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REVIEW ARTICLE

Engineering solid lipid nanoparticles for improved drug delivery: promises and challenges of translational research

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Abstract Nanotechnology is expected to revolutionize existing drug delivery. Many nanostructured systems have been employed for drug delivery and yielded some promising results. Solid lipid nanoparticles (SLN) have been looked at as a potential drug carrier system since last two decades. SLN do not show biotoxicity as they are prepared from physiological lipids. SLN are especially useful in drug delivery as they can enhance the absorption of drugs and improves the bioavailability of both hydrophilic and lipophilic drugs. This paper presents an overview about the various classes of SLN, comparison with available drug carrier systems, different ways of production, in vivo fate and biodistribution and various applications of SLN. Besides, aspects of stability, hurdles and strategies for SLN manufacturing with potential of clinical translation are also discussed.

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List of abbreviations

NDDS	Novel drug delivery system
SLN	Solid lipid nanoparticles
DDS	Drug delivery system
NLC	Nanostructured lipid carriers
SCF	Supercritical fluid technology
SFEE	Supercritical fluid extraction of emulsions
GAMA	Gas-assisted melting atomisation
O/W	Oil-in-water
CM	Mixing chamber
TEM	Transmission electron microscopy
SEM	Scanning electron microscopy
PCM	Phase contrast optical microscopy
AFM	Atomic force microscopy
PCS	Photon correlation spectroscopy
SAX	Synchrotron radiation X-ray
GPC	Gel permeation chromatography
SWCNT	Single-walled carbon nanotubes
TMS	Thermosensitive magneto liposomes
MTX	Methotrexate
MBC	Metastatic breast cancer
PNET	Phase nanoparticle engineering technology
cSLN	Cationic solid lipid nanoparticles
PTX	Paclitaxel
ADA	Adenosine deaminase
DNA	Deoxyribonucleic acid

Introduction

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic

objectives while minimizing side effects. Novel means of delivery particularly using nanocarriers, can allow branded drugs to be rescued from a bypass of generic competition (may be called "resurrection of drug"). Nanocarriers, in various forms, have the possibility of providing endless opportunities in the area of drug delivery and therefore are increasingly investigated to explore their application potential. During the last two decades, considerable attention has been given to the development of novel drug delivery system (NDDS) [1–3]. The rational for control drug delivery is to alter the pharmacokinetics and pharmacodynamics of drug substance in order to improve the therapeutic efficacy and safety through the use of novel drug delivery system [4, 5].

Although, the drug delivery system (DDS) concept is not new, great progress has recently been made in the treatment of a variety of diseases. Targeted delivery of drugs to the diseased lesions is one of the most important aspects of DDS [6, 7]. To convey a sufficient dose of drug to the lesion, suitable carriers of drugs are needed. These drug carriers can be broadly classified according to the specific needs of the therapy and ranges from few nanometers (colloidal carriers), to the micrometer range (microparticles) and to several millimeters (implants) [8, 9].

Implants and microparticles are too larger than nanoparticles for drug targeting and intravenous administration. Therefore, colloidal carriers especially nanoparticulates have attracted increasing attention during recent years. Investigated systems include nanoparticles, nanoemulsions, liposomes, nanosuspensions, micelles, soluble polymer–drug conjugates [10, 11]. Nano- and microparticles for their attractive properties occupy unique position in drug delivery technology [5, 12]. Recent trends indicate that, NDDS are especially suitable for achieving controlled or delayed release formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and high therapeutic indices [5, 12–14].

Besides more traditional matrix or reservoir drug delivery system, colloidal drug delivery system has been investigated primarily for site-specific drug delivery, for controlled drug delivery, and also for the enhancement of dissolution rate/bioavailability of poorly water-soluble drugs [15–17]. They improve the solubility of hydrophobic compounds and render them suitable for parenteral administration. Nanotechnology is a new direction in science and technology, which is intensively developed during the last decade and represents one of the most important directions in the technological developments of the leading countries in the twenty-first century [11]. By analogy with existing microtechnologies, the nanotechnologies may be considered as the technologies operating with nanometre objects [18].

Nanoparticulate drug delivery systems are being explored for the purpose of solving the challenges of drug delivery. NDDS provide methods for targeting and releasing therapeutic compounds in very defined regions. These vehicles have the potential to eliminate or at least ameliorate many problems associated with drug distribution [8, 19–21].

NDDS can be defined as the DDS where nanotechnology is used to deliver the drug at nanoscale. Below 100 nm, materials exhibit different, more desirable physical, chemical, and biological properties. Nanoparticles were first developed in around 1970s, as carriers for vaccines and anticancer drug delivery with the aim to release the drug in the vicinity of target tissue [19, 22, 23]. For these purposes, primary routes of administration under investigation are parenteral route; however, other routes such as the oral, ocular, or topical routes are also being investigated [24, 25]. The nanoparticles (NPs) may offer some advantages such as protection of drugs against degradation, targeting the drugs to specific sites of action, organ or tissues, and delivery of biological molecules such as proteins, peptides, and oligonucleotides [26]. A number of different strategies have been developing which can modify the physicochemical characteristics of the NPs, and thus their interactions within the biological systems (Fig. 1).

Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) are novel colloidal delivery systems consist of a biocompatible lipid core and an amphiphilic surfactant as an outer shell with a mean diameter ranging from 50 to 1,000 nm [12]. These represent an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes, and polymeric micro- and nanoparticles. In the 1980s, Speiser and co-workers first reported SLN for drug delivery applications [27, 28]. These are aqueous colloidal dispersions, the matrix of which comprises of solid biodegradable lipids. These solid lipids are used instead of liquid oils offers a very attractive idea to achieve controlled drug release, because drug mobility in a solid lipid should be considerably lower compared with a liquid oil. Solid lipids have been used for several years in the form of pellets in order to achieve a retarded drug release after peroral administration (e.g. Mucosolvan® Retard Capsules) [20]. In contrast to other available conventional dosage forms, colloidal carriers prove to be best (Table 1). There colloidal dimensions and the controlled release behavior enable drug protection and administration by parenteral and non-parenteral routes thus emphasizing the versatility of this nanoparticulate carrier [4].

Advantages of SLN [12, 16, 29]

- Small in size and relatively narrow size distribution which provide biological opportunities for site specific drug delivery

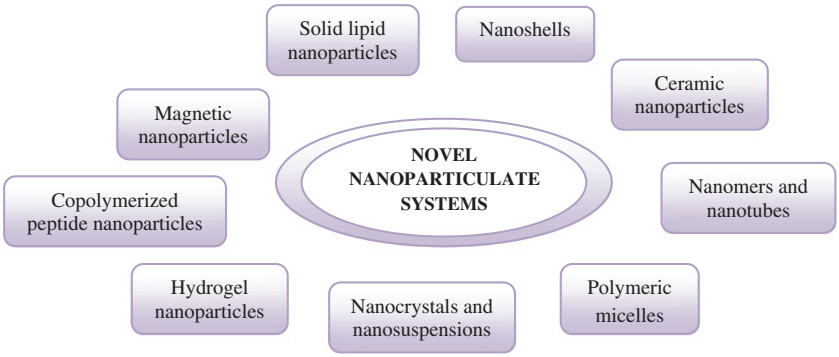

Fig. 1 Classification of novel nanoparticulate system

- Controlled release of active drug over a long period can be achieved
- Protection against chemical degradation of drug
- Possible sterilization by autoclaving and gamma irradiation [8]
- They can be lyophilised as well as spray dried
- No toxic metabolites are produced
- Avoidance of organic solvents
- Ease of industrial scale production by hot dispersion technique
- Surface modification can easily be accomplished which offer potential for site-specific drug delivery

Classification of SLN

Various classes of SLN are commercially available which predicts the nature of the formulation and simultaneously the release profile [1] (Fig. 2). SLN offers combitorial advantages of both traditional systems and novel system of medicine but avoids the lacuna/short comings associated with traditional systems. They exhibit major advantages such as modulated release, improved bioavailability, protection of chemically labile molecules like retinol, peptides from degradation, cost effective excipients, improved drug incorporation, and wide application spectrum [1, 2]. However, there are certain limitations associated with SLN, like limited drug loading capacity and drug expulsion during storage, which can be minimized by the next generation of solid lipids, Nanostructured lipid carriers (NLC). NLC are lipid particles with a controlled nanostructure that improves drug loading and firmly incorporates the drug during storage [10, 16, 29]. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. Owing to their properties and advantages, SLN and NLC may find extensive application in topical drug delivery, oral, and parenteral administration of cosmetic and pharmaceutical actives. Cosmeceuticals is emerging as the biggest application target of these carriers. Carrier systems like SLN and NLC were developed with a perspective to meet industrial needs like scale up, qualification, and validation, simple technology, low cost etc. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary

Table 1 Comparison of conventional available dosage forms with colloidal carriers [19, 22, 26, 27]

Dosage form	Comments
Tablets and capsules	Convenient and commonest dosage forms but likely to be imperfect as drug cannot be absorbed in the alimentary tract or if the patient (geriatric and pediatric) cannot swallow them
Injections and infusions	Rapid action but impractical for treating chronic (long term) illness
Pessaries and suppositories	These can deliver the drug to particular area where required but have limited general use
Solutions, suspensions and elixirs	Useful for geriatric and pediatric but are bulky and less useful if the drug is unpalatable or unstable in presence of water
Ointments, creams and paints	Restricted to topical application
Aerosol and dry powder inhalations	Site-specific especially design to deliver drugs to lungs but can be difficult to administer the dose correctly
Transdermal patches	Convenient if the dose needs to be released over a long period but can cause irritation
Colloidal carriers	By pass first pass metabolism; provide site specific and maintains desired concentration of drug by facilitating both control and sustained release profile effectively

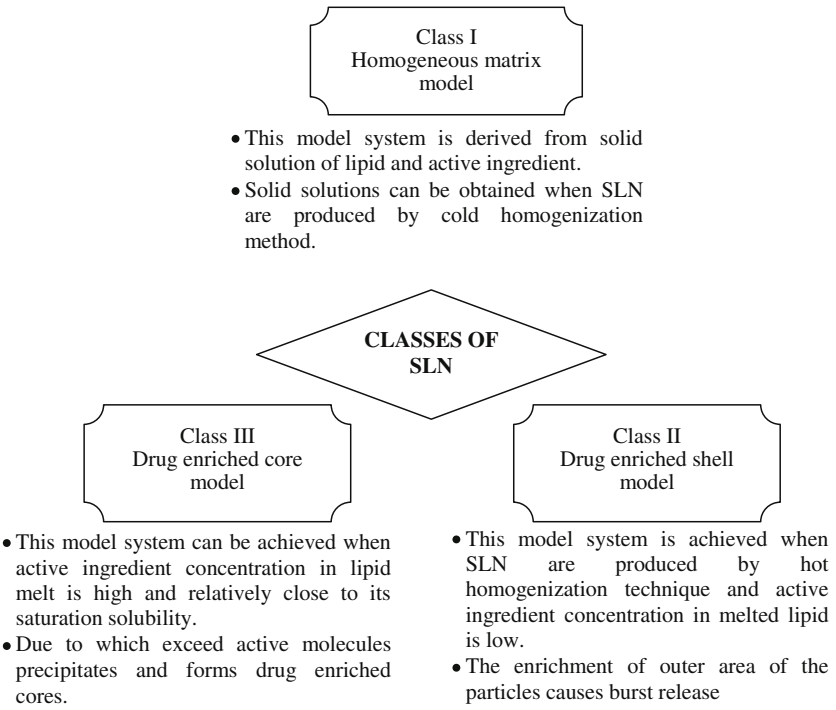

Fig. 2 Classes of SLN

levels of drug targeting [15]. Table 2 illustrates comparison between various drug carrier systems.

Methods of preparation of SLN

The production of SLN can be realized by various techniques. Generally, all these techniques require a common step, that is, the formation of a precursor oil-in-water "nanoemulsion" followed by subsequent solidification of the dispersed lipid phase [7]. To overcome the polydispersity and larger than desired droplet sizes, researchers often subject the precursor emulsions to large mechanical forces. For this purpose, two main techniques were then established: the high-pressure homogenisation described by Muller and

Table 2 Comparison of available novel drug carrier system [11, 25]

Sample no.	Properties	SLN	Polymeric nanoparticles	Liposomes	Lipid emulsion
1	Definition	Submicron colloidal carriers (50–1,000 nm) which are composed of phospholipids	Sub nano-sized colloidal structure composed of synthetic/ semi-synthetic polymers	Outer bilayer of amphipatic molecules (phospholipids) with an aqueous component inside (phospholipids)	Neutral lipophilic oil core surrounded by mono-layer of amphilic lipid
2	Systemic toxicity	Low	> or = SLN	Low	Low
3	Cytotoxicity	Low	> or = SLN	Low	Low
4	Residue from organic solvent	No	Yes	May/may not	No
5	Large scale production	Yes	No	Yes	Yes
6	Sterilization by autoclave	Yes	No	No	Yes
7	Sustained release	Yes	Yes	< or = SLN	No
8	Avoidance of reticoendothelial system	Yes	No	Yes	Yes

Runge [20] and the microemulsion-based technique. Unlike most polymeric microsphere and nanoparticles systems, SLN production techniques do not need to employ potentially toxic organic solvents, which may also have deleterious effect on protein drugs [30, 31]. Preparation of SLN were reported to be a more cost effective and technically more simple alternative, particularly for poorly soluble drugs and yield a physically more stable product than liposomes; conventional colloidal drug carriers. There are various methods for preparation of SLN which includes (Fig. 3):

1. Hot homogenization technique [8, 30]

   Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (Ultra-Turrax®). The quality of the pre-emulsion is vital important as it affects the quality of the final product to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. High pressure homogenisation of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase [20]. The homogenization step can be repeated several times to get desired output (Fig. 4a).
2. Cold homogenization technique

   In this technique, homogenization is carried out by using solid lipid and thus, called as high pressure milling of a suspension. Effective temperature control and regulation is needed in order to ensure the unmolten state of the lipid due to the increase in temperature during homogenization [32]. Cold homogenization offers strategies to over-come short coming associated with hot homogenization technique includes:

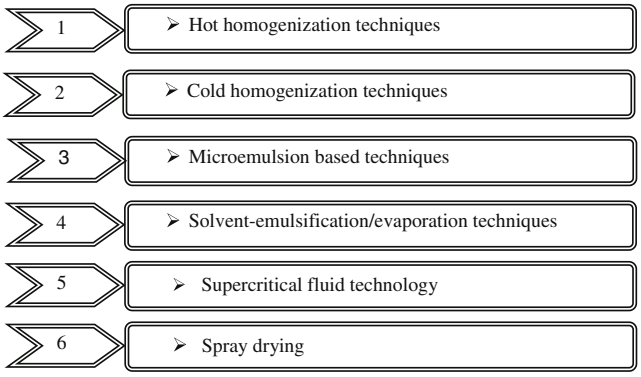

Fig. 3 Manufacturing techniques for SLN

   1. Temperature-induced drug degradation
   2. Drug distribution into the aqueous phase during homogenization
   3. Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super-cooled melts

   In formulating SLN by hot/cold homogenization techniques some of the steps are common. The drug containing melt is rapidly cooled (e.g. by means of liquid nitrogen or dry ice) which favors a homogenous distribution of the drug within the lipid matrix (Fig. 4b).
3. Microemulsion-based SLN preparations

   These methods of SLN preparation are based on the dilution of microemulsion [33, 34]. Preparative steps involves stirring of an optically transparent mixture at 65–70 °C, so as to form microemulsion, which is typically composed of a low-melting fatty acid, an emulsifier, co-emulsifiers, and water. The hot microemulsion is dispersed in cold water (2–3 °C) under stirring [35]. The dilution process is critically determined by the composition of the microemulsion. In this method, no energy is required to achieve submicron particle sizes as microemulsion is used which is a significant advantage.
4. Solvent emulsification/evaporation

   In this method, lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) then is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The mean particle size depends on the concentration of the lipid in the organic phase [36, 37]. Very small particles could only be obtained with low fat loads (5 % *w*/*v*) related to the organic solvent. With increasing lipid content, the efficiency of the homogenization declines due to the higher viscosity of the dispersed phase. The significant advantage of this procedure over the cold homogenization is avoidance of any thermal stress (Fig. 5d).
5. Supercritical fluid technology

   Supercritical fluid (SCF) technology has gained increasing interest in the last years for nanoparticles production. SCF is obtained above its critical pressure and temperature: above this fluid's critical point, the solubility of a substance in the fluid can be modulated by a relatively small change in pressure. Due to its low critical point at 31 °C and 74 bar, and its low cost and nontoxicity, carbon dioxide is the most widely used SCF. Two main SCF-based methods have been developed for SLN production: supercritical fluid extraction of emulsions (SFEE) and gas-assisted melting atomisation (GAMA).

   SFEE is based on a simple principle, whereby the

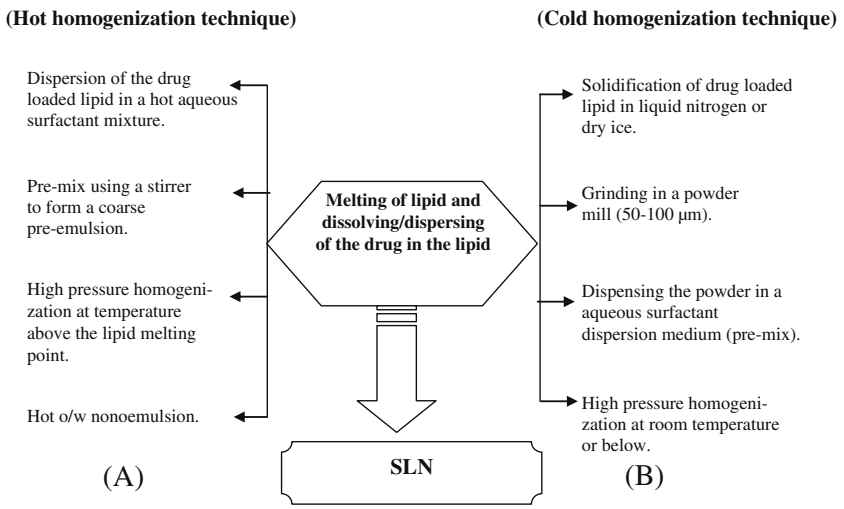

Fig.4 **a** Hot homogenization technique, **b** cold homogenization technique

lipid nanosuspensions are produced by supercritical fluid extraction of the organic solvent from oil-in-water (O/W) emulsions [38]. O/W emulsions are introduced into an extraction column from the top and simultaneously, supercritical carbon dioxide (CO_2) is introduced countercurrently from the bottom. When the O/W emulsion containing the lipid and the drug is introduced into the supercritical CO_2 phase, solvent extraction into the supercritical CO_2 phase occurs, leading to precipitation of lipid–drug material dissolved in the organic phase as composite particles [39, 40]. One of the advantages of this technique is that the solvent extraction efficiency using supercritical CO_2 is much higher than for the conventional methods, such as solvent evaporation, liquid extraction, and dilution, allowing a fast and complete removal of the solvent and a more uniform particle size distribution [41].

In GAMA method, lipids are placed in a thermostated mixing chamber (CM), where they are melted and kept in contact with supercritical CO_2 at selected temperature and pressure conditions. Then, the lipid-saturated mixture is forced through a nozzle by opening the valve at the bottom of the CM: the rapid depressurisation of the mixture creates a high degree of supersaturation and the precipitation of microparticles, which are collected by a collection system and dispersed in water by vortexing and by ultrasound treatment, in order to obtain suspensions [42, 43].

6. Spray-drying technique

Spray drying is a one–step process which converts a liquid feed to a dried particulate form: in the case of lipid particles, the feed is an organic solvent solution, which is first atomised to a spray form that is put immediately into thermal contact with a hot gas, resulting in the rapid evaporation of the solvent to form dried solid particles. The dried particles are then separated from the gas by means of a cyclone, an electrostatic precipitator, or a bag filter [42, 44].

SLN have found widespread use in drug delivery, counting more than a dozen approved variants with

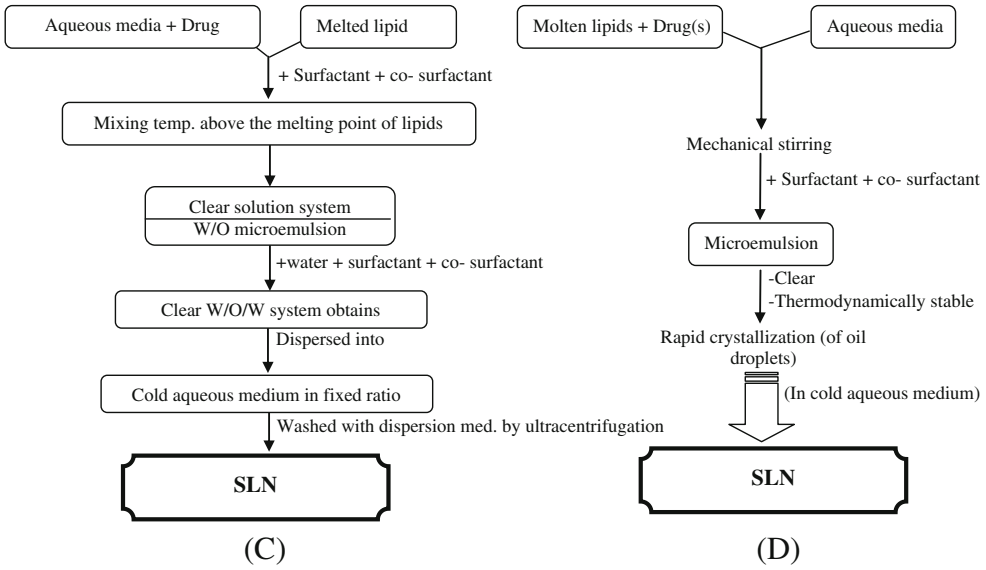

Fig. 5 **c** Microemulsion-based SLN preparations. **d** Solvent emulsification/evaporation

indications ranging from cancer to infection. This drug delivery system is designed to liberate the drug(s) under the extracellular environment conditions in the target particular cells or its microenvironment, and the drug has to be able to penetrate the cell membrane either passively by diffusion, or actively by specific transporters, or via receptor-mediated endocytosis. Table 3 represents some of the drugs used for SLN.

Role of ingredient in SLN preparation

In the preparation of nanoparticles, the ingredients play a significant and determined role by which these are prepared at an efficient rate. It is solely depends on the type of technique is used for example in hot homogenization; it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids. The ingredients used generally include solid lipid(s), emulsifier(s), and water. The term lipid is used here in a broader sense and includes triglycerides, partial glycerides, fatty acids, steroids, and waxes. All classes of emulsifiers (with respect to molecular weight and charge) have been used to stabilize the lipid dispersion. It is reported that the combination of emulsifiers might prevent particle agglomeration more efficiently. The choice of the emulsifier depends on the administration route and is more limited for parenteral administrations. Table 4 shows an overview of ingredients which are commonly used for manufacturing of SLN.

Table 3 List of some of the drugs used for SLN [11, 12]

Technology	Advantage	Disadvantage	Drugs
High homogenization techniques	General applicability to most drugs	High number of homogenization cycles	Albendazole
	Useful for formation of very dilute as well as highly concentrate nanosuspension	Prerequisite for drug to be in micronized state and suspension formation before homogenization	Amphotericin B
	Simple technique	Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer	Atovaquone
	Aseptic production possible		Azithromycin
	Low risk of product contamination		Budesonide
			Bupravaquone
			Clofazamine
			Disodium cromoglycate
			Fenofibrate
			Glucocorticoid drugs
			Ibuprofen
			Itraconazole
			Nifedipine
			Omeprazole
			Paclitaxel
			Spironolactone
Cold homogenization techniques	Easy process	Generation of residue of milling media	Clarithromycin
	No organic solvent require-short grinding time		Glisentide
			Indomethacin
			Naproxen
			Nifedipine
			Phenytoin
Microemulsion-based techniques	Simple process	Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a nonsolvent	Carbamazepine
	Low-cost equipment	Growing of drug crystals needs to be limit by surfactant addition	Cyclosporine
	Ease of scale up		Griseofulvin
			Retinoic acid

Table 4 General ingredients for manufacturing of SLN [1, 11]

Sample no.	General ingredients	Role of ingredients	Examples
1	Solid lipid (s)	To provide media for uniform dispersion of drug(s) To provide stability to the formulation	Triglycerides (e.g. tristearin), partial glycerides (e.g. Imwitor), fatty acids (e.g. stearicacid), steroids (e.g. cholesterol), and waxes (e.g. cetylpalmitate)
2	Emulsifier (s)	Various classes of emulsifiers (with respect to charge and molecular weight) can be used to stabilize the lipid dispersion. Combination of emulsifiers prevents particle agglomeration more efficiently	Soya lecithin (Lipoid S 75, Lipoid S 100); egg lecithin (Lipoid E 80); phosphatidylcholine (Epikuron170, Epikuron 200); Poloxamer 188; Poloxamer 182; Poloxamer 407; Poloxamine 908; Tyloxapol; Polysorbate 20 Polysorbate 60; Sodium cholate
3	Water	To provide the aqueous media	Distilled water

Characterization parameters for SLN

An adequate characterization offers control of the quality in the product. The characterization methods should be sensitive to the every aspect of SLN performance and should avoid artifacts [45]. Characterization of SLN involves various critical factors to be considered due to very small size and complexity of system. As lipids and fats are basic constituent of SLN, they are soft condensed material in general and are very complex systems, which not only in their static structures but also with respect to their kinetics of supramolecular formation. Hysteresis phenomena or supercooling can gravely complicate the task of defining the underlying structures. Some of the characterization parameters for SLN are tabulated (Table 5).

In vivo fate and biodistribution of SLN particles

The in vivo fate of the SLN particles determines the bioavailability and their absorption inside the body. The in vivo fate of the SLN particles will mainly concern with these points:

1. Route of administration
2. Interactions of the SLN with the biological surroundings including:
   (a) Distribution processes (adsorption of biological material on the particle surface and desorption of SLN components into the biological surrounding)
   (b) Enzymatic processes (e.g. lipid degradation by lipases and esterase)

SLN are composed of physiological or physiologically related lipids or waxes. Therefore, pathways for transportation and metabolism are present in the body which may contribute to a large extent to the in vivo fate of the carrier [46]. Figure 6 represents the sequence of events to be occurring during the in vivo transport of SLN in the body. Phagocytosis and endocytosis which are the general mechanism of body functions are utilized for the effective distribution of SLN inside the body.

Possible routes of administration for SLN

The main interest of nanoparticles is their ability to achieve tissue targeting and enhance the intracellular penetration of drugs. The transportation of SLN in body mainly governs by [11]:

1. Peroral administration
   Aqueous dispersions or SLN loaded traditional dosage forms, e.g. tablets, pellets, or capsules. This, after peroral administration, is altered due to the high ionic strength and acidity in microclimate of stomach.
2. Parenteral administration
   On administration by parenteral route SLN showed higher blood concentration in comparison to a commercial drug solution. Concerning the body distribution, SLN were found to cause higher drug concentration in lung, spleen, and brain while, the solution led to distribution more into liver and kidneys [34]. The absorption of a blood protein to particle surfaces assumed to be responsible for the uptake of SLN in brain by mediating the adherence to the endothelial cells of blood–brain barrier [20, 47].
3. Transdermal administration
   SLN dispersion produces semisolid gel like system and found suitable for direct application to skin which simultaneously increases the elastic properties. Low lipid content (5 % *w*/*v*) SLN dispersion of smallest particle size and low viscosity are unsuitable for dermal application on the other hand on increase of solid lipid content of SLN [48].

Drug entrapment into SLN

The drug distribution in SLN governs the type of release pattern which can be achieved by selecting proper

Table 5 Characterization parameters of SLN [45, 48, 75–77]

Sample no	Characterization parameters	Analytical methods/Instrumentations
1	Shape and surface morphology	Transmission electron microscopy (TEM)
		Scanning electron microscopy (SEM)
		Phase contrast optical microscopy (PCM)
		Atomic force microscopy (AFM)
		Freeze fracture microscopy
2	Vesicle size and size distribution	Electron microscopy (SEM/TEM)
		Optical microscopy
		Photon correlation spectroscopy (PCS)
3	Electrical surface potential and surface pH	Zeta potential measurement
		pH-sensitive probes
4	Surface charge and electrophoretic mobility	Laser light scattering technique
5	Surface hydrophobicity	Hydrophobic interaction chromatography
		Two-phase partition
		Radiolabel probe
		Contact angle measurement
		X-ray photoelectron spectroscopy
		Synchrotron radiation X-ray (SAX)
6	Density	Gas pycnometre
7	Molecular weight	Gel permeation chromatography (GPC)
8	Rheology	Viscometer
9	In vitro release	Dialysis membrane dissolution test apparatus

ingredient and the type of technique for SLN production. Possibly three strategies which offer the drug distribution pattern and consequently the release behavior patterns includes [49]: (a) homogeneous matrix: these are formed when the melting points of drug and lipid becomes in steady state; (b) lipid-enriched core: these are resulting when lipid melts at higher temperature than that of drug; and (c) drug-enriched core: these are resulted when lipids liquefy at an early point than that of drug as shown in Fig. 7. These categories are known to produce variety of system to be applied for various applications to provide the release pattern of choice.

Drug loading might result in strong changes of the SLN characteristics (particle size distribution, zeta potential, lipid modifications etc.). However, several alternative incorporation sites (micelles, mixed micelles, liposomes, drug nanosuspensions) exist in addition to the complex physicochemical status of the lipid (supercooled melt and several modifications) [8].

Hurdles and Strategies for SLN manufacturing

Although, numerous methods are available for production of SLN at industrial scale, but major lacuna associated with these methods is that these suffers from certain hurdles at various levels. These consequently affects the quality as well as production rate decreases if are not adjusted/rectified. Therefore hurdles need to be effectively overcome for this purpose, certain strategies have to be practiced which allows successful production of nanoparticles, as shown in Table 6.

Storage stability of SLN

The physical stability of the SLN during prolonged storage can be determined by monitoring changes in Zeta potential, particle size, drug content, appearance, and viscosity as a function of time [47, 49–51]. External parameters such as temperature and light appear to be of primary importance for long-term stability. The zeta potential should in general

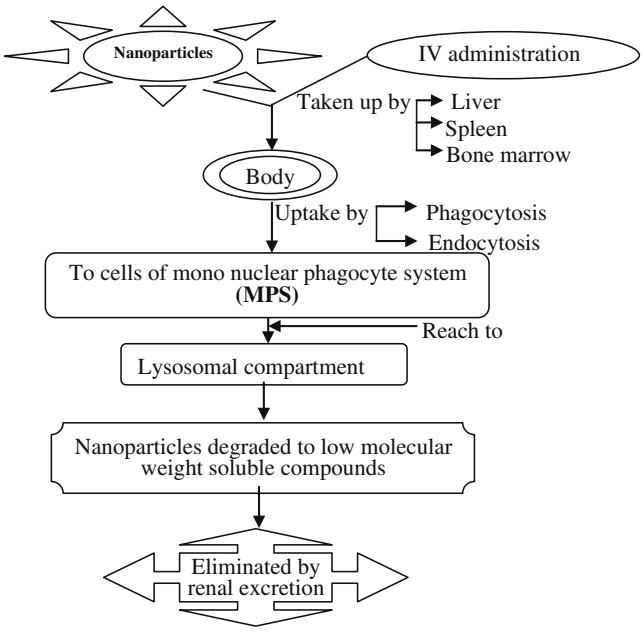

Fig.6 In vivo fate of SLN

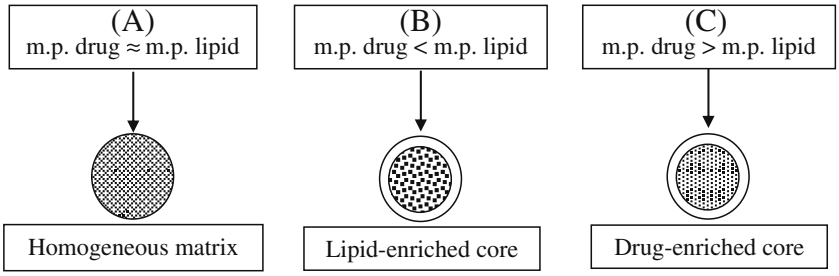

Fig.7 Types of release patterns of SLN

remain higher than −60 mV for a dispersion to remain physically stable. Values of approximately −15 mV were reported to lead to a distinct coalescence of emulsion droplets in parenteral nutrition. A rapid growth of particle size was observed when the SLNs were stored at 50 °C, with a decrease in their zeta potential. The most favorable storage temperature is generally 4 °C. However, in some cases, long-term storage at 20 °C did not result in drug-loaded SLN aggregation or loss of drug, compared to 4 °C storage conditions. Various methods such as lyophilization and spray drying have been proposed to optimize the stability [51]. Lipids chosen have the property that do not hydrolyze in aqueous suspension (another advantage over nanoparticles made from polymers, such as PLGA, which hydrolyzes with a rate that is dependent on polymer structure, and therefore these must be lyophilized for particular purpose). The very small particle size and density close to unity of SLNs means gravity has little effect on the particles in dispersion, and Brownian motion is sufficient to maintain colloidal dispersion without creaming or sedimentation. Reversion of such separation can usually done by gentle agitation. Standard preservatives are essential for SLNs made with

Table 6 Hurdles and strategies for SLN manufacturing [11, 47, 49, 50]

Sample no	Hurdles in SLN manufacture	Strategies
1	High pressure-induced drug degradation	High shear stress is the major cause of free radical formation and which results in decreased molecular weight of polymers simultaneously causes: Cavitation: can be solved by application of back pressure As high molecular weight compounds are more sensitive to degradation, therefore low molecular weight compounds can be used
2	Lipid crystallization and drug incorporation Considerations:	
	1. The shape of lipid nanodispersions	Platelet shapes have much larger surface areas compared to spheres; therefore, higher amount of the drug will be localized directly on the surface of the particles
	2. Gelation phenomena	Gelation phenomena describes the transformation of a low-viscosity SLN dispersion into a viscous gel. It generally happens during the i.v. injection into a living species, the life of this organism is put at risk. Gelation can be retarded or prevented by the addition of co-emulsifying surfactants with high mobility (e.g. glycocholate); maintenance at optimum temperature range and other environmental conditions
	3. The presence of several lipid modifications	Lipid modifications include improvement of quality like, lower density and ultimately, a higher capability to incorporate guest molecules (e.g. drugs) which should be characterized by DSC, X-ray, and NMR techniques
	4. The existence of supercooled melts	The main reason for the formation of supercooled melts is the size dependence of crystallization processes and thus provides stability. The size of particles should be monitored maintained throughout the process
3	Co-existence of several colloidal species	The presence of several colloidal species is an important point to consider as it may causes the degradation of formulation. The kinetics of the degradation will be determined by: (1) the chemical reactivity of the drug; and (2) the concentration of the drug in the aqueous medium or at the lipid/water interface. By increasing the matrix viscosity will decrease the diffusion coefficient of the drug inside the carrier and therefore, will stabilize the formulation
4	Low drug loading capacity	Improved by selection of proper drug carrier (nanosphere, nanopellets etc.); use of optimized drug: polymer ratio; selection of suitable drug loading technique etc.
5	Kinetics of distribution process	The promoters of gelation (like high temperature, light, shear stress) increase the kinetic energy of the particles and favor collision of the particles which produces instabilities to the formulations, therefore should be considered.

natural lipids, and not made by an aseptic process, which provides long-term stability against biological growth [49].

Applications of SLN

Role of SLN in cancer therapy

The main challenges associated with therapy of cancer includes, lack of selectivity of anticancer drugs towards neoplastic cells, narrow therapeutic index of most anticancer compounds, and emergence of resistant cell sublines during the chemotherapeutic treatment may require the use of higher doses of these drugs and consequently enhances the toxicity of the treatment [34–37]. In order to decrease the toxicity of the drugs and enhance the selectivity many drug delivery systems have been developed. This includes SLN that have received a greater interest for drug targeting. Targeting tumors with SLN shows enhanced endocytotic activity towards neoplastic cells. The ultimate goal of nanomedicines is to create medically useful nanodevices that can function inside the body. Among the newly developed nanomedicine, SLN offers the most promising applications for various cancer treatments. They would serve the two important purposes of localized drug delivery and specific targeting. Nanoparticles can serve as customizable, targeted drug delivery vehicles capable of ferrying chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. This may allow for small doses of toxic substances as the drugs are delivered directly into the target tissue [52–55].

Targeting

Most of the drugs used to treat cancer are toxic to both tumor and normal cells, thus the efficacy of chemotherapy is always limited by the side effects of the drug. To increase the selectivity of the drugs toward the cancer cells and reduce the toxicity for normal tissue is the primary goal and can be achieved by SLN [56, 57]. Surface modification of the nanoparticles can also enhance the permeability of the drugs to create high permeability nanoparticle-based cancer therapeutics so, as nanoparticles can become more therapeutically effective drug transport vehicles [58].

SLNs: a novel drug delivery system of choice

Polymeric nanoparticles are suitable delivery systems for brain due to [59],

- High concentration gradient across the blood–brain barrier, by enhanced retention in the brain–blood capillaries
- Presence of nanoparticles facilitates opening of tight junctions
- Transcytosis of nanoparticles through the endothelium

Moreover, the SLN system could be generally applied for the delivery of many chemotherapeutic agents in chemotherapy-resistant cancers. Compared with other cytotoxic drug carriers, SLN as carrier efficiently enhanced apoptotic death of cancer cell line by inducing a greater accumulation of entrapped bioactive in the cells [60–66]. Some of such roles of nanocarriers in cancer targeting are depicted in Table 7.

Role of SLN in vaccine delivery

Various biodegradable polymeric nanoparticles and microparticles are explored for delivery of vaccine formulation in controlled manners which possess adjuvant properties by parenteral or mucosal administration routes [67]. As most of the peptide or protein antigens are ineffective for mucosal immunization due to proteolytic degradation at mucosal sites, these in association with particulate carriers by microencapsulation or adsorption is an established strategy improves vaccine efficacy. Among the biodegradable polymers used for antigen microencapsulation the PLA/PLGA are the most commonly used. PLA/PLGA microspheres are very useful antigen delivery systems that are ingested by macrophages and dendritic cells, providing lasting immunity thanks to sustained release at relatively predictable times of the microencapsulated or adsorbed material [68, 69].

Role of SLN in enhancing stability of drug

Matrix encapsulation nature of SLNs can also protect drugs from adverse conditions encountered in the GIT. Metabolism of drugs especially by hydrolysis in GIT or in plasma can be controlled by encapsulating them in SLNs. SLNs control the release of drug from the solid lipid matrix and, therefore, prevent direct exposure of the drug to metabolizing enzymes. Bioactive compounds, namely, carotenoids, omega-3 fatty acids, or phytosterols, are necessary to improve long-term health. SLNs have been effectively used to improve stability of such bioactives while enabling their sustained release from particulate matrix [70].

Role of SLN in reduction of toxicity and side effects of drug(s)

SLN have high encapsulation of drug and sustained release property due to lipid matrix; therefore, the direct exposure of the drug to body tissue is minimized and this aids in the reduction of drug-induced toxicity for, e.g. triptolide-loaded SLNs shown to alleviate the problems of solubility and toxicity [71].

Role of SLN in gene delivery

Gene therapy is a rapidly advancing field with great potential for the treatment of genetic and acquired systemic

Table 7 Role of nanocarriers used in cancer targeting [60–66, 78–80]

Nanocarrier	Cytotoxic agent	Tumor type	Contribution	Ref.
Nanospheres	Mitoxantrone	Breast cancer and its lymph node metastases	Slower elimination rate Higher drug concentration in lymph nodes compared with mitoxantrone solution Lower drug concentration in other tissues The inhibition rate of the nanospheres against breast cancer was much higher and lymph node metastases were efficiently inhibited by the nanospheres	[60]
Folate–hapten conjugate	Hapten	Mice liver	Increase the potency of drug Reduces toxicity of many cancer therapies Facilitates discovery and development of a variety of folate-targeted drugs for the diagnosis and therapy	[61]
Single wall carbon nanotubes (SWCNT)	Paclitaxel	Murine 4 T1 breast cancer	Reported chemically functionalized SWCNT Potentially tumor-targeted in mice and exhibited biocompatibility and less toxicity Shows promising and high treatment efficacy for future cancer therapy with low drug doses	[62]
Albumin-bound nanoparticles	Paclitaxel	Advanced solid malignancies	Potential results in phase I clinical study of escalating doses of the lapatinib in patients with advanced solid tumors Dynamic contrast enhanced magnetic resonance imaging studies in a subset of patients confirmed a decrease in tumor vascular permeability	[63]
Thermosensitive magneto-liposome	Methotrexate	Skeletal muscular tissue	Thermosensitive magnetoliposomes (TMs) encapsulated with methotrexate (MTX) were prepared TMs prepared by reverse-phase evaporation can archive a good magnetic targeting effect and fast drug release in response to hyperthermia Implies great potential of application in cancer therapy	[64]
Albumin-bound nanoparticles	Carboplatin/ trastuzumab	HER-2 overexpressing metastatic breast cancer	A phase II clinical trial shows efficacy and safety of albumin-bound paclitaxel nanoparticles First-line therapy for women with HER2-overexpressing metastatic breast cancer (MBC)	[65]
SLN	Doxorubicin	Metastatic breast cancer	Nanoparticles using biocompatible compounds, assessed the in vitro hemolytic effect Proves their potential in vivo effects on drug retention and apoptosis intensity The nanoparticles efficiently enhanced apoptotic cell death through higher accumulation of doxorubicin in cancer cells This approach may be viable in overcoming the chemoresistance of adriamycin resistant breast cancer	[66]
Pluronic F127 polymer nanocrystals	Paclitaxel and camptothecin	Murine breast cancer	Investigated new three-phase nanoparticle engineering technology (3PNET) Shows clear potential for clinical development Excellent antitumor activity Low toxicity Ease of scale-up manufacture Suitable for hydrophobic drugs	[78]
Aerosol–OT (surfactant) (AOT) and sodium alginate	Doxorubicin	Balb/c mice bearing drug-resistant syngeneic JC tumors	Reported combinatorial anticancer activity of doxorubicin and methylene blue Resulted in enhanced tumor accumulation of both doxorubicin and methylene blue Significant inhibition of tumor cell proliferation Increased induction of apoptosis	[79]
Cationic SLN	For co-delivery of paclitaxel and siRNA	Epithelial carcinoma	Cationic SLN (cSLN) for co-delivery of paclitaxel (PTX) and siRNA formulated Resulted in enhanced tumor inhibition action	[80]

diseases as well as for vaccination. SLN can protect nucleic acids from digestion in biological fluids and have shown to enter into cells by endocytosis. SLN facilitates the introduction of genetic material (plasmid DNA) into target cells to enhance or correct protein expression [72, 73].

Commercially available nanodrug delivery systems

Despite the challenges which include the huge volume of expenditure involved and the regulatory stages (preclinical and clinical stages, phases 1–4) which are mandatory

Table 8 Nanodrug delivery systems in the market [74]

Nanoparticle system	Active ingredient	Indication	Trade name	Company
Polymeric nanoparticles	Adenosine deaminase	Adenosine deaminase (ADA) enzyme deficiency	Adagen	Enzon Pharmaceuticals Inc., Bridgewater, NJ, USA
	L-asparaginase	Acute lymphoblastic leukemia	Onscaspar	Enzon Pharmaceuticals, NJ, USA
	Glatiramer acetate	Relapsing-remitting multiple sclerosis	Copaxone	Teva Pharmaceuticals, Tikva, Isreal
	Pegaptanib sodium	All types of neovascular age-related macular degeneration	Macugen	Nektar Therapeutics, San Carlos, CA, USA; OSI Pharmaceuticals, Melville, NY, USA
	Pegylated interferon alfa-2a	Hepatitis C	Pegasys	Nektar Therapeutics, CA, USA
	Pegfilgrastim	Neutopenia	Neulasta	Nektar Therapeutics, CA, USA; Amgen Inc, Thousand Oaks, CA, USA
	Peginterferon alfa-2b	Hepatitis C	PEG-INTRON	Nektar therapeutics, CA, USA
	Pegvisomant	Acromegaly	Somavert	Nektar therapeutics, CA, USA
Liposomes	Amphotericn B	Fungal infections	Abelcet	Enzon Pharmaceuticals Inc., Bridgewater, NJ, USA
	Cytarabine	Lymphomatous Meningitis	Depocyt	Enzon Pharmaceuticals Inc., NJ, USA
	Amphotericn B	Fungal infections	AmBisome	Gilead Sciences Inc., Foster City, CA, USA
	Daunorubicin	Kaposi's sarcoma	Daunoxome	Gilead Sciences Inc., CA, USA
	Doxorubicin	Advanced breast cancer	Myocet	Zeneus/Cephalon, Inc., Frazer, PA, USA
	Inactivated Hepatitis A virus	Hepatitis A	Epaxal	Berna Biotech, Bern, Switzerland
	Inactivated influenza surface antigen	Influenza	Inflexal V	Berna Biotech, Bern, Switzerland
	Morphine	Analgesia	DepoDur	EKR Therapeutics, Bedminster, NJ, USA
	Verteporfin	Age-related macular degeneration	Visudyne	QLT Inc., Vancouver, British Colombia, Canada; Norvatis, Basel, Switzerland
	Doxorubicin	Ovarian cancer and Kaposi's sarcoma	Doxil	Ortho Biotech, Bridgewater, NJ, USA
	Doxorubicin	Ovarian cancer, Kaposi's arcoma, and breast cancer	Caelyx	Schering-Plough, Kenilworth, NJ, USA
	Estradiol	Menopausal Hot flushes	Estrasorb	Novavax, Rockville, MD, USA
	Beractant (bovine lung homogenate)	Respiratory distress syndrome	Survanta	Abbott Laboratories, IL, USA
	Bovactant(bovine lung lavage)	Respiratory distress syndrome	Alveofact	Boehringer Ingelheim GmbH, Ingelheim Germany
	Poractant alfa (porcine lung homogenate)	Respiratory distress syndrome	Curosurf	Chiesi Farmaceutici SpA, Parma, Italy
Polymeric micelles	Paclitaxel	Cancer chemotherapy	Genexol-PM	Samyang Pharmaceutical, Daejeon City, Korea
Nanocrystalline drugs	Rapamune	Sirolimus	Immuno suppressant	Elan Corporation, Dublin, Ireland; yeth Pharmaceutical, Madison, NJ, USA
	Emend	Aprepitant	Antiemetic	Elan Corporation, Dublin, Ireland; Merck and Co., Inc. Whitehouse Station, NJ, USA
	Tricor	fenofibrate	Hyperlipidemia	Elan Corporation, Dublin, Ireland; Abbott Labs, Illinois, USA
	Megace	Megestrol acetate	Anorexia, Cachexia	Elan Corporation, Dublin, Ireland; Pharmaceuticals, Woodcliff Lake, NJ, USA
Protein (albumin) nanoparticles	Abraxane	Paclitaxel	Metastatic breast cancer	Abraxis BioScience, Los Angeles, CA, USA; Astra Zeneca, London, UK
Lipid colloidal dispersion	Amphotec	Amphotericin B	Fungal infections	InterMune, Brisbane, CA, USA

in order to obtain regulatory approval before a drug product can get into the market, some nanodrug delivery systems have made it to the market. Table 8 shows the list of some of nanodrug delivery systems in the market [74]:

Future prospects

SLNs as carriers improve therapeutic performance by either oral or parenteral or topical route. The hydrophobic nature of solid lipids offers the lateral advantage of high payload of lipophilic and amphoteric molecules, ranging from small molecules to large proteins. SLN proved to be easy to scale up, even if some process parameters are still critical and can negatively influence their stability over time; suitable strategies can be adopted in order to overcome these problems. SLN can be administered by various routes, according to the therapeutic target, and, since they are composed of physiological or physiologically related lipids, there in vivo fate depends on the pathways for transport and metabolism present in the body.

SLNs improve the inherent properties of drugs by recuperating both solubility and permeability. Targeting of drug-loaded SLNs to specific organs, coupled with their sustained release properties makes SLNs effective carriers for potent and toxic therapeutic agents (such as anticancer agents). Further, avoidance of organic solvent during preparation and ease of industrial scale-up make these SLNs more amenable to commercialization in comparison to other nanoparticulate carriers. Considering the excellent attributes of SLN as delivery vehicles, various other functionalized SLN are under investigation and need to be explored.

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