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Novel approaches in solid lipid nano particles and drug targetting

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ABSTRACT

Solid lipid nanoparticles are at the new wave of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and research as well as in other varied sciences. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. By putting forward physiological safe lipids in place of polymers to prepare lipid nanoparticles, a novel formulation technique came into light. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers. In addition, wide pharmaceutical applications of SLNs in drug delivery are explored. Diverse instrumental techniques have been highlighted to characterize the physiochemical properties of SLNs. various routes of administration of SLNs as drug carriers are logistically reviewed and discussed. The different types of nanocarriers which were based on solid lipid like solid lipid nanoparticles, nanostructured lipid carriers, lipid drug conjugates are discussed with their structural differences. Different production methods which are suitable for large scale production and applications of solid lipid nanoparticles are described and aspects of solid lipid nanoparticles route of administration and their biodistribution are also incorporated. SLNs may open new vistas in therapy of complex diseases like cancer.

Keywords: Solid lipid nanoparticle, Drug targeting; Magnetic SLN; pH-sensitive, Homogenization, TEM, Biodistribution, Targeting, Colloidal drug carriers. Bioavailability enhancer, Vaccine adjuvant.

INTRODUCTION

Many of the recent formulation approaches utilize Nanotechnology that is the preparation of Nano sized structures containing the API [1]. Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100 nm. The overall goal of nanotechnology is the same as that of medicine: to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using controlled and targeted drug delivery approach [2]. Some of the important Drug Delivery System developed using Nanotechnology principles are-

Nanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion, Nanocrystals[3]. In this article the main focus is on Solid Lipid Nanoparticles (SLNs). Solid lipid nanoparticles or liposphere are rapidly emerging as new class of safer and proficient gene/drug delivery vectors. Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as - emulsions, liposomes and polymeric micro – and nanoparticle [4]. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1µm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution (Chowdary et al., 1997). SLNs are produced by replacing the liquid lipid (oil) of an o/w emulsion by a solid lipid or a blend of solid lipids, i.e. the lipid particle matrix being solid at both room and body temperature [5]. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of neutraceuticals, pharmaceuticals [6]. These are generally made up of a solid hydrophobic core containing the drug dissolved or dispersed [7]. SLNs are mainly prepared by high pressure homogenization or micro emulsification. SLNs prepared by any technique are in dispersion form which on long term storage results in instability mainly because of hydrolysis reactions so to increase their stability they can be converted into solid dry reconstituable powders through lyophilisation and a cheap and easy variant to lyophilisation is spray drying technique [8]. In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles. The reasons for the increasing interest in lipid based system are many – fold and include:

- Lipids enhance oral bioavailability and reduce plasma profile variability.
- Better characterization of lipoid excipients.
- Specific drug targeting and delivery, biocompatibile and greater safety, and development of safe medicines.
- Increased drug stability and high drug payload.
- Incorporation of lipophilic and hydrophilic drugs feasible
- No biotoxicity of the carrier.
- Possibility of controlled drug release and drug targeting.
- Avoidance of organic solvents and no problems with respect to large scale production and Sterilization.

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on Fig.1. This is the one of the most popular approaches to improve the oral bioavailability of the poorly water soluble drugs. They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable.

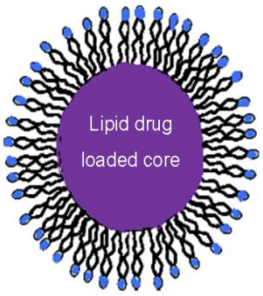

Fig. 1: Structure of solid lipid nanoparticle (SLN)

The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. Generally, they are made of solid

hydrophobic core having a monolayer of phospholipids coating. The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics [9]. There are major difference between lipid emulsion and liposomes. The basic structure of a lipid emulsion is a neutral lipophilic oil core surrounded by monolayer of amphiphilic lipid. In contrast, liposomes contain an outer bilayer of amphiphilic molecule such as phospholipid with an aqueous compartment inside [10].

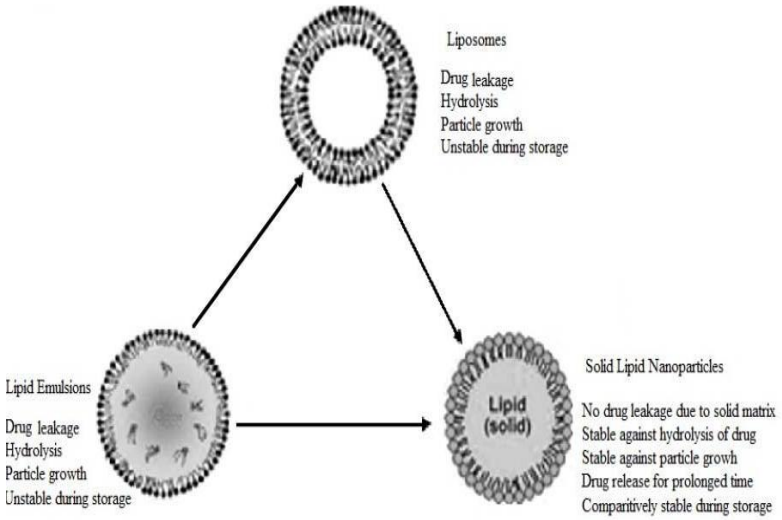

Fig. 2: A diagrammatic representation on SLN over emulsions and liposomes

The schematic representation of different particulate drug carriers such as emulsions and liposomes and their advantages are compared with SLNs in Fig. 2. SLNs combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes.

Principles of drug release from SLNs

The general principles of drug release from lipid nanoparticles are as

- Crystallinization behavior of the lipid carrier and high mobility of the drug lead to fast drug release.
- Higher surface area due to smaller particle size in nanometer range gives higher drug release.
- Slow drug release can be achieved when the drug is homogenously in the lipid matrix. It depends on type and drug entrapment model of SLN.

Advantages of SLN [11]

- In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity.
- Topical treatment of skin diseases with SLNs has the advantage that high drug levels can be achieved at the site of disease and systemic side effects can be reduced compared to oral or parenteral drug administration (Schafer-Kortin *et al*., 2007).
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
- The feasibility of incorporating both hydrophilic and hydrophobic drugs (Fundaro, 2000; Chen *et al*., 2001)
- SLNs particularly those in the range of 120–200 nm are not taken up readily by the cells present in the RES (Reticulo Endothelial System) and thus bypass liver and spleen filtration.
- Improved bioavailability of poorly water soluble molecules (Fahr and Liu, 2007)
- Enhanced drug stability. SLNs stable for three years have been developed. This is of more importance compared to the other colloidal carrier systems.

- Possibility of controlled drug release and drug targeting.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment.
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
- High concentration of functional compound achieved.
- SLNs can be lyophilized as well as spray dried.
- Possibility of scaling up.
- Much easier to manufacture than biopolymeric nanoparticles.
- Can be subjected to commercial sterilization procedures.
- No special solvent required and no biotoxicity of the carrier (Cavalli *et al*., 2000).
- Conventional emulsion manufacturing methods applicable.
- Feasible large scale production is possible and easier to validate and gain regulatory approval.
- Better control over release kinetics of encapsulated compound.
- Surface modification can be easily done.
- The carrier lipids are biodegradable and hence safe.

Disadvantages of SLN's [12]

- The low capacity to load water soluble drugs due to partitioning effects during the production process.
- Unpredictable gelation tendency.
- Unexpected dynamics of polymeric transitions.
- Particle growth and crystallization of drugs.
- High pressure induced drug degradation.
- Relatively high water content of the dispersions (70-99.9%).
- Drug expulsion from lipids.

During storage it was observed that drug was expelled out of SLN. The reason behind expulsion of drug was the highly ordered crystalline lipid matrix which was leaving very little space for drug molecules. To overcome the limitations of SLN, nanostructured lipid carriers (NLCs), Lipid drug conjugate (LDCs) and Polymer lipid hybrid nanoparticles (PLNs) were introduced. These carrier systems overcome observed limitation of conventional.

Nanostructured Lipid Carriers (Nlcs)

Nanostructured lipid carriers, introduced at the turn of the utopia, represent a new and improved generation of SLNs and are made of a solid lipid matrix entrapping liquid lipid nano-compartments, the blend being solid at body temperature. This new creation of lipid carriers (NLCs) was introduced to overcome the problems associated with SLNs, such as limited drug loading capacity, drug expulsion during storage and adjustment of drug release, long-term physical stability of the suspension *etc.* NLC is composed of solid lipids and a certain amount of liquid lipids with improved drug loading and increased stability on storage thereby reducing drug expulsion. NLCs have been explored for dermal delivery in cosmetics and dermatological preparations [13]. The goal was to increase the drug loading and prevent drug expulsion. This could be visualized in three ways. Three models of NLCs were proposed. In the first model, also known as imperfect type NLCs, particles are prepared from a lipid mixture of spatially different lipids (like glycerides) composed of different fatty acids. Use of spatially different lipids leads to larger distances between the fatty acid chains of glycerides and general imperfection of the crystal lattice. This would provide more space for accommodation of guest molecules in molecular form or as amorphous clusters. High drug loading could be achieved and drug expulsion from the lipid matrix during storage could be prevented with this model, due to distortion of the crystal lattice. This suggests that an increased number of imperfections leads to increased drug loading capacity and one could say that the perfectness of the NLC system lies in the imperfectness in its crystal lattice. The second model is also known as multiple type NLC, where drugs showing higher solubility in oils than in solid lipids can be dissolved in oil and yet be protected from degradation by the surrounding solid lipids. Multiple type NLCs are analogous to w/o/w multiple emulsions since these are oil-in-solid lipid-in-water dispersions. The third model, also known as amorphous type NLC, prevents the ongoing expulsion of the drug caused by crystallization or transformation of the solid lipid.

Here, the particles are solid but crystallization upon cooling is avoided by using special lipids such as hydroxyl octacosanyl, hydroxyl stearate, isopropyl myristate, etc. The NLCs have mainly been investigated in the topical and dermatological preparations in the delivery of clotrimazole, ketoconazole, other antifungal imidazoles and ascorbyl palmitate.

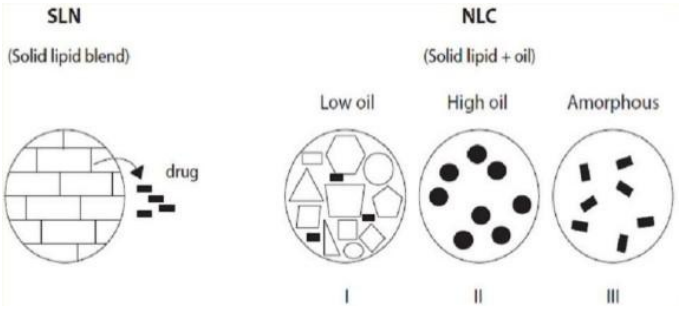

Fig. 3: Different types of NLC: I-Highly imperfect matrix; II-Multiple O/F/W type; III-Non-crystalline amorpous NLC (versus SLN with high crystallinity).

The NLCs were also prepared to investigate whether the duration of brain targeting and accumulation of drugs in the brain can be enhanced by intravenous delivery. Apomorphine as a model drug has been targeted, through certain vessels, to selected brain regions by in vivoreal-time bioluminescence imaging of the rat brain [14].

Lipid Drug Conjugates (LDC)

LDC nanoparticles can be termed as a special form of nanoparticles consisting of 100% LDC or a mixture of LDC with suitable lipids. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix. In order to overcome this problem, the so called LDC nanoparticles with improved drug loading capacities have been developed. An insoluble drug-lipid conjugate bulk is first prepared either by covalent linking or by salt formation. The obtained LDC is then processed with an aqueous surfactant solution to a nanoparticle formulation using high pressure homogenization technique. Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections [15]. LDC enables the incorporation of both hydrophilic (e.g., doxorubicin and tobramycin) and lipophilic (e.g., progesterone and cyclosporine A) drugs.

Polymer Lipid Hybrid Nanoparticles (PLNS)

Polymer-lipid hybrid nanoparticles take in great promise as a drug delivery vehicle in the treatment of a myriad of diseases such as breast cancer. A PLNs constitute three distinct functional components:

I. hydrophobic polymeric core to encapsulate poorly water-soluble drugs
II. hydrophilic polymeric shell to enhance PLN stability and circulation half-life
III. Lipid monolayer at the core and shell interface to promote drug retention inside the polymeric core.

Interactions among these components play an important role for successful fabrication and performance of PLNs. These hybrid NPs combine the merits of both liposomes and polymeric nanoparticles, two of the most popular drug delivery vehicles approved for clinical use, thereby serving as a robust drug delivery platform. It has been shown in vitro that hybrid NPs possess the ability of carrying poorly water-soluble drugs with high encapsulation and loading yields, tunable and sustained drug release profiles, excellent serum stability, and differential targeting of cells [16].

Material used to prepare SLNs

The GRAS (Generally recommended as safe) status lipids used to prepare SLNs along with stabilizing surfactants/emulsifiers.

Lipids

The lipids used to prepare SLNs remain solid at room and body temperature. The GRAS status lipids used to prepare SLNs include: (i). Saturated monoacid triglycerides: tristearin, tripalmitin,

trilaurin, trimyristin. (ii) Partial glycerides: glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate. (iii) Fatty acids: stearic acid, behenic acid, palmitic acid, decanoic acid. (iv) Steroids: cholesterol (v) Waxes: cetyl palmitate.

Surfactants/Emulsifiers

All classes of emulsifiers have been used to stabilize the lipid dispersions (Domb, 2008; Rawat *et al.*, 2011). Most widely used cateogory is non-ionic surfactants like Poloxamer 188, Poloxamer 407, Tweens and Spans.

Table no. 1: Lipids and Surfactants used for preparation of SLNs

Lipids	Surfactants
Triacylglycerols:	***Phospholipids:***
Tricaprin	Soy lecithin
Trilaurin	Egg lecithin
Trimyristin	Phosphatidylcholine
Tripalmitin	
Tristearin	
Acylglycerols:	***Ethylene oxide/propylene oxide***
Glyceryl monostearate (ImwitorÒ900)	***copolymers:***
Glyceryl distearate(Precirol)	Poloxamer 188
Glyceryl monooleate(Peceol)	Poloxamer 182
Glyceryl behenate (CompritolÒ 888 ATO)	Poloxamer 407
Glyceryl palmitostearate (PrecirolÒ ATO 5)	Poloxamine 908
Fatty acids:	***Sorbitan ethylene oxide/propylene***
Stearic acid	***oxide copolymers:***
Palmitic acid	Polysorbate 20
Decanoic acid	Polysorbate 60
Behenic acid	Polysorbate 80
Acidan N12	
Waxes:	***Alkylaryl polyether alcohol***
Cetyl palmitate	***polymers:***
Cetyl palmitate	Tyloxapol
Cyclic	***Bile salts:***
complexes:	Sodium cholate
Cyclodextrin	Sodium glycocholate
	Sodium taurocholate
	Sodium taurodeoxycholate
Hard fat types:	***Alcohols:***
Witepsol W 35	Ethanol
Witepsol H 35	Butanol
WitepsolÒ H 45	Butyric acid
WitepsolÒ E 85	Dioctyl sodium sulfosuccinate
	Monooctylphosphoric acid sodium

METHODS OF PREPARATION OF SOLID LIPID NANOPARTICLES

SLNs are prepared from lipid, emulsifier and water/solvent by using different methods and these methods are given below:

High Pressure Homogenization (HPH) technique

It is a reliable and powerful technique. HPH was the earliest method used for SLN preparation [17]. High pressure homogenization pushes a liquid with high pressure (100 - 2000 bar) through a narrow gap in the range of a few microns. This

technique arose from its use in the preparation of o/w emulsion for parenteral nutrition. Two general approaches of the homogenization step are hot and cold homogenization techniques:

Hot homogenization technique (HHT)

In hot homogenization method, the drug is added to the lipid at 5-10^{o}C above lipid melting point, then melt is dispersed with stirring in an aqueous surfactant solution at the same temperature. The pre-emulsion is then homogenized, and resulting hot o/w microemulsion is cooled to room temperature or lower temperature to produce SLN (Ekambaram *et al*., 2012). The hot homogenization technique can be used for lipophilic and insoluble drugs. As the exposure time to high temperature is relatively short, many heat sensitive drugs can be safely processed. The technique is not suitable for incorporation of hydrophilic drugs into SLN because higher portion drugs in water during homogenization results in low entrapment efficiency. Crystallization, temperature induces drug degradation and drug distribution into the aqueous phase is some problems. Aqueous dispersions of lipid nanoparticles-flurbiprofen solid lipid nanoparticles and flurbiprofen nanostructured lipid carriers were prepared by hot homogenization followed by sonication technique. Then aqueous dispersions of lipid nanoparticles were incorporated into the freshly prepared hydrogels for transdermal delivery [18].

Cold homogenization technique (CHT)

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: (i) Temperature-induced drug degradation (ii) Hydrophilic compounds partitioning into aqueous phase at elevated temperature (iii) Complexity of the crystallization.

The first step is same involving dispersion of drug in molten lipid. The melt is cooled, and solid lipid is ground to lipid microparticles. The lipid microparticles are then dispersed in a cold surfactant solution. Homogenization is conducted at room temperature or below, producing SLNs (Ekambaram *et al*., 2012). A hydrophilic and temperature-induced degradation drug, vinorelbine bitartrate loaded solid lipid nanoparticles were prepared by a cold homogenization technique [19]. In comparison to hot homogenization, in cold homogenization particle size and poly dispersity index are more. The cold homogenization only minimizes the thermal exposure of drug, but it does not avoid completely it due to melting of the lipid/drug mixture in the first step of preparation (Rabinarayan *et al*., 2010). This method is more suitable for heat sensitive products. It minimizes thermal exposure but does not avoid it. It is energy intensive process and result in formation of large particle size & broader size distribution.

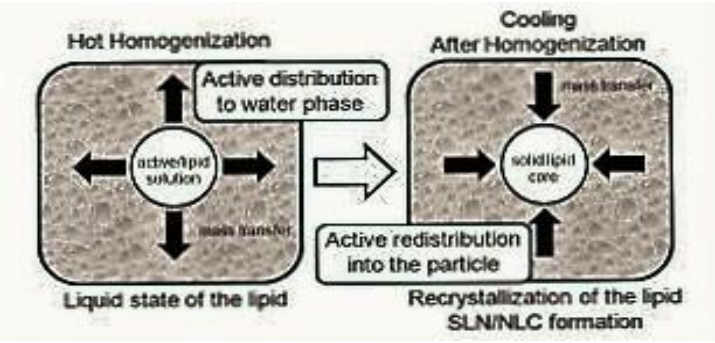

Fig 4: Partitioning effect on drug during the hot homogenization production of SLNs. Left; partitioning of drug from the lipid phase to the water phase at increased temperature. Right: Repartitioning of the drug cooling of the drug to the lipid phase during cooling of the produced O/W nanoemusion.

Ultrasonication/high speed homogenization

In this method, SLNs are also processed by ultrasonication or high speed homogenization. For smaller particle size, combination of both ultrasonication and high speed homogenization is required. Drug is added to hot lipid melt. Hot

aqueous phase is added to the hot lipid melt, emulsified by probe sonicator or by using high speed stirrer. Pre-emulsion is formed, sonicate it using probe sonicator, o/w nanoemulsion is formed which is filtered to obtain SLNs. This method offers many advantages like no temperature induced degradation, reduced shear stress and equipments are easy to operate. Demerits of method are: metal contamination, physical instability like particle growth upon storage, broader particle size distribution ranging into micrometer range. SLNs were successfully prepared by an ultrasonic and high speed homogenization method to improve the oral bioavailability of the poorly water-soluble drug cryptotanshinone. The incorporation of cryptotanshinone in SLNs had markedly changed the metabolism behavior and absorption is enhanced significantly by employing SLN formulations [20].

Solvent evaporation/emulsification technique

In this method (Krishna *et al*., 2011), drug and lipid are dissolved in a water immiscible organic solvent (cyclohexane, dichloromethane, toluene, chloroform). Emulsification is done in an aqueous phase using high speed homogenizer. The emulsion is evaporated to remove organic solvent by stirring at room temperature under reduced pressure (40-60 mbar). Lipid will precipitate to form SLNs. Solid lipid nanoparticle delivery systems of oridonin have been formed using stearic acid, soybean lecithin and pluronic by emulsion evaporation–solidification at low temperature. The SLN formulation of risperidone was formulated using response surface methodology of design of experiment. The SLN was prepared by solvent evaporation method and characterized by non-destructive methods of analysis [21].

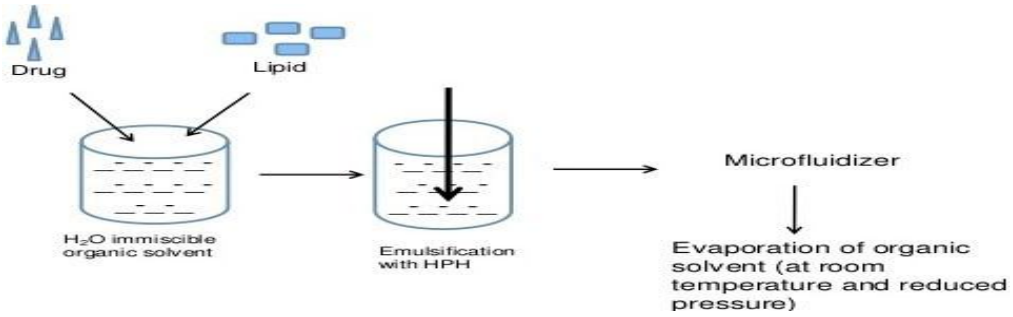

Fig 5: Solvent evaporation technique

Solvent emulsification - diffusion method

In Solvent emulsification - diffusion method, lipid matrix is dispersed in water. Emulsification is done in an aqueous phase under reduced pressure. Lipid precipitates in aqueous medium. Nanoparticle dispersion is obtained. The average diameter of obtained particles is 30-100 nm. It avoids any type of thermal stress. It is an extremely energy intensive process and involves use of organic solvents (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate). Cyclosporine solid lipid nanoparticles prepared by emulsification diffusion method will improve absorption and bioavailability [22]. Doxorubicins SLN were prepared by solvent emulsification-diffusion method using Glyceryl caprate (Capmul®MCM C10) as lipid core, and curdlan as the shell material.

Double emulsion method

This method is developed for mainly hydrophilic drugs and is based on solvent emulsification-evaporation method. Double emulsification is carried out to form w/o/w double emulsion. Drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. Drug is dissolved in aqueous solution, emulsified in melted lipid and stabilized by stabilizer. Then this stabilized

emulsion is dispersed in aqueous phase containing hydrophilic emulsifier. Thereafter, the double emulsion is stirred and isolated by filtration. Formation of high percentage of microparticles occurs by this method. This technique is mainly used to encapsulate hydrophilic drug (peptides). A major drawback of this technique is the formation of high percentage of micro particles. Sodium cromoglycate containing SLN was tried to be prepared by this method but the formed colloidal system gave the average particle of micrometer range. Insulin loaded SLN was prepared by a novel reverse micelle-double emulsion technique, using sodium cholatephosphatidyl choline based mixed micelle.

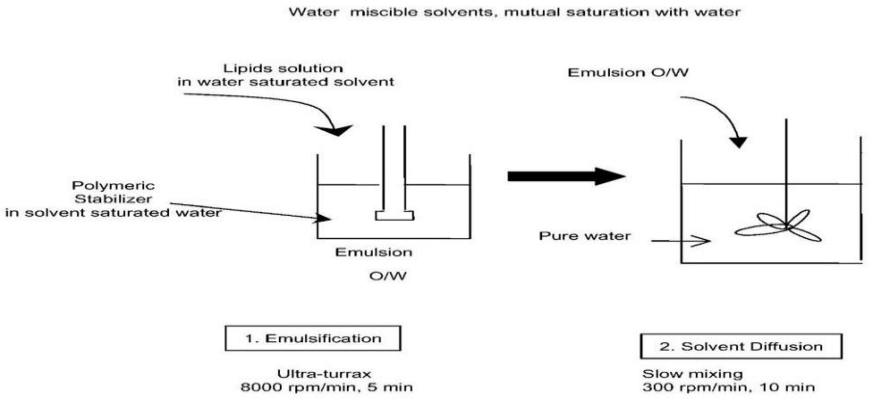

Fig 6: Double Emusion method

Microemulsion based technique

Microemulsions are two-phase systems repressed of oil and aqueous phases. This method (Rabinarayan *et al*., 2010) is based on the dilution of microemulsion. They are made by stirring an optical transparent mixture of lipid, emulsifier, co-emulsifier and water at 65-70^{oC}. The hot microemulsion is dispersed in cold water (2-3^{oC}) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. There will be formation of suspension of lipid particles, filter and wash with dispersion medium and SLNs are obtained. Low mechanical energy is required and is theoretically stable. Low nanoparticle concentrations are one problem of this method. Cationic solid lipid nanoparticles could carry saquinavir for the improved medication of individuals infected by human immunodeficiency viruses fabricated by microemulsion method. Different methods for preparation of SLNs were summarised in table 2.

Spray drying method

This method is an alternative technique (Rabinarayan *et al*., 2010) to the lyophilization process. It can transform an aqueous SLN dispersion into a solid product by spray drying. The best results obtained are with 1% SLN concentration in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v). It is a cheaper method in comparison to lyophilization. Problems encounterd are**:** use of lipid with melting point more than 70°C, particle aggregations because of high temperature, shear force and partial melting of particles [23].

Melting dispersion technique

In melting dispersion technique drug and solid lipid were melted in an organic solvent which is regarded as oil phase and simultaneously water phase was also heated to same temperature as oil phase. Then the oil phase is added slowly in to a small volume of water phase with continuous stirring at higher rpm for few hrs. Then it was cooled down to room temperature to give SLNs. Reproducibility was more than ultrasonication method but less than that of solvent emulsification evaporation method [24].

Membrane contactor technique

In membrane contactor 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 advantages of this technique are its facility of use, the control of the SLN particle size by suitable choice of process parameters. The aqueous phase was stirred continuously and circulates tangentially 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. Here both the aqueous and organic phases were placed in the thermostated bath to maintain the required temperature and nitrogen was used to create the pressure for the liquid phase. Vitamin E loaded SLN are prepared using using a membrane contactor technique to allow large scale production and their stability is demonstrated [25].

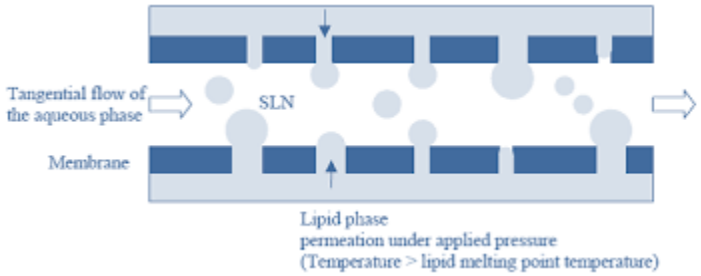

Fig. 5: Schematic drawing of the membrane contactor for the SLN preparation

Supercritical fluid (SCF) method

In SCF method many gases like carbon dioxide, ammonia, and ethane are used [26], but carbon dioxide is best for SCF technique because it is much safer in comparison to other gases and it does not cause the oxidation of drug material (Rabinarayan *et al*., 2010). Carbon dioxide (99.99%) was the good choice as a solvent for this method (Gasco, 1993). This technique generally uses organic solvents (DMSO, DMFA) because they are fully miscible in SCF-CO2. This technique contains several methods for production of nanopartices which are: Rapid expansion of supercritical solution (RESS) ii) Particles from gas saturated solution (PGSS) iii) Gas/supercritical antisolvent (GAS/SAS) iv**)** Supercritical fluid extraction of emulsions (SFEE).

Solvent injection technique

Solvent injection technique is a new approach to prepare SLN and it has following advantages like use of pharmacologically acceptable organic solvent, easy handling and fast production process without technically sophisticated equipment. In this technique, the solid lipid was dissolved in water miscible solvent (e.g. ethanol, acetone, isopropanol) or a water-miscible solvent mixture. Then this organic solvent mixture was slowly injected through an injection needle in to stirred aqueous phase with or without surfactant. Then the dispersion was filtered with a filter paper in order to remove any excess lipid. The presence of surfactant within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize the formed SLNs until solvent diffusion was complete by reducing the surface tension.

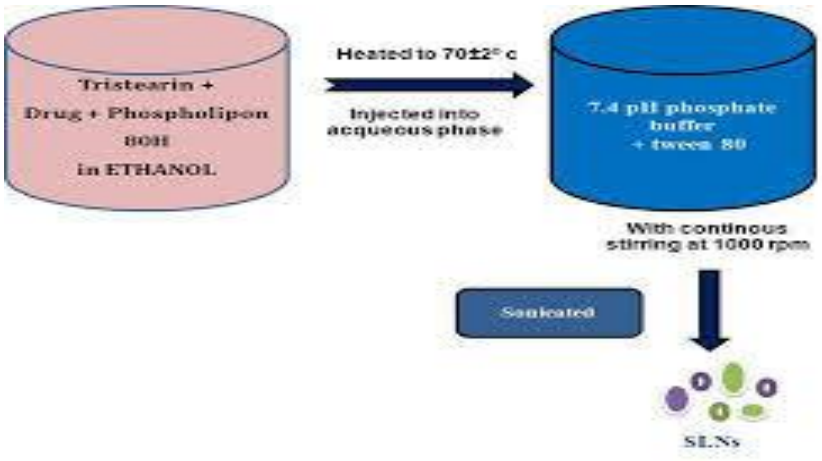

Figure 5. Schematic representation of solvent injection method

Film ultrasound dispersion

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.

Precipitation technique

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The glycerides will be dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles [27].

TYPES OF SOLID LIPID NANOPARTICLES

The types of SLNs depend on the chemical nature of the active ingredient, type and concentration of lipids, the solubility of actives in the melted lipid, nature and concentration of surfactants, method of production and the production temperature. Therefore three incorporation models have been proposed for study.

SLN, Type I or homogenous matrix model

The SLN Type I is derived from a solid solution of lipid and active ingredient. A solid solution can be obtained when SLN are produced by the cold homogenization method. A lipid blend can be produced containing the active ingredient in a molecularly dispersed form. After solidification of this blend, it is grounded in its solid state to avoid or minimize the enrichment of active molecules in different parts of the lipid nanoparticles.

SLN, Type II or drug enriched shell model

It is achieved when SLN are produced by hot homogenization technique, and the active ingredient concentration in the melted lipid is low. During the cooling process of the hot o/w nanoemulsion, the lipid will precipitate first leading to a steadily increasing concentration of active molecules in the remaining melt; an outer shell will solidify containing both active and lipid. The enrichment of the outer area of the particles causes burst release. The percentage of active ingredient localized in the outer shell can be adjusted in a controlled shell model.

SLN, Type III or drug enriched core model

Core model can take place when the active ingredient concentration in the lipid melt is high & relatively close to its saturation solubility. Cooling down of the hot oil droplets will in most cases reduce the solubility of the active in the melt. When the saturation solubility exceeds, active molecules precipitate leading to the formation of a drug enriched core.

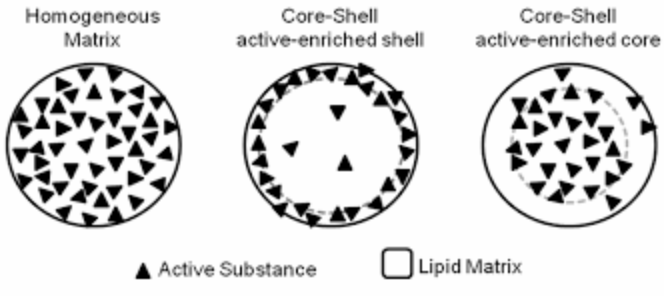

Fig. 7: Types of Drug incorporation models

PHYSIOCHEMICAL CHARACTERIZATION OF SLN'S

Particle Size and Shape [27]

SLNs are submicron sized, particle size and shape is determined by:

Photon Correlation Spectroscopy (PCS)

It is an established method which is based on dynamic scattering of laser light due to Brownian motion of particles in solution/suspension. This method is suitable for the measurement of particles in the range of 3 nm to 3 mm. The PCS device consists of laser source, a sample cell (temperature controlled) and a detector. Photomultiplier is used as detector to detect the scattered light. The PCS diameter is based on the intensity of the light scattering from the particles.

Electron Microscopy

Electron Microscopy methods such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used to measure the physical characterization like overall shape and morphology of lipid nanoparticles. It permits the determination of particle size and distributions.SEM uses electrons transmitted from the surface of the sample while TEM uses electrons transmitted through the sample. TEM has a smaller size limit of detection.

Atomic Force Microscopy (AFM)

It is an advanced microscopic technique which is applied as a new tool to image the original unchanged shape and surface properties of the particles. AFM measures the force acting between surface of the sample and the tip of the probe, when the probe is kept in close proximity to the sample which results in a spatial resolution of up to 0.01 nm for imaging.

Static light scattering (SLS)/ Fraunhofer diffraction

This method studies the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in which size is the primary variable. It is fast and rugged method, but requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities.

Measurement of zeta potential

Zeta potential is used to measure the charge on the particles (Muller, 2000). It allows prediction about the storage stability of colloidal dispersion because of repulsion between particles. Malvern Zetasizer is most widely used instrument for measurement of Zeta potential. A zeta potential measurement can also be helpful in designing particles with reduced RES uptake. Zeta potential below -25 mV and above + 25mV are required for full electrostatic stabilization of the formulation.

Determination of Incorporated Drug

Amount of drug incorporated in SLNs influences the release characteristics; hence it is very important to measure the amount of incorporated drug. The amount of drug encapsulated per unit weight of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium by ultracentrifugation, centrifugation, filtration or gel permeation chromatography. The drug can be assayed by standard analytical technique such as spectroscopy and HPLC methods.

Measurement of degree of crystallinity and lipid modification

Thermodynamic stability and lipid packing density increase while drug incorporation rates decrease in the following order:
Super cooled melt < α-modification < β'-modification < β-modification.
Due to the small size of the particles and the presence of emulsifiers, lipid crystallization and modification changes might be highly retarded. Differential scanning calorimetry (DSC) & X-ray scattering are used to investigate the status of the lipid. DSC uses the fact that different lipid modifications possess different melting points and melting enthalpies. By means of X-ray scattering it is possible to assess the length of the long and short spacings of the lipid lattice. It is highly recommended to measure changes of the SLN dispersion because solvent removal will lead to modifications. Sensitivity problems and long measurement times of conventional X-ray sources might be overcome by synchrotron irradiation (Westesen *et al.*, 1993). Infrared and Raman spectroscopy are useful tools for investigating structural properties of lipids (Garti *et al.*, 1998).

Acoustic methods

Acoustic spectroscopy measures the attenuation of sound waves are a means of determining sizes 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.

Nuclear magnetic resonance (NMR)

Nuclear magnetic resonance (NMR) can be used to determine both the size and the qualitative nature of SLNs. Any modification in functional groups can be detected by NMR spectroscopy.

Surface element analysis

It can be analyzed by Electrophoresis and Laser Doppler anemometry methods.

Polydispersity Index

As SLNs/NLCs are usually polydisperse in nature measurement of polydispersity index (PI) is important to know the size distribution of the nanoparticles. The lower the PI value, the more monodispered the nanoparticle dispersion is. Most of the researchers accept PI value less than 0.3 as optimum value. PI can be measured by PCS.

In-vitro and *ex-vivo* methods for the assessment of drug release from SLNs

Various methods used to study the *in vitro* release of the drug from SLNs

IN-VITRO DRUG RELEASE

Dialysis tubing

In-vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in a prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for drug content using a suitable analytical method (U.V. spectroscopy, HPLC etc.). The maintenance of sink conditions is essential. This method however suffers from the limitation of a lack of direct dilution of the SLNs by the dissolution medium. The drug release of camptothecin SLN using a dynamic dialysis method in phosphate buffered saline has been reported.

Reverse dialysis

In this technique a number of small dialysis sacs containing 1 ml of dissolution medium are placed in SLN dispersion. The SLNs are then displaced into the dissolution medium. The direct dilution of the SLNs is possible with this method; however the rapid release cannot be quantified using this method.

Franz diffusion cell

The solid lipid nanoparticle dispersion is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The dispersion is then dialyzed against a suitable dissolution medium (simulated gastric medium/simulated intestinal medium/simulated plasma) at room temperature, the samples are withdrawn from the dissolution medium at suitable intervals and analyzed for drug content using a suitable instrumental method (U.V. spectroscopy, HPLC). The maintenance of sink condition is essential and the method suffers from

the limitation of lack of direct dilution of the SLNs by the dissolution medium.

EX-VIVO MODEL FOR DETERMINING PERMEABILITY ACROSS THE GUT

Ahlin et al. demonstrated passage of Enalaprit SLNs across rat jejunum. In short, the rat jejunum was excised from the rats after sacrificing the animal. The jejunum 20–30 cm distal from the pyloric sphincter was used. The jejunum was rinsed to remove the luminal contents after washing with ice cold standard Ringer solution. The tissue was then cut into segments, opened up along the mesenteric border and placed between two Easy Mount side-by-side diffusion chambers with an exposed tissue area of 1 cm2 . The mucosal side was bathed with ringer buffer containing 10mM mannitol and the serosal side with ringer buffer containing 10mM glucose. The enalaprilat loaded nanoparticles were placed on the mucosal side, dispersed in ringer containing the paracellular transporter sodium fluorescein confirming for tissue integrity. Similar type of study will be carried out here also.

Animals and administration of drug formulations

Male Wistar rats and Swiss albino mice are used for pharmacokinetic and tissue distribution studies, respectively.

Intraduodenal administration

Rats are anaesthetized by an intraperitoneal injection of 60 mg/kg of thiopentone sodium (short acting anaesthetic agent). Small incisions are made at abdomen, duodenum is located and similar formulations are administered directly into the duodenum with syringe. Blood samples are collected and processed as described in intravenous route.

Biodistribution studies

Tissue distribution studies are carried out in Swiss albino mice after a 7-day acclimatization period. At predetermined time points (like 15, 30, 45, 60, 90, 120, 180, 360 and 720 min) three animals at each time point from each group is given anaesthesia and blood is collected via cardiac puncture. Tissues of interest (brain, liver, spleen, kidney, and heart) are collected immediately after cervical dislocation at different time points and they were blotted dry with tissue paper. Serum and tissue samples are frozen at -20 0C until analysis.

Serum and tissue sample analysis

Serum and tissue samples are evaluated. The method involves extraction of drug. The data is recorded and calculated using Winchrome software.

Pharmacokinetic analysis

Serum concentration versus time data for drug in individual rats are analyzed by non-compartmental estimations using WinNonlin software (version 1.1). Relative bioavailability (F) of SLNs are obtained. Maximum serum concentration (Cmax) and the time to reach Cmax (Tmax) are taken directly from the observed concentration versus time profiles. The area under the concentration– time curve (AUC) and the area under the first moment curve (AUMC) is calculated using the linear trapezoidal rule. Mean residence time (MRT) is determined by dividing AUMC by AUC. The relative bioavailability (Fr) is defined as ratio of AUC of drug loaded SLN to the AUC of other drug formulation when same doses are administered and calculated [28].

Storage stability of SLN

The physical properties of SLN's during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity as the function of time. External parameters such as temperature and light appear to be of primary importance for long term stability. The zeta potential should be in between -100 to + 100 mV for a dispersion to remain physically stable.

4^{o}C - Most favorable storage temperature.

20^{o}C - Long term storage did not result in drug loaded SLN aggregation or loss of drug.

50^{o}C - A rapid growth of particle size is observed.

Effect of sterilization

To see the effect of sterilization on particle size, zeta potential and entrapment efficiency, blank and drug dispersions are autoclaved at 121°C for 20 min.

Statistical analysis

Size and entrapment efficiency of SLNs are compared using the Student's t-test. Statistical analyses are also performed.

Routes of Administration and Applications of SLN's in drug delivery

The *in vivo* behavior of the SLN particles will mainly depend on the following points: Interactions of the SLN with the biological surroundings including: distribution processes (Adsorption of biological material on the particle surface and desorption of SLN components into to biological surroundings) and enzymatic processes. Various administration routes are,

Parenteral administration

Peptide and proteins drugs are usually available for parenteral use in the market. Since theirconventional oral administration is not possible due to enzymatic degradation in GI tract. Parenteralapplication of SLN reduces the possible side effects of drug incorporated with the increased bioavailability.These systems are very suitable for drug targeting.

Oral administration

Controlled release behavior of SLNs is reported to enable the bypass of gastric and intestinal degradation of the encapsulated drug, and their possible uptake and transport through the intestinal mucosa .However, the assessment of the stability of colloidal carriers in GI fluids is essential in order to predict their suitability for oral administration.

Rectal administration

When rapid pharmacological effect is required, in some circumstances, parenteral or rectal Administration is preferred. This route is used for pediatric patients due to easy application.

Nasal administration

Nasal route is preferred due to its fast absorption and rapid onset of drug action also avoid in degradation of labile drugs in the GIT and insufficient transport across epithelial cell layers.

Respiratory delivery

Nebulisation of solid lipid particles carrying anti-tubercular drugs, anti-asthmatic drugs and anticancer was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary action.

Transdermal administration

Since the epidermal lipids are found in high amounts in the penetration barrier, lipid carriers (liposomes, SLN, NLC *etc*.) attaching themselves to the skin surface and allowing lipid exchange between the outermost layers of the stratum corneas and the carrier appear promising. Incorporation of SLN dispersion in an ointment or gel, by reduction of the lipid content of the SLN dispersion, is necessary to achieve a formulation that can be easily administered to the skin.

Ocular administration

Biocompatibility and muco-adhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting.

Topical administration

SLN are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids.

Targeted delivery

One of the most challenging aspects in pharmaceutical research is targeted delivery of drug molecules to a specific organ, tissue or specific cellular sites. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles, a new frontier was opened for improving drug delivery. However, despite these challenges, nano drug delivery is a development that cannot be ignored and so the challenges will be tackled with time.

There are several potential applications of SLNs, some of which are given below:

SLNs in tuberculosis disease (Pandey *et al*., 2005)

Antitubercular drugs such as rifampicin, isonizide, pyrazinamide-loaded SLN systems are

able to decrease the dosing frequency and improve patient compliance.

SLNs for parasitic diseases

Antiparasitic therapy is the only choice of treatment for parasitic infections. The reason being that these infections do not elicit pronounced immune response hence effective vaccination may not be possible. SLN due to their small particle size and inherent structure, exhibit good potential in the treatment of parasitic infections like malaria, leishmaniasis etc

SLN as targeted carrier for anticancer drug to solid tumor

SLNs are useful as drug carriers to treat neoplasms (Shenoy *et al*., 2005). Tumor targeting has been achieved with SLNs loaded with drugs such as methotrexate (Ruckmani *et al*., 2006) and camptothecin (Yang et al., 1999). Tamoxifen, an anticancer drug is incorporated in SLN to prolong release of drug after i.v. administration.

Stealth nanoparticles

These provide a novel and unique drug-delivery system they evade quick clearance by the immune system. Such nanoparticles can target specific cells. Stealth SLNs have been successfully tested in animal models with marker molecules and drugs. Antibody labelled stealth Lipobodies have shown increased delivery to the target tissue in accessible sites.

SLN as Gene vector carrier

SLN can be used in the gene vector formulation (Rudolph *et al*., 2004). Several reports of SLNs carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids are reported (Hayes *et al*., 2006). The gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide(TAT 2) into SLN gene vector. The lipid nuclicacid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid andDNA are separately dissolved by removing the organic solvent, stable and homogeneously size dlipid-nuclic acid nanoparticle (70-100 nm) wereformed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

SLNs are used for Potential Agriculture Application

Essential oil extracted from *Artemisia arboreseens* incorporated in SLN is able to decrease the rapid evaporation in comparison to emulsions and these systems are used in agriculture as an appropriate carrier of ecologically safe pesticides (Lai *et al*., 2006). The SLN were prepared here by using Compritol 888 ATO as lipid and Poloxamer 188 or Miranol Ultra C32 as surfactant.

SLNs are widely used for Topical Use

SLNs are used as topical formulations of various drug like anticancer drugs (Chen *et al*., 2006), Vitamin-A (Jenning *et al* 2006), Isotretinoin, Flurbiprofen (Santos *et al*., 2002). Vitamin A-loaded SLNs can be prepared using glyceryl behenate. This method is useful for improving the penetration as well as to obtain sustained release effects. Isotretinoin-loaded SLNs are formulated for topical delivery of drug. Formulation of the Flurbiprofen-loaded SLN gel for topical application provides an advantage of delivering the drug directly to the site of action, which will give higher tissue concentrations. Miconazole nitrate loaded SLN were prepared by modified solvent injection method and characterized for surface morphology, particle size and drug entrapment. Corticosteroids are therapeutic agents generally used in the treatment of skin diseases such as eczema or psoriasis. Topical SLN products show enormous prospective for treating dermatological conditions by targeting corticosteroids to dermal disease sites while decreasing systemic drug absorption.

Solid lipid nanoparticles for antimicrobial drug delivery

SLNs contain occlusive excipients that, upon appliance on skin, readily form a thin film to lessen water evaporation and retain skin moisture. This occlusive property promotes molecule penetrations into the skin. SLNs encapsulated antimicrobial agents such as retinol and retinylpalmitate have shown better drug penetration rate and slower drug expulsion than the free drug counterparts. SLNs can facilitate the delivery of anti-tuberculosis drugs such as Rifampin, Isoniazid and Pyrazinamide to the lungs as well as to the lymphatic systems. SLNs

can provide a sustained release of the carried antimicrobial payloads, which then can effectively eliminate the infectious microbes harbored at these lymphatic sites.

SLNs for liver targeting

Liver-targeting SLNs with a hepatoprotective drug, cucurbitacin B (Cuc B), using a galactosylated lipid, N-hexadecyl lactobionamide (N-HLBA) were prepared. The galactosyl-lipid N-HLBA was prepared via the lactone form intermediates of lactobionic acid and synthesized by anchoring galactose to hexadecylamine lipid. The Cuc B-loaded galactosylated SLNs and conventional SLNs were successfully prepared by a high-pressure homogenization method. The encapsulation of Cuc B in SLNs resulted in the improvement of cytotoxic activity and galactosyl ligand could further improve the cellular accumulation and cytotoxicity of Cuc B. The incorporation of N-HLBA into SLNs considerably improved the liver targetability of Cuc B-loaded SLNs and galactosylated SLN had a great potential as a drug delivery carrier for improved liver targetability. The different drugs incorporated in SLNs for different therapeutic activities were summarised in table 3.

Solid Lipid Nanoparticles for Lymphatic Targeting

The solid lipid nanoparticles (SLN) were developed and evaluated for the lymphatic uptake afterintraduodenal administration to rats.

SLN as carriers for peptides and Protein and delivery

Increasing attention has been paid to the pulmonary route for systemic delivery of peptide and protein drugs, such as insulin. The SLN production is based on solidified emulsion (dispersed phase) technologies. Therefore, due to their hydrophilic nature most of proteins are expected to be poorly microencapsulated into the hydrophobic matrix of SLN, tending to partition in the water phase during the preparation process, which is further enhanced by the use of surfactants as emulsion stabilizers. Therapeutically relevant peptides (e.g. calcitonin, cyclosporine a, somatostatin), protein antigens (e.g.hepatitis B and malaria antigens) and model protein drugs (e.g. bovine serum albumin and lysozyme) have been investigated for drug release kinetics, protein stability and *in vivo* performance.

Solid Lipid Nanoparticles for Targeted Brain Drug Delivery

The extremely small particle size of solid lipid nanoparticles, which are less than 50 nm, might be beneficial with respect to drug targeting. Small carrier size generally favors reduced uptake by the reticuloendothelial system. Drug targeting might also be possible by surface modification of solid lipid nanoparticles. SLNs can improve the ability of the drug to penetrate through the blood-brain barrier and is a promising drug targeting system for the treatment of central nervous system disorders. 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)[41]. The state of the art on surfactant coated poly (alkylcyanoacrylate) nanoparticles specifically designed for brain targeting is given by emphasizing the transfer of this technology to solid lipid matrices. One approach of drug targeting is the incorporation of the substance into colloidal carriers such as polymeric nanoparticles, or solid lipid nanoparticles (SLNs) which have been used for intravenous injection. The next challenge is to direct the colloidal drug carriers to the desired site of action e.g. tumor tissue or brain. After intravenous injection, particles immediately interact with plasma proteins. The adsorbed plasma protein patterns are regarded as the determining factor for the *in vivo* fate of the carriers. The blood–brain barrier (BBB) represents a strict barrier for water-soluble, charged and high molecular weight drugs. Mistry *et al.* suggested that the existence of a direct nose-to-brain delivery route for nanoparticles administered to the nasal cavity and transported *via* the olfactory epithelium and/or the trigeminal nerves directly to the CNS is relevant in the field of drug delivery as well as new developments in nanotechnology [29].

Transfection Agent

Cationic SLNs for gene transfer are formulated using the same cationic lipid as for liposomaltransfection agents. The differences

and similarities in the structure and performance between SLN and liposomes were investigated. PCS showed that the prepared SLNs were smaller in diameter than the corresponding liposomes while AFM supported the expected structural differences. DNA binding differed only marginally. Cationic lipid composition governs the in vitro transfection performance than the colloidal structure it is arranged in. Hence, cationic SLN extends the range of highly potent non-viral transfection agents by one with favorable and distinct technological properties. Combination of cationic SLN with the nuclear localization signal TAT2 increased transfection efficiency hundredfold.

SLN for Improved Delivery of Antiretroviral Drugs to the Brain

Human immunodeficiency virus (HIV) can gain access to the central nervous system during theearly course of primary infection. Once in the brain compartment the virus actively replicates to form anin dependent viral reservoir, resulting in debilitating neurological complications, latent infection and drug resistance. 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 nano carriers, significant increase in the drug bioavailability to the brain is expected to be achieved. Recent studies show that the specificity and efficiency of ARVs delivery can be further enhanced by using nanocarriers with specific brain targeting, cell penetrating ligands or ABC transporters inhibitors. Futurere search should focus on achieving brain delivery of ARVs in a safe, efficient, and yet cost-effective manner.

SLN in cosmetics

Solid lipid nanoparticles (SLN) are novel delivery systems for pharmaceutical and cosmetic active ingredients. SLN possess some features which make them promising carriers for cosmetic applications: (Wissing *et al*., 2001):

- The protection of labile compounds against chemical degradation has been shown, e.g. forretinol and tocopherol.
- Depending on the produced SLN-type, controlled release of the active ingredients is possible. SLN with a drug-enriched shell show burst release characteristics whereas SLN with a drug-enriched core lead to sustained release.
- SLN act as occlusive's, i.e. they can be used in order to increase the water content of the skin.
- SLN show a UV-blocking potential, i.e. they act as physical sunscreens on their own and can be combined with molecular sunscreens in order to achieve improved photo protection.

Solid lipid nanoparticles for parasitic diseases

Antiparasitic chemotherapy is the only choice of treatment for parasitic infections like malaria, leishmaniasis, tryanosomiasis the reason for this is that these infections do not elicit pronounced immune response hence effective vaccination may not be possible. Solid lipid nanoparticles (SLNs) and nano structured lipid carriers (NLCs) represent a second generation of colloidal carriers and have emerged as an effective alternative to liposomes mainly due to their better stability profile, ease of scalability and commercialization and relative cost efficacy. Moreover, SLN and NLC due to their particulate nature and inherent structure exhibit good potential in the treatment of parasitic infections. Recent reports including our investigation have validated their utility at least to some extent. However, the need of hour is to undertake extensive investigations on SLN and NLC matrices in order to extend their versatility with respect to encapsulation ability and target ability and effective and economical approach for the delivery of anti-parasitic drugs.

Solid lipid nanoparticles for ultrasonic drug and gene delivery

Drug delivery research employing micelles and nanoparticles has wide application in ultrasonic drug and gene delivery in recent years. Of particular interest is the use of these nano vehicles that deliver high concentrations of cytotoxic drugs to diseased tissues selectively, thus reducing the

agent's side effects on the rest of the body. Ultrasound, traditionally used in diagnostic medicine, is finding a place in drug delivery in connection with these nanoparticles. In addition to their non-invasive nature and the fact that they can be focused on targeted tissues, acoustic waves have been credited with releasing pharmacological agents from nanocarriers, as well as rendering cell membranes more permeable. Ultrasonic drug delivery from micelles usually employs polyether block copolymers and has been found effective in vivo for treating tumors. Ultrasound releases drug from micelles, most probably via shear stress and shock waves from the collapse of cavitation bubbles. Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes *in vitro* and *in vivo*. The small packaging allows nanoparticles to extravasate into tumor tissues. Ultrasonic drug and gene delivery from nanocarriers has tremendous potential because of the wide variety of drugs and genes that could be delivered to targeted tissues by fairly non-invasive means.

SLNs in breast cancer and lymph node metastases

Photodegradation and low bioavailability are chief hurdles for the therapeutic use of curcumin. Transferrin-mediated SLNs were formulated to increase photo stability and enhance its anticancer activity against MCF-7 breast cancer cells. The anticancer activity of curcumin is enhanced with transferrin-mediated SLNs compared to curcumin solubilized surfactant solution and apoptosis is the mechanism underlying the cytotoxicity. Mitoxantrone-loaded SLNs local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug. Efficacy of doxorubicin has been reported to be enhanced by incorporation in SLNs. Doxorubicin was complexed with soybean-oil-based anionic polymer and dispersed collectively with a lipid in water to form doxorubicin loaded solid lipid nanoparticles. The system has improved its efficacy and reduced breast cancer cells [30].

Table 2: A List of Drugs and Polymers Used for the Preparation of SLNS using Different Methods

Drug	Polymer	Method of preparation
Diazepam	Compritol® 888; glyceryl palmitostearate	High-shear homogenization and ultrasound techniques
Olanzapine	Hydrogenated soyaphosphatidyl choline	Modified high pressure homogenization
Clozapine	Dynasan114,116	Hot homogenization
Vitamin A	Compritol 888ATO, Miglyol 812	Hot homogenization
Retinol	Dynasan 116	Hot homogenization
Alendronate NP	PLGA, Ethyl acetate, PF68	Double emulsion solvent diffusion
Insulin	PEG'Glycolgrafted chitosan	Ionic gelation
Paclitaxel	Tripalmitin, phosphatidylcholine	Microemulsion
Insulin	Hydrophobized cholesterol bearing pullulan	Ultra sonication
Vinpocetine	Glyceryl monostearate, DCM, soyalecithin	Ultrasonic solvent emulsification
Insulin	Cetyl palmitate	Solvent emulsification evaporation
Mitoxantrone	Glyceryl behenate, Campritol 888ATO, lecithin	Ultra sonication
Insulin	Cetyl palmitate	Solvent emulsification evaporation
5-Fluorouracil	Dynasan 114, 118, triglyceride, soyalecithin	Double emulsion Solvent evaporation
Methotrexate	Cetyl alcohol, Campritol 888 ATO, Tween 80	Microemulsion congealing technique
Domperidone	Dynasan 114, cetyl resinoleate, soy phosphotidylecholine 99%	Hot homogenization
Amikacin	Cholesterol, Tween 80	Solvent diffusion technique and homogenization
Lamivudine	Stearic acid, PVA	Emulsion solvent diffusion technique
Itraconazole	Pluronic, tween	Microemulsion dispersion technique
Adefovil	poloxamer 188, stearic acid,	Solvent diffusion method

Risperidone	Compritol 888 ATO, sodium lauryl sulphate	Solvent evaporation method
Atazanavir	Pluronic®F-68	Thin film hydration technique
Ofloxacin	Palmitic acid, poly vinyl alcohol	Hot homogenization and ultrasonication method
Tetrandrine	Precirol® ATO 5, glyceryl monostearate, stearic acid	Melt–emulsification and ultrasonication technique
Terbinafine	Sodium alginate, Chitosan	Microemulsion technique
Miconazole	Compritol 888 ATO, propylene glycol, tween 80, and glyceryl monostearate	Hot homogenization method
Doxorubicin	Glyceryl caprate, curdlan	Solvent emulsification-diffusion method
Vinorelbine itartrate	Glyceryl monostearate	Cold homogenization
Cryptotanshinone	Compritol 888 ATO	Ultrasonication or high speed homogenization
Saquinavir	Stearylamine	Micro emulsion technique
Indomethacin	Tripalmitin	Supercritical fluid technology
Oxybenzone	Tristearin	Solvent injection technique
Saquinavir	Stearylamine	Micro emulsion technique
Stearic acid	Stearic acid	Solvent emulsification-evaporation technique

Table 3: Shows List of Drugs Incorporated In SLNS

Pharmacological activity	**Drugs**
Hormonal Drugs	Hydrocortisone, Cortisone, Prednisolone, Deoxycorticosterone, Progesterone, Estradiol, Mifepristone, Betamethasone, Sildenafil Citrate, Insulin.
Antifungal Drugs	Ketoconazole, Miconazole, Itraconazole, Econazole, Terbinafine, Amphotericin.
Cardiovascular Drugs	Verapamil, Nifedipine, Nitrendipine.
Antiviral Drugs	Aciclovir, Saquinavir, Penciclovir, Adefovir, Dipivoxil, Thymopentin, 3-Azida-3-deoxyuridine, Oxymetrine, Quinine, Choloroquine.
Anticancer Drugs	Camptothecin, Etoposide, Paclitaxel, Docetaxel, Vinorelbine, Vinpocetine Doxorubicin, Idarubicin, Adriamycin, Mitoxantrone, Methotrexate, 5-Fluorouracil, Oxaliplatin, Tamoxifen, Ubidecarenone, Cholesteryl Butyrate, Chlorambucil, Temozolomide, β-elements, Podophyllotoxin, All trans retinoic acid.
Antitubercular Drugs	Rifampicin, Isoniazid, Pyrazinamide.
Antibacterial Drugs	Ciprofloxacin, Tobramycin, Clotrimazole
Vitamins	Vitamin-A, Vitamin-E, Vitamin-K, Ascorbyl Palmitate, Retinol.
Antifungal Drugs ,	Ketoconazole, Miconazole, Itraconazole, Econazole, Terbinafine, Amphotericin.
Drugs acting on Nervous System	Diazepam, Oxazepam, Carbamazepine
Anxiety and Epilepsy	Olanzapin
Antipsychotic Drugs	Risperidone, Clozapine
Parkinson's disease Drugs	Piribedil
Immunosupressant Drugs	Cyclosporin, Tacrolimus
Antiretroviral	Zidovudine, Saquinqvir
Glaucoma Drugs	Timolol, Pilocarpine, Tetracaine.
Hypolipidaemic Drugs	Lovastatin, Simvastatin
Anaesthetic drugs	Actarit

Anaesthetic drugs	Etomidate
Antiarthritic Drugs	Reserpidone
Adrenergic Dru	Domperidone
Antiemetic Drugs	Praziquantel
Anthelmintic Drugs	Praziquantel
Antiasthmatic Drugs	Sodium Cromoglycate
Steroidal Drugs	Clobestasol Propionate
Antidiabetic Drugs	Repaglinide, Insulin
Antiparkinsonism	Apomorphine
Sunscreen	Oxybenzone, Tocopherol acetate
Tuberculosis	Rifampicin, Isoniazid

CONCLUSION

SLNs are a type of lipid nanoparticles and proven to be promising drug carriers prepared from physiologically safe lipids and emulsifiers. They are more beneficial than liposomes, emulsions and polymeric nanoparticles in terms of safety, drug loading capacity, modulated release profiles and stability of encapsulated drugs. They can be prepared with easily scalable advance techniques. Best SLN formulation is prepared by optimizing type and concentration of lipids/emulsifiers. The problems related with SLNs are drug expulsion from lipid matrix and loading of hydrophilic drugs. By using combination of solid lipid and liquid lipid to prepare lipid matrix, loading capacity can be enhanced and drug expulsion can be minimized. Hence SLNs are novel formulations which can open new areas of drug delivery systems. SLN offer an effective, promising, economical and patient-friendly device for administration of drugs by various routes and we can expect many patented dosage forms in the form of SLNs in the future.

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