen protective. Occlusive properties, increase in skin hydration, modified release, increase of skin penetration and

avoidance of systemic uptake. The first two cosmetic products containing lipid nanoparticles were introduced to the market in 2005.

7.11. **SLN applied to the treatment of malaria:** The main disadvantages of conventional chemotherapeutic drugs in malaria treatment is development of multi drug resistance, and non specific targeting to inter cellular parasites. Nanosized carriers have been receiving special attention with the aim of minimizing the side effects of drug therapy, such as poor bioavailability and the selectivity of drugs. Several nanosized delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria[62].

8. CONCLUSION: The main advantages of SLNs are large scale up is possible and drug can be effective with in less dose incorporation. Moreover SLNs particles are in sub micron size due to this, more effective surface area and good bioavailability is possible. Recent studies on brain targeting, lungs targeting, ophthalmic delivery provides significant cellular uptake of drugs with less cytotoxicity. The formation of liquid crystals and formulation with supper cooled melt produces stability problem, which could be the major challenges for scientists. NMR, ESR and synchrotron irradiation will help the drug nanosuspensions coexist in the sample. Unfortunately, these aspects have not always been considered and the terminus 'drug incorporation' in the SLN literature is often misleading. *In vito* and *in vivo* studies must be carried away to understand proper dynamics and molecular label activity of SLNs.

9. REFERENCES:

1. Kreuter, J. (1991). Peroral administration of nanoparticles. Adv Drug Del Rev 7: 71-86.

2. Chowdary, K.P.R., Rao, AS. (1997). Nanoparticles as drug carriers. Indian Drugs 34(10):549-56.

3. Muller, R.H., Runge, S.A., Ravelli, V., Thünemann, A.F., Mehnert, W., Souto, E.B. (2008)

4. Cyclosporine-loaded solid lipid nanoparticles (SLN): drug-lipid physicochemical 392 interactions and characterization of drug incorporation. Eur J Pharm Biopharm. 68(3): 535-544.

5. Mulla, J.S., Khazi, I.M., Jamakandi, V.G. (2010). Solid lipid nanoparticles: Potential IJNDD 2(3): 82-87.

6. Schwarz, C., Mehnert, W., Lucks, J.S., Muller, R.H. (1994). Solid lipid nanoparticles (SLN) for controlled drug deli-very I. Production, characterization and sterilization. J Control Release 30(1): 83-96.

7. Mehnert, W., Mader, K. (2001) Solid lipid nanoparticles: Production, characterization, applications. Advanced Drug Delivery Review. 47: 165-196.

8. Krishna Sailaja A, Amareshwar P, Chakravarty P. Formulation of solid lipid nanoparticles and their applications. CPR 2011, 1(2), 197-203.

9. Ahlin P, Kristl J, Kobar S. Optimization of procedure parameters and physical stability of solid lipid nanoparticles in dispersion. Acta Pharm. 1998, 48, 257-67.

10. Jahnke S. The theory of high pressure homogenization, in: Muller RH, Benita S, Bohm B. editors. Emulsions and nanosuspensions for the formulation of poorly soluble drugs, Stuttgart Medpharm Scientific Publishers. 1998, 77-2005.

11. Ekambaram, P., Abdul Hassan Sathali, A., Priyanka, K. (2012). Solid Lipid Nanoparticles: A Review. Sci Revs Chem Commun 2(1): 80-102.

12. Elldem, T., Speiser, P., Hineal, A. (1991). Optimization of spray-dried and congealed lipid microparticles and cha-racterization of their surface morphology by scanning electron microscopy. Pharm Res 8: 47-54.

13. Muller, R.H., Mäder, K., Gohla, S.H. (2000) Solid Lipid Nanoparticles For Controlled Drug Delivery- A Review of the State of the art. Eur J Pharm Bio Pharm 50(1): 161-177.

14. Trotta, M., Debernardi, F., Caputo, O. (2003) Preparation of Solid Lipid Nanoparticles by a solvent emulsification-diffusion technique. Int J Pharm. 257: 153-160.

15. Chen YJ, Jin RX, Zhou YQ, Zeng J, Zhang H, Feng QR. Zhongguo Zhong Yao Za Zhi 2006, 31, 376-9.

16. P. Chattopadhyay, B.Y. Shekunov, D. Yim, D. Cipolla, B. Boyd, S. Farr, Advanced Drug Delivery Reviews 2007, 59, 444–53.

17. Gasco MR. United State Patent.US 188837, 1993.

18. Gasco MR. Pharm Tech Eur , 1997, 9, 52-58.

19. Kuo Y.-C., Chen H. International Journal of Pharmaceutics, 2009; 365, 206-13

20. Mueller B.W, Mikroemulsionen als neue Wirkstoff-Traegersysteme, in: R.H. Mueller, G.E. Hildebrand (Eds.), Pharmazeutische Technologie., 1998; pp. 161-168.

21. Waghmare AS, Grampurohit ND, Gadhave MV, Gaikwad DD, Jadhav S. Solid lipid nano particles. A promising drug delivery System IRJP. 2012, 3(4), 100-107.

22. Li, Z., Li, X., Zheng, L., Lin, X., Geng, F., Yu, L. (2010) Bovine serum albumin loaded solid lipid nanoparticles prepared by double emulsion method. Chem Res Chinese Universities. 26(1): 136-141.

23. Singh S, Dobhal AK, Jain A, Pandit JK, Chakraborty S., Chem Pharm Bull, 2010, 58, 650-5.

24. M Garcıa-Fuentes, D Torres, MJ Alonso, Biointerfaces. 2002, 27, 159-68.

25. Catherine Charcosset, Assma El-Harati, Hatem Fessi., Journal of Controlled Release, 2005, 108, 112–120.

26. MA Schubert, CC Muller-Goymann, Eur J Pharm Biopharm. 2003, 55, 125–31.

27. Wang T, Wang N, Zhang Y, Shen W, Gao X, Li T. Colloids Surf B Biointerfaces. 2010, 79, 254-61.

28. Arvind Gulbake, Aviral Jain, Piush Khare, Sanjay K. Jain, Journal of Microencapsulation, 2010; 27, 226–233.

29. Bhaskar K. Anbu J Ravichandiran V. Venkateswarlu V. and Rao Y.M, Lipids in health and disease, 2009, 6.

30. Motwani, S.K., Chopra, S., Talegaonkar, S., Kohli, K., Ahmad, F.J., Khar, R.K. (2008). Chitosan–sodium alginate nanopar-ticles as submicroscopic reservoirs for ocular delivery: Formulation, optimization and in vitro characterization. Eur J Pharm Biopharm 68(3): 513-525.

31. Hu L, Xing Q, Meng J, Shang C. AAPS PharmSciTech. 2010, 11, 582-87.

32. Singh S, Dobhal AK, Jain A, Pandit JK, Chakraborty S., Chem Pharm Bull, 2010, 58, 650-5.

33. P. Chattopadhyay, B.Y. Shekunov, D. Yim, D. Cipolla, B. Boyd, S. Farr, Advanced Drug Delivery Reviews 2007, 59, 444–53.

34. Fu qiang Hu, Jian You, Feng Wan, Fu de Cuib, Yu Sun, Yong-Zhong Du, International Journal of Pharmaceutics 343, 2007, 270–76.

35. Dianrui Zhang, Tianwei Tan, Lei Gao, Nanotechnology,2006, 17, 5821.

36. Sinha Ranjan Vivek, Srivastava Saurabh, Goel Honey, Jindal Vinay, Solid Lipid Nanoparticles (SLN'S) – Trends and Implications in Drug Targeting, International Journal of Advances in Pharmaceutical Sciences, volume 2, 2010, 212-238.

37. Cavalli ER. Marengo L, Rodriguez, Gasco MR, Effects of some experimental factors on the production process of solid lipid nanoparticles, Eur J Pharm Biopharm volume 2, 1996, 110-15.

38. Sinha Ranjan Vivek, Srivastava Saurabh, Goel Honey, Jindal Vinay, Solid Lipid Nanoparticles (SLN'S) – Trends and Implications in Drug Targeting, International Journal of Advances in Pharmaceutical Sciences, volume 2, 2010, 212-238.

39. Bhatt Ashvin D, Pethe A M, Lipid Technology- A Promising Drug Delivery SystemFor Poorly Water Soluble Drugs, International Journal Of Pharma Research And Development, volume 1, 2010, 1-11.

40. Schwarz WC. Mehnert JS, Lucks, Muller RH, Solid lipid nanoparticles (SLN) for controlled drug delivery Production, characterisation and sterilization. J Control Release, volume 3, 1994, 83-96.

41. Melike Uner, Gulgun Yener, Int. J. Nanomedicine, **2(3)**, 289-300 (2007).

42. Annette Zur Mehlen, Cora Schwarz and Wolfgang Mehnart, Eur. J. Pharm. Biopharm., **45**, 149-155, (1998).

43. Akanksha Garud, Deepti Singh, Navneet Garud; Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications, International Current Pharmaceutical Journal 2012, 1(11): 384-393 http://www.icpjonline.com/documents/Vol1Issue11/08.pdf.

44. P. Ekambaram, a. Abdul hasan sathali and k. Priyanka; Solid lipid nanoparticles: a review; sci. Revs. Chem. Commun.: 2(1), 2012, 80-102Issn 2277-2669.

45. Rahul Nair*, K.S.Arun Kumar, K.Vishnu Priya, M.Sevukarajan; Recent Advances in Solid Lipid Nanoparticle Based Drug Delivery Systems; Rahul Nair et al / J Biomed Sci and Res., Vol 3 (2), 2011,368-384.

46. Wissing, S.A., Kayser, O., Muller, R.H. (2004). Solid lipid nanoparticles for parenteral drug delivery. Adv Drug Deliv Rev 56(9): 1257-1272.

47. Olbrich, C., Bakowski, U., Lehr, C.M., Müller, R.H., Kneuer, C. (2001). Cationic solid-lipid nanoparticles can efficiently bind and transfect plasmid DNA. J Control Release 77(3): 345-55.

48. Yung-Chih Kuo, Cheng –Te Liang .Inhibition of human brain malignant glioblastoma cells using carmustine-loaded cationic solid lipid nano perticals with surface anti-epithelial growth factor .Biomaterials 32(2011)3340-3350.

49. Murthy, R.S.R. (2005) Solid lipid nanoparticles as carriers for anti-cancer drugs to solid tumours. Drug Deliv 12: 385-392.

50. Shenoy VS, Vijay IK, Murthy RS. J Pharm Pharmacol, 2005, 57, 411-22.

51. Ruckmani K, Sivakumar M, Ganeshkumar PA., J Nanosci Nanotechnol, 2006, 6, 2991-5.

52. MelikeUner, GulgunYener, solid lipid nanoparticles overview, Int. J. Nanomedicine, 2007, 289-300.

53. Xin-Hua Tian, Xiao-Ning Lin, Feng Wei, Wei Feng, Zhi-Chun Huang, Peng Wang, Lei Ren, Yi Diao. Enhanced brain targeting of Temozolomide in polysorbate-80 coated polybutyl cyanoacrylate nanoparticles. International Journal of Nano medicine 2011:6 445–452.

54. Wolfgang Mehnart and Karsten Mader, Adv. Drug. Deliv. Rev., **47**, 165-196 (2001).

55. Lee, W.A., Ennis, R.D., Longenecker, J.P., Bengtsson, P. (1994). The bioavailability of intranasal salmon calcitonin in healthy volunteers with and without permeation en-hancer. Pharm Res.

56. Vila, A., Gill, H., McCallion, O., Alonso, M.J. (2004). Trans-port of PLA-PEG particles across the nasal mucosa: effect of particle size and PEG coating density. J Control Release 98(2): 231-244.

57. Vila, A., Gill, H., McCallion, O., Alonso, M.J. (2004). Trans-port of PLA-PEG particles across the nasal mucosa: effect of particle size and PEG coating density. J Control Release 98(2): 231-244.

58. Videira, M.A., Botelho, M.F., Santos, A.C., Gouveia, L.F., de Lima, J.J., Almeida, A.J. (2002). Lymphatic uptake of pulmonary delivered solid lipid nanoparticles. J Drug Target 10(8): 607-613.

59. Friedrich, I., Reichl, S., Müller-Goymann, C.C. (2005). Drug release and permeation studies of nanosuspensions based on solidified reverse micellar solutions (SRMS) Int J Pharm 305(1-2): 167–75.

60. Dingler, A., Blum, R.P., Niehus, H., Müller, R.H., Gohla, S. (1999). Solid lipid nanoparticles (SLN™/Lipopearls™) – a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products. J Microencapsul. 16(6): 751-767.

61. Wissing, S.A., Muller, RH. (2003). Cosmetic applications for solid lipid nanoparticles (SLN) Int J Pharm 254(1): 65-68.

62. Chen, H., Chang, X., Du, D., Liu, W., Liu, J., Weng, T., Yang, Y., Xu, H., Yang, X. (2006). Podophyllotoxin-loaded solid lipid nanoparticles for epidermal targeting. J Control Release 110(2): 296-306.

63. ShuyuXie, Luyan Zhu, Zhao Dong and Yan Wang, Colloids and Surfaces, Bio interfaces, 2011, 382-387.