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Solid Lipid Based Nano-particulate Formulations in Drug Targeting

*Bibhash Chandra Mohanta, Subas Chandra Dinda,
Narahari Narayan Palei and Jyotirmoy Deb*

Abstract

Recently, targeted drug delivery systems have gained much more interest for delivering varieties of drugs as well as imaging agents specifically to the targeted disease cells or tissues. These are well known for their increased precision and accuracy in mode of drug delivery along with reduced side effects. Though numerous carriers are being employed for drug targeting, the solid lipid based nanoparticles (SLNs) are preferred over them owing to their ability to encapsulate wide varieties of drugs, biocompatibility, ease of surface modification, scaling up feasibility, and possibilities of both active as well as passive targeting to various organs. Surface of these drug loaded SLNs can be modified by conjugating different ligands to enhance their tissue/organ targeting ability and therapeutic efficacy to much higher extent. In this chapter, we have discussed about the SLNs and their different surface modified forms for passive as well as active targeting to different organ such as (colon, breast, lungs, liver, kidney, brain, eyes, etc.) in combating different diseases.

Keywords: SLNs, targeted drug delivery, imaging, colon, breast, eye, lungs, liver, kidney, brain

1. Introduction

Drug delivery refers to the approaches or methods or technologies of administering or transporting active pharmaceutical ingredient(s) and other xenobiotics through different routes for achieving the desired therapeutic effect in human or animal safely. The pharmacokinetics and pharmacodynamics issues of drugs are the most important considerations of drug delivery which is profoundly integrated with dosage form and route of administration. The kinetics of drug release, drug concentration profile in the plasma, onset of action, duration of action, site of action, and side effects of a drug deeply influenced by the DDS.

2. Conventional vs. targeted drug delivery systems

2.1 Conventional drug delivery systems

Conventional drug delivery system is also known as classical drug delivery system or traditional drug delivery system, which sometimes unable to maintain the

steady-state plasma concentration as desired for a specific time period and may not be able to deliver the drugs to the specific site of organ or tissues may be because of barriers in transportation for which it may be needed to administer with multiple doses at a regular time interval or need to go for targeted drug delivery systems.

2.2 Targeted drug delivery systems

Targeted drug delivery system (TDDS) is popularly known as smart drug delivery system. The aim of the TDDS is to localize, target and to have a protected interaction of a drug with the diseased cells/tissues of interest for a prolonged period of time. TDDS helps in maintaining the requisite plasma and tissue drug levels in the body and protects the healthy tissues from damage may be some times caused by the drugs [1]. It offers various benefits over conventional DDS such as localization of a drug to the desired or specific site, enhancement of therapeutic efficacy, reduction in the dosing frequency and toxic side effects, controlled biodistribution of drug, modulated pharmacokinetics, and improved patient compliances [2]. The TDDS is a highly integrated DDS which needs the coordinated effort from various experts such as biologist, chemist, engineers for its fabrication and optimization.

2.3 Nanotechnology vs. drug delivery systems

Nanotechnology is defined as the technology which allows studying, controlling, manipulating and manufacturing of structures or devices in the nanoscale. It is a multi-disciplinary scientific field applying engineering and manufacturing principles at the molecular level. These nanosized objects/structures/devices, e.g. “nanoparticles” exhibit unique properties and function that distinctly differ from those seen from the items made up from the same materials. Nanomaterials possess many unique characteristics such as mechanical, optical, magnetic, electrical, and biochemical, which provoke them to intermingle with complex cellular functions in an exceptional manner [3].

Since its introduction in 1959, the nanotechnology brought a great revolution in all areas of sciences and particularly in drug formulation and drug delivery system design. Nanomedicine is the medical application of nanotechnology, which plays an imperative role in the medical biology, diagnosis, monitoring, prevention and treatment of diseases. Since last few decades, owing to the rapid developments in nanotechnology and carrier materials, a great advancement in the nanoparticulate DDS has been noticed and they are taking the lead among all types of DDS [4].

The nanoparticulate DDS possesses numerous advantages such as higher intracellular uptake (cells and tissues have a greater affinity and acceptability to the nanoparticles as compared to micro/macro molecules), ability to penetrate into sub-mucosal layer (nanometric size), greater suitability for administration through the systemic circulation (nanometric size), greater feasibility/flexibility to develop into a targeted DDS for targeting various sites/organs. Thus, the nanometric size, tailored surface, and cross functionality of these nanoparticles will continue to explore many unexplored research areas and may help in designing and developing new biomedical applications [5].

2.4 Colloidal drug carrier and solid lipid nanoparticles

The term “colloid” is applied to the dispersed system where the dispersed phase particles size are very fine and generally below 1 μm . Thus, the biphasic drug carrier containing very fine dispersed phase particles ($<1 \mu\text{m}$) which sequester, transport

and retain the active drug en route, while they deliver the drug within or in the vicinity of a target is popularly known as colloidal drug carrier. These colloidal drug carriers comprise nanoparticles, liposome, niosome, nanospheres, multiple emulsion, and nanosuspensions, etc. [6]. Colloidal carriers aid in solubilization of lipophilic drug, protect the sensitive drug from degradation in biological fluid, reduce toxic side effect, improve patient compliances, prolong the duration of action and drug targeting potentiality [7].

Though the polymeric nanoparticulate DDS have shown hugely impressive performance for providing therapeutic benefits in the case of long term delivery of a therapeutic agent, but still, the number of polymeric nanoparticulate formulations in the market is still limited. This is because of polymeric toxicity, high cost of polymers, and lack of feasibility for scaling up. Lipid based nanoparticulate DDS are proposed as an alternative to polymeric nanoparticulate DDS and gained tremendous attention in the field of nanomedicine. These comprise liposomes, niosomes, nanoemulsions, solid lipid nanoparticles (SLNs) and nanostructured lipid carrier (NLCs), etc. [5].

SLNs are the second generation lipid nanocarriers that overcome most of the limitations associated with conventional drug delivery system and other colloidal lipid/polymeric nano carriers. It promises to offer numerous benefits including biocompatibility and biodegradability, physiochemical stability, lower toxicity, ability to incorporate both hydrophilic and lipophilic drugs, improved bioavailability, enhanced *in vitro* and *in vivo* stability of drugs, controlled-release characteristics, site specificity in drug delivery as well as feasibility in pilot scale up along with its suitability in drug delivery through different routes of administration [4].

2.5 Solid lipid nanoparticles and drug targeting

In the emerging field of nanomedicine, SLNs is at the forefront. It is made up from biocompatible/physiological lipids (e.g. partial glycerides, triglycerides, fatty acids, wax, and steroids) that remain in solid form at room temperature. Numerous techniques are being developed for the fabrication of SLNs using the biocompatible/physiological lipid which has records of innocuous use in medicine [8]. Apart from drugs, the essential materials for fabricating SLNs are solid lipids as matrix materials, emulsifiers, stabilizers, and water. The nanometric size and larger surface area of SLNs is suitable to be embedded with some potential functionalized ligands, antibodies, moieties, and other functional groups that help in drug targeting [5].

The real success of lipid nanoparticles relies on the development of dosage forms that are able to improve the therapeutic index of the drugs by mounting their concentration specifically at the targeted site or organs. Drugs can be incorporated in SLNs which lead to offer a new model in drug delivery that could be applied for drug targeting. The therapeutic payload of various categories of drugs (such as anti-infective, anticancer drugs, anti-inflammatory, etc.), antigens, proteins, and nucleotides can be enhanced in specific site and organs by associating with SLNs. On another side, SLNs face numerous challenges which include rapid clearance, serum instability (dependent on the specific formulation) and nonspecific uptake by the mononuclear phagocytic system (play a major role for opsonizing the foreign particles and remove SLNs from the circulation) [9]. The above mentioned limitations can be nullified by conjugating different ligands to the surface of SLNs which could help to increase the circulation time and targeted delivery of the drug to the specific site. The targeting properties to a specific site can be further enhanced by selecting surface markers [10]. Thus, in this article, we focused on SLNs and various ligand conjugated SLNs which act as suitable carriers for targeting to different sites such as lungs, brain, liver, breast, eyes, colon, kidney, etc.

3. Solid lipid nanoparticles for lungs targeting

Targeted delivery of a drug to the lungs is gaining much more interest at the present time, for the treatment of lungs cancer, tuberculosis, and other airborne diseases where lungs are the primary site of action or site administration of drugs [11]. In order to get maximum therapeutic benefits from lungs delivery, a suitable DDS with appropriate physicochemical properties are necessary and SLN along with ligand conjugated SLN are the most fitted on this ground.

3.1 Solid lipid nanoparticles for active lungs targeting

The lungs offer a very high surface area for rapid absorption of drugs owing to high vascularization and avoidance of the first pass effect. Sometimes, targeted delivery of certain drugs to the lungs is very important not only for improving the bioavailability and therapeutic activity but also for reducing the systemic side effects [5].

To achieve a prolonged hypoglycemic effect, Liu et al. developed insulin-loaded nebulized SLNs which were administered through intrapulmonary route. The hypoglycemic effects, stability of SLN during nebulization, and deposition pattern of the drug were evaluated. SLNs exhibited excellent protective effect for insulin against degradation or leakage from nanospheres and were relatively stable during nebulization *via* jet nebulizer. Nebulized insulin SLNs helped in improving the bioavailability and showed significantly higher hypoglycemic effect as compared to insulin phosphate buffer solution administered through pulmonary route. Thus nebulized insulin-SLNs could be a promising DDS for the treatment of diabetes [12]. In another study Bi et al. successfully developed freeze dried insulin-SLNs suitable for intra-tracheal administration through a spray. High preservation of insulin was noticed in SLNs after spray freeze drying. They had performed *in vivo* studies on diabetic rat and observed a prolonged hypoglycemic effect [13].

Rifampicin (RIF) were successfully encapsulated into the SLNs that delivered RIF specifically to the alveolar macrophage (AM) with strong antimycobacterial efficacy (MIC reduced to 1/8 fold than that of the free drug). Generally, mycobacterium safely multiplies in the AM (acts as an incubator), as the mycobacterium is resistant to the biocidal mechanism of AM. The developed SLNs were more stable and the particle sizes were very much suitable for improving RIF's uptake by AMs which are particle size dependent [14]. Similarly, Rifabutin loaded SLNs significantly improved uptake of the drug by the macrophages which were demonstrated in an *in vitro* model [15].

Co-administration of RIF and isoniazid through SLN formulation significantly reduced (60%) degradation of RIF (from 48.81 to 12.35%) from acidic gastric pH owing to the presence of isoniazid. The developed SLNs promoted targeted delivery of drug to the brain with enhanced bioavailability and lesser side effect that could be helpful in the case of cerebral tuberculosis [16].

Significantly higher biodistribution of dexamethasone acetate (DXM) to the lungs was achieved through intravenous administration of DXM loaded SLNs. The area under curve (AUC) of DXM- SLNs was increased by 17.8-fold as compared to DXM-solution. The maximum concentration of the DXM in the lungs was observed at 0.5 h post DXM-SLNs injection [17].

Similarly higher biodistribution of amikacin (AMK) in the lungs was achieved by pulmonary administration of AMK-SLNs as compared to the free drug administered through i.v., which could be helpful in the treatment of cystic fibrosis [18].

3.2 Ligand conjugated solid lipid nanoparticles for passive lungs targeting

Lungs targeted delivery of drugs is a challenging task due to the mucociliary clearance. In this regard, the ligand-anchored DDS not only proves its potential in achieving improved site-specific drug delivery, but also it reduces the chances of drug uptake by reticulo-endothelial system (RES). It is believed to play a major role in congenital defense and exhibit diversified biological activities such as antimicrobial, anticancer, immunomodulation, an exertion to control cell growth, binding, and inhibition of numerous biologically active compounds. However, clinical success of such approaches relies on the choice of appropriate ligand free from immunogenic potential with the potential to provoke cargo internalization by the target cell [19].

The mechanism of receptor mediated endocytosis of ligand anchored SLNs and drug release technique has been shown in **Figure 1**.

3.2.1 Lactoferrin (Lf) conjugated solid lipid nanoparticles

In lung associated diseases, receptors of Lactoferrin (80-kDa iron-binding glycoprotein) is overexpressed in the lungs. Thus, Lf conjugated DDS may become a promising tool for targeted delivery of drugs to lungs in lung-associated diseases [20]. Rifampicin (RIF) loaded SLNs were successfully prepared and were coupled with Lf via carbodiimide chemistry i.e., coupling of the Lf carboxylic group with the stearylamine amine group present on the surface of the previously formed RIF loaded SLNs in the presence of N-ethyl-N-(dimethylaminopropyl)-carbodiimide (EDC). An *in vivo* biodistribution study revealed 3.05 time higher drug uptakes by the lungs in case of Lf-RIF-SLNs as compared to unconjugated RIF-SLNs. It was further confirmed from fluorescence photomicrographs that clearly showed access of the Lf-coupled SLNs into the lung. Thus, lactoferrin is an efficient molecule that can be used for targeting active agents directly to the lungs [21].

3.2.2 Wheat germ agglutinin (WGA) conjugated solid lipid nanoparticles

Conjugation of bioadhesive ligand molecules with SLNs helps in improving drug absorption/bioavailability by increasing residence time in the GIT and reducing

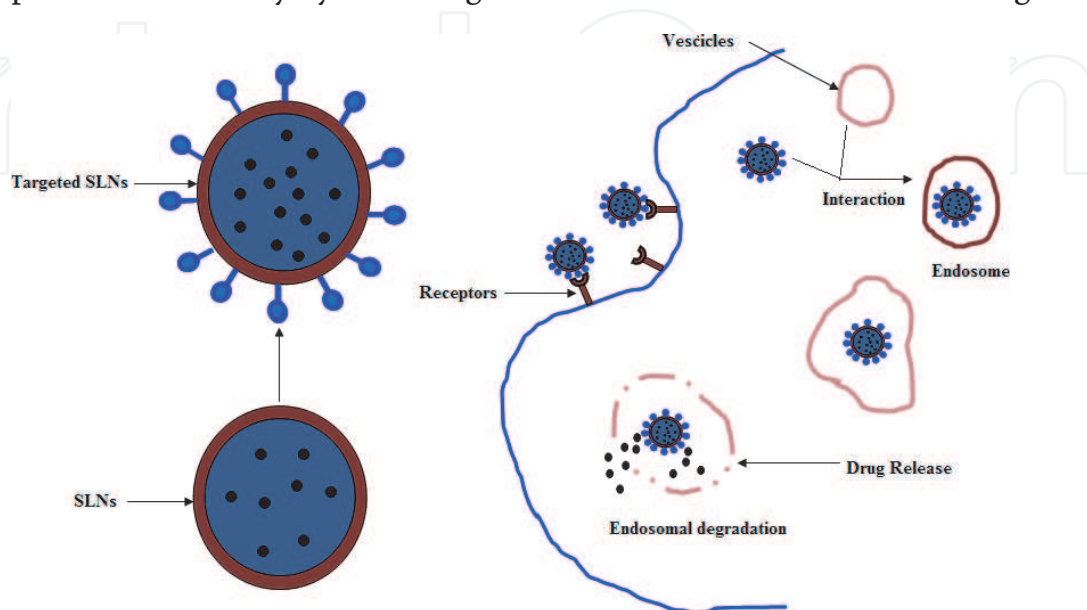


Figure 1.
Mechanism of receptor mediated endocytosis of ligand anchored SLNs and drug release technique.

dosing frequency. Lectins (a group of diverse proteins/glycoproteins) are the bioadhesive ligand and have stable structure and receptor binding ability. It offers resistance to enzymatic digestion/degradation, which helps in its *in vivo* survival for a prolonged time period [22]. Wheat germ agglutinin (WGA) is an example of nontoxic plant lectin which binds particularly to N-acetyl-D-glucosamine and sialic acid on cell surfaces. Conjugation of WGA with SLNs could be helpful for targeted delivery of antitubercular drugs to the lungs.

WGA conjugated SLNs loaded with rifampicin (WRSLNs) were successfully developed for lungs specific delivery of rifampicin (RIF). The conjugation of WGA to RIF loaded SLN was carried out by two-steps carbodiimide reaction reported by Ertl et al. with slight modification [23]. Even after conjugation with the SLNs, the WGA retained its bio-recognition activity and sugar-binding specificity [24]. From the *in vivo* study result, the interaction of WRSLNs with porcine mucin was confirmed. However, non-conjugated SLNs did not show any conjugation with the porcine mucin. The WRSLNs were stable at refrigerated temperature and also in presence of electrolytes up to 1.0 M Na₂SO₄ concentration. The WRSLNs were 10 times more stable than RIF-SLN which could be owing to the steric stabilization by lectin present on nanoparticle surface. Prepared WRSLNs had shown narrow size distribution, controlled release of a drug, retention of biorecognition activity and improved physical stability of drug against electrolyte induced flocculation [25].

3.2.3 Mannose conjugated solid lipid nanoparticles

Studies on tuberculosis revealed overexpression of the mannose receptors specifically on alveolar macrophages (AM) surfaces [26]. Keeping it in mind attempts were taken to develop mannosylated SLN to deliver antitubercular drugs targeting to alveolar macrophages which have higher affinity for mannose. Rifabutin loaded mannosylated SLNs were successfully developed. Manosylation was done by ring opening reactions followed by reaction of aldehyde groups of mannose in 0.1 M sodium acetate buffer (pH 4.0) with the amino groups of lipid. This leads to formation of Schiff's base ($-N=CH-$), which may then get reduced to secondary amine ($-NH-CH_2-$) and remain in equilibrium with Schiff's base at basic pH. *In vivo* studies were conducted to evaluate for their cytotoxicity, targeting potential, AM uptake, and hematological studies. It was reported that mannosylation improved uptake (up to 6-fold) of rifabutin by the AM. Moreover, mannosylated rifabutin-SLNs were less immunogenic and helped in sustained delivery of drug. Thus, the mannosylated SLNs may be employed for AM targeted delivery of rifabutin for effective management of TB [27].

Overexpression of mannose receptors in case of lungs cancer was reported by numerous investigators. The mannosylated-distearoyl phosphatidyl-ethanolamine SLNs loaded with paclitaxel (PTX) was developed for lungs targeted delivery of PTX. Manosylation was done by ring opening reaction followed by reaction of an aldehyde group of mannose with the free amine group provided by stearylamine and DSPE in sodium acetate buffer (pH 4.0). The stability testing data indicated that SLNs formulations stored at $4 \pm 2^\circ\text{C}$ were more stable than those stored at $27 \pm 2^\circ\text{C}$. It was revealed that mannosylated SLNs deliver significantly higher concentration of drug to the alveolar cell sites and showed improved antiproliferative efficacy as compared to PTX solution and PTX-SLNs [28].

3.2.4 Folate conjugated solid lipid nanoparticles

The folate receptors (α - form) are overexpressed on the surface of lung tumor cells. The extents of the overexpression are different in different types of lung tumors (adenocarcinomas—72%, squamous cell carcinomas—51%, small cell

Sl. no	SLN (Type)	Lipids	Preparation method	Drugs	Target	Model	Comments	Ref.
01	SLN	SA, PA	Reverse micelle-double emulsion	Insulin	Lungs	Male SD rats	Improved hypoglycemic effect	[12]
02	SLN	SA, PA	Modified lipid film hydration method	RIF	AM	SD rats	Improved drug uptake by AMs.	[14]
03	SLN	SL, GTS	Ultrasonication with high pressure homogenization	DXM	Lungs	Mice	Improved therapeutic efficacy targeting to lungs	[17]
04	Lf-SLNs	SL	Solvent injection method	RIF	LfR	Albino rats	Targeted delivery of RIF to Lungs	[21]
05	WGA-SLN	SA, GMS	Single emulsification followed by solvent evaporation	RIF	Mucin	Porcine	Controlled release of RIF	[25]
06	Msy-SLN	TSN	Modified solvent injection method	RFB	MR	J774 & albino rats	AM specific drug delivery. Enhanced therapeutic efficacy.	[27]
07	Msy-SLN	TSN, DSPE	Modified solvent injection method	PTX	MR	A549 & Male albino rat	Alveolar cell site delivery of drug with enhanced anti-proliferative efficacy.	[28]
08	Ft-SLN	CHO, GS	Nano precipitation method	PTX	FR	HeLa & M109-HiFR cells	Prolonged drug residence time, reduced MIC	[30]

Table 1.
 List of SLNs and their different ligand conjugated forms for lungs cells targeting.

carcinoma—25%, and lung metastases—30%) [29]. These receptors allow folate derivatives to bind preferentially that permits intracellular incorporation of folate derivative by endocytosis.

Folate-conjugated copolymer of polyethylene glycol (PEG) and N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC) SLNs loaded with Paclitaxel (PTX) were successfully developed. The conjugation of folate-conjugated PEG and HTCC to RIF-SLN was carried out by carbodiimide mediated coupling chemistry. Pulmonary administration of the developed F-PEG-HTCC-SLNs selectively delivered the PTX to the lung's cancer cells with improved penetrability and prolonged lung residence. Moreover, the developed SLN significantly reduced the *in vitro* half-maximum inhibitory concentration of PTX in M109-HiFR cells [30].

List of SLNs and their different ligand conjugated forms for lungs targeting have been summarized in **Table 1**.

4. Solid lipid nanoparticles for brain targeting

Targeted delivery of drugs to the brain for is gaining much more interest at the present time, not only for the treatment of brain tumor and other neurodegenerative disorders but also for their diagnosis. Brain targeted delivery of drugs is the most challenging task because of the presence of strongest physiological barrier, i.e.,

blood brain barrier (BBB). It is a highly selective semipermeable membrane barrier constituted by specialized microvascular endothelial cells, basement membrane and glial cells (astrocytes, neurons, and pericytes). As long as the BBB remains integral, the drugs remain ineffective in the brain. Though BBB is a major issue for it, yet it offers scores of opportunities such as presence of numerous transport proteins and specialized receptors [5].

Conventional approach for the treatment of brain tumor and other brain-related disorders needs a higher dose of the drug that leads to systemic toxicity and substantial adverse effects on CNS and vital normal tissues. However, various researchers have reported SLNs to be a suitable DDS targeting the brain as the SLNs possess numerous unique characteristics, such as improved uptake of SLN by the brain due to lipidic nature, bioacceptability and biodegradability nature, non-toxic, nano sized particles suitable for prolonged circulation time in blood scale up feasibility, absence of burst drug release effect [31]. Thus, SLN could be used as potential as well as promising candidate for brain targeting.

4.1 Solid lipid nanoparticles for active brain targeting

SLNs are the most acceptable brain targeted DDS employed in brain tumor owing to their ability to escape and/or inhibit P-glycoprotein in the blood–brain barrier [32]. Camptothecin (CMP) loaded SLN were successfully developed for the treatment of glioma. Encapsulation of drug in phospholipids and conjugation with the peptide enhances the permeation of drug across BBB, which leads to brain targeted delivery of the drug. The developed SLN was stable in terms of size and charge within a year of storage which might be due to appropriated acidic pH (inclusion of behenic acid into the lipid core of the SLNs). DMPC (1,2-dimyristoyl-sn-glycero-3-phosphocholine) membrane helps in efficient release of the incorporated CMP into the brain parenchyma crossing the BBB. Against glioma, the developed SLNs showed higher cell death or antitumor activity using the lowest maximal inhibitory concentration (IC₅₀) values. Biodistribution study revealed higher accumulation of CMP in the brain in the case of SLNs as compared to other non-encapsulated drugs. However, pharmacokinetics study revealed lower deposition of CMP in peripheral organs indicating lesser toxicological effects in the vital organ. Thus, in short, the SLNs exhibited enhanced accumulation, distribution, and retention of camptothecin in the animal brain along with superior *in vitro* antitumor activity against glioma [33].

Riluzole (RLZ), a potent neuroprotective agent is useful in the treatment of neurodegeneration including traumatic brain injury and amyotrophic lateral sclerosis. RLZ-SLNs were able to deliver the riluzole successfully to the brain which helps in preventing acute cell damage induced by glutamate in neurodegenerative diseases of motor neurons. Moreover, it also protects dopamine neuron in the case of Parkinson's disease. Stability studies on RLZ-SLNs were also carried out at pH 1.1, 5.5 and 7.4, and in human plasma which revealed the absence of riluzole degradation in all the investigated media [34].

Vinpocetine (VIN), a derivative of vincamine alkaloid, useful against chronic cerebral vascular ischemia. VIN loaded SLN were successfully developed and achieved the objectives of delivering the drugs to the brain. Release kinetics of the developed SLN followed zero-order sustained release profile [35].

4.2 Ligand conjugated solid lipid nanoparticles for passive brain targeting

4.2.1 Lactoferrin conjugated solid lipid nanoparticles

Augmentation of drug uptake into the brain is a subtle mission in the treatment of brain tumor. Lactoferrin (Lf) receptor present on the BBB in different species

along with the cell surface of glioblastomas [36]. Keeping it in mind, various researchers tried to target lactoferrin receptor through conjugation of lactoferrin with SLNs for active targeting to brain tumor. Moreover, this conjugated system showed higher stability, and drug payload.

Lactoferrin (Lf) conjugated SLNs loaded with docetaxel (DTX) were able to show effective brain targeting efficiency. Carbodiimide chemistry was employed for conjugation of Lf on SLN surface (Lf-SLN). Receptor saturation studies and distribution studies of lipidic nanoparticles in the brain indicated brain targeting mechanism for uptake in brain tumor cell and brain respectively. The Lf-SLNs were more stable. It not only showed significantly higher DTX concentration in the brain but also showed superior apoptotic activity when compared with unconjugated SLNs and DTX. Thus it was confirmed that conjugation of Lf to SLN significantly improved the targeting potential of the DTX for brain tumor [37].

4.2.2 Tamoxifen-Lactoferrin cross conjugated solid lipid nanoparticles

P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRAPs) are localized on brain microvascular endothelial cells (BMEC) which pump out the substances/drug out from the central nervous system. Tamoxifen (Tf), a selective estrogen receptor modulator possibly reverse the capability of efflux transporters like MRAPs in cancer cells [38]. Thus, incorporation of Tf could help in preventing a wide range of medication from efflux loss. Lactoferrin (Lf) receptors are overexpressed in BMEC and glioblastoma multiforme (GBM) cells. It is reported that the Lf cause inhibition to the multiplication of malignant GBM cells.

Tamoxifen (Tx) and lactoferrin (Lf) cross-conjugated carmustine (CRM)-loaded SLNs were developed. For conjugation of Tx on CRM-SLN, the carbonyl groups of the SLN were first activated with 0.1% (w/v) carbodiimide and 0.05% (w/v) N-hydroxysuccinimide. The suspended SLNs were then crosslinked with 0.05%, 0.1%, 0.15%, or 0.2% (w/v) Tx at 150 rpm and 25°C for 3 h and centrifuged. Further Lf conjugation was done by reacting Lf (0.02%, 0.04%, 0.06%, or 0.08%) (w/v) with the activated CRM-SLNs and Tx-CRM-SLN. The conjugated SLNs were more stable which could be due to inclusion of behenic acid into the lipid core. These were efficiently penetrated through a monolayer of human BMEC and human astrocytes and to target GBM cells. A 10-fold increase in the permeability of BBB and improved the sustained release of CRM was achieved with the help of the developed SLNs as compared to unconjugated CRM-SLNs. Thus, TX and Lf cross-conjugated SLNs enhance the BBB permeability of the drug with improved anti-proliferative action against GBM [39].

4.2.3 PEG conjugated solid lipid nanoparticles for gene delivery

Treatment of brain tumor through siRNA is preferable, as it can target specifically to one gene and is able to silence it in a post-transcriptional way. Moreover, siRNA can target several functional proteins available at the BBB [40]. Treatment of brain tumor through siRNA, needs a safe, stable, effective carrier which must be able to cross the BBB. The SLNs are mostly preferred as it meets most of the criteria which siRNA needs. Targeted delivery of gene by SLNs is a bi-stage system. Conjugation of angiopep to SLN surface for targeting the low-density lipoprotein receptor-related protein-1 (expressed in BBB) is the initial step. The proteolytic cleavage of PEGylated lipopeptide, which releases PEG, glutamic acid residues and release of siRNA for high silencing efficiency is the second stage [5].

siRNA encapsulated SLNs were successfully developed using a combination of titrable cationic lipids. For effective gene delivery, it was PEGylated after

incorporating MMP-cleavable lipopeptide. The *in vitro* study indicated that the developed SLNs showed higher uptake and gene knockdown efficacy. SLNs also showed low cytotoxicity which was owing to masking of intrinsic positive charge of SLNs by PEGylated cleavable lipopeptide. In *in vivo* studies, angiopep functionalization played a vital role as a mediator of transport across the BBB and targeting to glioma [41].

4.2.4 Apolipoprotein E conjugated solid lipid nanoparticles

Low density lipoprotein (LDL) receptors are overexpressed on the BBB and apolipoprotein E (AP-E), a plasmatic protein is easily recognized by these receptors. Resveratrol (RSV), polyphenolic flavonoid promises to offer neuroprotective effects which are helpful in neurological disorders like Alzheimer's, Parkinson's, Huntington's diseases, brain ischemia, and epilepsy. The AP-E conjugated resveratrol (RSV) SLNs were successfully developed. The binding of ApoE to the SLNs surface was carried out by spontaneous interaction between the previously biotinylated ApoE and the covalently attached avidin on the SLNs surface, resulting

Sl. no	SLN (Type)	Lipid (s)	Preparation method	Drugs	Target	Model	Comments	Ref.
01	SLN	CP, DMPC	High shear homogenization and ultrasonication techniques	CMP	Brain	Human glioma & Monocytic cell line. Wistar rats	Enhanced accumulation of CMP. Superior <i>in vitro</i> antitumor activity	[33]
02	SLN	COMP, SPC	Warm oil-in-water microemulsion technique	RLZ	Brain	Male SD rats	Higher bioaccumulation of RLZ in brain.	[34]
03	SLN	SA, GMS, PRE, GTP	High shear homogenization and ultrasonication techniques	VIN	Brain	—	Zero-order sustained drug release kinetics	[35]
04	Lf-SLN	GMS, SA, SL	Emulsification and solvent evaporation method	DTX	Lf Receptors	U-87 MG cell lines & Swiss albino mice	Improved the brain targeting potential	[37]
05	Tf-Lf-SLNs	TPM, DSPE	Homogenization followed by centrifugation	CRM	Tf and Lf Receptors	U87MG, HBMECs	Higher BBB permeability. Superior anti-proliferative action	[39]
06	SLN	POPC, DSPE, CHO, DM	Detergent dialysis technique	siRNA	Angiopep	bEnd.3 cell, U87MG cells,	Higher uptake and gene knockdown efficacy	[41]
07	AP-E - SLNs	CP	High shear homogenization followed by sonication technique	RSV	LDL Receptor	hCMEC/D3 Cell line	Brain targeted delivery of RSV	[42]

Table 2.

List of SLNs and their different ligand conjugated forms for brain cell targeting.

in two different ApoE-functionalized SLNs: SLN-DSPE-ApoE and SLN-Palmitate-ApoE. These conjugated SLNs were sufficiently stable and were able to prevail over the issues of RSV like low solubility, degradation but also to help its brain targeted delivery. Brain targeted delivery of RSV by such SLNs follows a bi-stage system. The AP-E-RSV-SLNs mimic lipoprotein particles that are endocytosed into the BBB endothelium via the LDL receptor and then transcytosed to the brain [42].

List of SLNs and their different ligand conjugated forms for brain cell targeting have been summarized in **Table 2**.

5. Solid lipid nanoparticles for liver targeting

Though targeted delivery of a drug to the liver is a challenging task, still, it is an interesting approach in the treatment of various liver disorders. In the treatment of liver disorders, drugs targeting to the liver, face irresistible obstacles from various physiological barriers and processes like uptake by the reticuloendothelial system, mechanical entrapment by the pulmonary vascular bed, and opsonization process [43].

Numerous approaches are being proposed to enhance bioaccumulation/biodistribution of drugs to liver and hepatocytes. These approaches include both active targeting as well as passive accumulations of nanoparticulate formulation due to ligand (carbohydrate, peptide, antibodies conjugation) conjugated nanoparticles. Recently, liver targeted deliveries of drugs by the SLNs are gaining much attention in the treatment of various types of liver disorders. Thus, various liver targeting strategies using SLNs are enlightened below.

5.1 Solid lipid nanoparticles for active targeting

Baicalin (BCL), a natural product obtained from *Scutellaria baicalensis* (Family: Labiatae) popularly used in the treatment of Hepatitis-B and liver fibrosis. BCL loaded SLNs were developed. The prepared SLNs were stable and were able to enhance the therapeutic efficacy of BCL by improving its biodistribution in the liver. *In vivo* biodistribution, targeting evaluation and *in vitro* anti-oxidant study reveals that the developed BCL-SLNs have substantial liver targeting, improved anti oxidative and hydroxyl radical scavenging abilities [44].

Ficus benjamina (Family: Moraceae) is rich in phenolic (chlorogenic, p-coumaric, ferulic and syringic acids) and total flavonoid content that are effective against chronic alcoholism induced fatal liver and cardio-renal injury. Ethanolic extract of *Ficus benjamina* (FB) loaded in SLNs (FBSLNs) helped in bioaccumulation of the phenolic and flavonoid content in the liver due to lipophilic nature of SLNs. *In vivo* evaluation of FBSLNs against hepatic and cardio-renal injury revealed its hepatoprotective activity which was further evident from various biological parameters and histopathological photomicrography. In the liver, accumulation of aldehyde level was reduced that validated the detoxifying nature of FBSLN. Moreover, restoration of aberrant cardio-renal biomarkers and histological consequences revealed the cardio-renal protective potential of FBSLNs [45].

Berberine (BBR), an active constituent of *Coptis chinensis* (Family: Ranunculaceae) have potential pharmacological effects on type-2 diabetes. It has already been validated that BBR enhances glucose and lipid metabolism through the activation of adenosine monophosphate-activated protein kinase (AMPK) and improve insulin sensitivity. BBR loaded SLNs (BBR-SLNs) were developed to improve the beneficial effect of BBR on hepatosteatosis. The effect of BBR-SLNs on lipid metabolism were studied which revealed gaining of body weight and reduction

in liver weight with simultaneous reduction of serum alanine transaminase and liver triglyceride level. Biodistribution study reported 20-fold increase in the concentration of drug in the liver than that of blood. Moreover, it reduced the accumulation of fat and lipid droplet size. It was also noticed that the expression of lipogenic genes was down-regulated and lipolytic gene was up-regulated in BBR-SLNs treated livers which could be helpful in the treatment of hepatosteatosis [46].

Cisplatin (CSPT) is an anti-cancer drug which is used in the treatment of many malignancies including hepatocellular carcinoma, lungs carcinoma, etc. The CSPT loaded SLNs (CSPT-SLNs) were successfully developed and were stable in terms of drug content after storage for 3 months in different temperature and humid conditions. *In vivo* tissue distribution study revealed that the developed CSPT-SLNs were able to deliver a higher amount of CSPT particularly to the liver as compared to the brain, lungs, and kidney [47].

Sorafenib (SFB), a potent multi-kinase inhibitor possess anti-tumor angiogenesis effect (block vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR)) and is preferentially used in the treatment of hepatocellular carcinoma. The SFB loaded SLNs (SFB-SLNs) were developed with an objective of improving bioavailability and reducing adverse effects. The results of the stability test showed that SRF-SLNs remained stable for more than 1 month at room temperature. *In vivo* study of SFB-SLNs revealed improved bioavailability (increased by 66.7%) with remarkably higher bioaccumulation of drug in the liver (2.20-fold higher drug selectivity index value) when compared with the SFB suspension [48].

Primaquine phosphate (PP) is an antimalarial drug that acts on the primary tissue forms of the Plasmodium which after growth within the liver, initiate the erythrocytic stage. Thus, PP loaded SLNs (PP-SLNs) were developed with an aim to deliver liver schizonticide PP directly to the hepatocytes. Stability of the PP-SLNs in suspension was tested for a period of 3 months in terms of size, poly-dispersity, ζ -potential, and pH. There were no noteworthy changes **in size, poly-dispersity, ζ -potential, or pH occurred over time**. *In vivo* study report revealed that the developed SLNs were highly effective (>20%) against hypnozoites/liver stage of all malarial species with a reduced dose when compared with the conventional oral dose [49].

5.2 Solid lipid nanoparticles delivering gene

The fibrous scars occurring in the liver due to the increased production and deposition of hepatic extracellular matrix (ECM) components are called liver fibrosis reduce the physiological performance of the liver. Hepatitis viral infection is one of the major reasons for liver fibrosis and cirrhosis. Administration of antifibrotic therapeutics (e.g. connective tissue growth factor (siRNA) responsible for the cellular and molecular basis of fibrogenesis) is one of the most preferable approaches for the treatment of liver fibrosis. The siRNA loaded cationic SLNs (cSLNs) were developed by gently mixing CSLNs with siRNA at various weight ratios of cSLN to siRNA in 0.1 M PBS (pH 7.4) and then incubated at room temperature for 15 min. Naturally obtained low-density lipids (LDLs) were used in the preparation. The developed cSLN were able to silence the targeted gene in the presence of serum with notably low cytotoxicity. The cSLNs were PEGylated which were hydrodynamically stable and were able to protect their siRNA cargo from nuclease degradation during systemic circulation. The developed cSLNs loaded with siRNA administer through intravenous route delivered siRNA exclusively to the liver and resulted in a considerable reduction in collagen content and pro-fibrogenic factors with spectacular progress of pathophysiological symptoms in a liver fibrosis rat

model. Biodistribution study revealed site-specific delivery and accumulation of siRNA loaded cSLNs to the liver tissues [50].

5.3 Solid lipid nanoparticles for passive targeting

5.3.1 Polyethylene glycol conjugated (PEGylated) solid lipid nanoparticles for passive targeting

PEGylated SLNs are reported to be preferentially accumulated in the liver as the kidney is unable to clear the same. Thus, in liver disorders, liver targeting strategy using PEGylation technique is used for delivering numerous drugs. Paclitaxel (PTX) loaded PEGylated SLNs were successfully developed for targeting the liver, in the case of hepatic carcinoma. The cellular uptake study revealed that PTX loaded PEGylated SLNs showed prolonged circulation time in plasma and higher bioaccumulation of drug in the liver when compared with the PTX solution [51].

The preferential drug targeting ability of PEGylated SLNs to cancer cells have been shown in **Figure 2**.

5.3.2 Galactosylated lipid [*N*-hexadecyl lactobionamide] conjugated solid lipid nanoparticles

The parenchymal cells of the liver contain asialoglycoprotein receptors which recognize terminal b-D-galactose or N-acetylgalactosamine residues. The *N*-hexadecyl lactobionamide (N-HLBA) was synthesized via an amide bond between the amine group of hexadecylamine and the carboxyl group of lactobionic acid. The

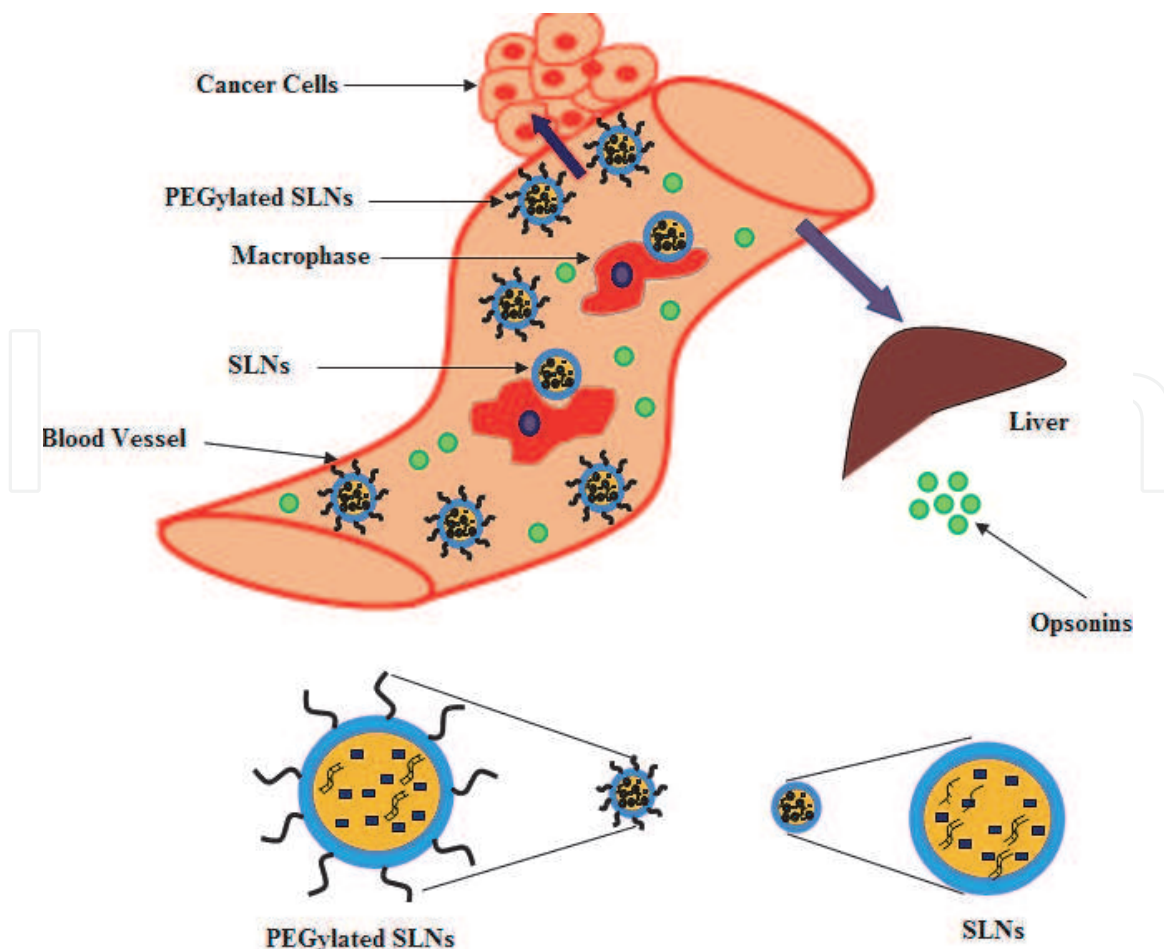


Figure 2.
PEGylated SLN in targeting preferentially to cancer cells.

lactobionic acid was converted to 1,5-lactone that contain more reactive amine groups. Cucurbitacin B (CurB), a tetracyclic triterpene shows significant pharmacological activities including anti-tumor, anti-hepatitis, hepatocurative and hepatoprotective. The CurB loaded N-hexadecyl lactobionamide (N-HLBA) conjugated SLNs were developed for liver-targeted delivery of CurB. The N-HLBA SLN with anchored galactose moiety via amide bonds might achieve effective liver-targeting delivery *in vivo* by retaining the surface galactose in blood stream, and by exposing a higher amount of galactose to the liver parenchymal cells. The optimum zeta potential held up the physical stability whereas the optimum particle size distribution offered the convenience for intravenous administration and deep penetration into targeting area. The Biodistribution study of the CurB loaded N-hexadecyl lactobionamide (N-HLBA) conjugated SLNs revealed a 2.5-fold increase

Sl. no	SLN (Type)	Lipid (s)	Preparation method	Drugs	Target	Model	Comments	Ref.
01	SLN	SL, GMS	Emulsification ultrasonic dispersion method	BCL	Liver	Rats	Improved biodistribution of BCL in Liver, Superior anti oxidative and hydroxyl radical scavenging abilities	[44]
02	SLN	SA	Hot-homogenization followed by ultra-sonication	FB	Liver	HepG2 cell line, Rats	Anti-oxidant, anti-inflammatory and detoxification potential	[45]
03	SLN	GL, SP, TP	Hot Emulsification Technique	BBR	Liver	Male db/db mice,	Down regulate the lipogenic gene and Up-regulate the lipolytic gene.	[46]
04	SLN	SA	Warm emulsification followed by sonication	CSPT	Hepatocellular carcinomas	Wistar rats	Higher bioaccumulation of drug in liver	[47]
05	SLN	GB	High-speed shearing followed by ultrasonication	SFB	Liver	Female SD Rats	Improved bioavailability, higher bioaccumulation in liver	[48]
06	SLN	SA	Modified multiple emulsion solvent evaporation technique	PP	Hepatocytes	3D7, Mice	Improved antimalarial activity	[49]
07	C-SLN	CO	Modified emulsification and solvent evaporation method	siRNA	LDL Receptor	Rat, HSCs and hepatocytes	Spectacular progress of pathophysiological symptoms in liver fibrosis	[50]
08	PEG-SLN	GT, CHO	Solvent-emulsification method	PTX	Hepatocytes	HepG2, MCF7, PANC-1	Higher liver bioaccumulation of PTX	[51]
09	G-SLN	COMP	High-pressure homogenization	CurB	ASGP Receptor	Wistar rats	Enhanced antitumor and hepatoprotective activity	[52]

Table 3.
List of SLNs and their different ligand conjugated forms for liver cell targeting.

in the amount of CurB in the liver when compared with CurB-SLN. *In vitro* cytotoxicity study revealed enhancement of cytotoxicity. The experimental result validated the liver targeting ability of N-HLBA conjugated SLNs [52].

List of SLNs and their different ligand conjugated form for liver targeting have been summarized in **Table 3**.

6. Solid lipid nanoparticles for breast cell targeting

Breast cancer is the most common form of cancer and the second most deadly disease among the woman around the globe. The breast cancer new incidences and mortality rate has been increased by 20 and 14% since 2008.

Recently, controlled release of the drugs to the targeted site of the disease using a nanocarrier vehicle is getting more attention as it enhances the therapeutic efficacy of the drugs. Solid lipid nanoparticulate (SLN) formulations possess an endless potential to deliver active chemotherapeutic molecules in a programmed prototype to improve bioavailability and nullify the side-effects. The bio-compatibility and bio-degradability characteristics of SLNs promise to offer a lesser toxic product as compared to polymeric nanoparticles which forced to consider it as an idealistic targeted drug delivery system for breast cancer therapy [5].

6.1 Solid lipid nanoparticle for active breast cell targeting

6.1.1 SLNs for photodynamic therapy

Photodynamic therapy is one of the emerging approaches in the treatment of cancer which comprises application of a photosensitizer followed by laser irradiation of tumor lesions. Temoporfin (TP), a photosensitizer loaded in thermoresponsive SLNs were developed with an objective to improve anticancer activity through site specific drug delivery. The copolymer poly(ethylene oxide)-block-poly(ϵ -caprolactone) copolymers (PEO₄₅-b-PCL₇) were synthesized by the mechanism of catalyst-free ring opening polymerization of ϵ -caprolactone which was initiated by poly(ethylene oxide) monomethyl ether (MPEO). These copolymers were acts as a stabilizer in the preparation of thermoresponsive SLN. The stability study report revealed that the developed SLNs had higher stability in human serum within the blood transport to tumor tissue. *In vitro* phototoxicity study revealed higher phototoxic activity of TP against breast cancer cells due to its faster bioaccumulation in the targeted cancer cells. The *in vivo* anticancer efficacy of TP-SLN was remarkably higher as compared to the commercial TP formulation [53].

6.1.2 Manganese (Mn) II complex solid lipid nanoparticles

Transition metal complex (e.g., Manganese II complex $[\text{Mn}_2(\mu(\text{C}_6\text{H}_5)_2\text{CHCOO})_2(\text{bipy})_4]^{2+}$) has been extensively used for cancer therapy nowadays due to its potential anticancer activity (interact with the DNA). Mn(II) complex loaded SLNs were developed that showed superior cytotoxicity activity on breast cancer cells. The zeta potential value of the product was higher indicating good physical stability and dispersion quality of the SLNs. Cell proliferation assay revealed that the normal cell death rate was lower with Mn(II) SLNs which indicated lesser toxicity of the product to the normal cell. Moreover, higher early apoptosis rate was observed with Mn(II) complex SLN as compared to Mn(II) alone [54].

6.2 Solid lipid nanoparticles for passive breast cell targeting

6.2.1 Fucose conjugated solid lipid nanoparticles

Fucose receptors are overexpressed in the breast cancer cell. Thus, conjugation of fucose to SLNs was proposed to deliver the drug specifically to breast cancerous cells. Fucose conjugated methotrexate (MTX) loaded SLNs were developed to achieve enhanced targeting potential for breast cancer cells. Fucosylation of MTX-SLNs was related with opening of fucose ring and reaction of its aldehyde group with free amino functionalities expressed over the surface of MTX-SLNs in sodium acetate buffer (pH 4.0). The above process led to the formation of Schiff's base ($-N=CH$). The Schiff's base might be reduced to secondary amine ($-NHCH_2$) and establish equilibrium with Schiff's base. Physical stability of prepared SLNs was higher which could be due to positive zeta potential value that provides repulsive interaction between nanosized lipid particles preventing particle aggregation. The *ex vivo* study revealed higher cellular uptake as well as higher cytotoxicity at lower IC₅₀ of MTX. The *in vitro* study results showed increased rate apoptosis with a change in lysosomal membrane permeability and a higher rate of lysosomal membrane degradation. The *in vivo* study revealed maximum bioavailability and tumor targeting efficiency with minimum secondary drug distribution to other organs [55].

6.2.2 Folic acid functionalized solid lipid nanoparticles

The folate receptor (FR) is one of the most widely evaluated receptor for active targeting of anticancer therapeutics in the case of in breast cancer cells. Folic acid has many advantages over antibody ligands such as small size, non-immunogenicity, non-toxicity, ease of handling, stability and low cost [56]. Several researchers had reported earlier that the FA functionalized SLNs were able to deliver the chemotherapeutic agent, particularly to the cancerous cells. Thus, FA functionalized SLNs co-encapsulated with Docetaxel (DTX) and Curcumin (CUR) were successfully developed to enhance its therapeutic efficacy against breast cancer cells. FA-stearic acid (FA-SA) conjugate was synthesized by classical 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC) chemistry and incorporated in the DTX-CUR-SLN. Additionally, PEG-stearic acid (PEG-SA) was incorporated to obtain FA-DTX-CUR-SLN. The DTX-CUR-SLN and FA-DTX-CUR-SLN formulations were found to be stable at refrigerated condition for 2 months. Both the formulations showed sign of instability at accelerated condition (25°C/65% RH). The developed FA functionalized SLNs exhibited improved pharmacokinetic parameters, superior cancer cell targeting efficiency, and improved therapeutic efficacy of DTX. Folic acid was believed to be responsible for the targeting efficacy of the developed SLNs to the breast cancer cell. This conjugated system showed significant increase in area under the curve and mean residence time of the drug. Co-conjugation (FA and PEG) to SLNs co-encapsulated with DTX and CUR responsible for synergistic activity of both DTX and CUR. Moreover, bioaccumulation of DTX in heart and kidney was found very low which signified avoidance of vital organ toxicity [57].

6.2.3 Cetamide and trimethylphytyosphingosine-iodide co-conjugated solid lipid nanoparticles

The sphingosine-1-phosphate (S1P), phytosphingosine, ceramides, and sphingosine are the metabolites of sphingolipids and are reported as essential structural

components of cell membranes or important mediators of cellular process that regulate the proliferation, survival, and death of cells. Moreover, sphingosines including N,N,N-trimethylsphingosine (TMP-I) have been reported for their role as a negative modulator of transmembrane signaling through protein kinase C (PKC) as well as an inhibitor of sphingosine kinase-1 (SK-1), controlling the various membrane-associated signaling mechanisms associated with cell growth and inhibitory apoptosis in tumor cells [58]. Ceramide, a kind of sphingosine conjugated with fatty acid residue, is also reported to enhance the sensitivity of MDR-acquired cancer cell lines to chemotherapeutic agents [59]. Thus, attempts were made to employ ceramide (CD) and trimethylphytosphingosine-iodide (TMP-I) as a targeting agent for docetaxel (DTX) loaded SLNs. The prepared SLNs were physically stable without any significant change in their physical appearance, drug content, and particle size over a period of 8 weeks at 4°C. CD enhanced the DTX sensitivity in MDR-acquired cancer cell lines. *In vivo* clearance of drug and tumor growth inhibitors were significantly decreased in case of CD and TMP-I conjugated SLNs when compared with the marketed product. Thus, CD and TMP-I conjugated DTX-SLN could serve as a potentials alternative parenteral formulations of DTX [60].

Sl. no	SLN (Type)	Lipid(s)	Drugs	Preparation method	Target	Model	Comments	Ref.
01	SLN	TD	TMP	Modified hot homogenization and ultrasonication method	Breast Cancer cell	4T1, MDA-MB-231, Female Nu/Nu mice- MDA-MB-231	Exhibited improved phototoxicity and anticancer efficacy	[53]
02	Mn (II) Complex-SLN	COMP	Mn (II) complex	Hot homogenization method	Breast Cancer cell	MCF-7 and HUVEC cell line	Possessed superior anticancer activity with reduced toxic effect.	[54]
03	F-SLN	PL90NG, PL, STA, GEL	MTX	Hot microemulsion method	Fucose Receptor	MCF-7 Cell line & Female SD rat	Improved bioavailability and tumor targeting efficiency with minimum secondary drug distribution in various organs.	[55]
04	FA-PEG-SLN	GMS, SA	CUR, DTX	Modified ethanol injection method	Folic acid Receptor	MCF-7 & MDA-MB-231 Cell line. Female Wistar Rat	Synergistic cancer efficacy due to coencapsulation of DTX and CRM along with targeted delivery of drugs	[57]
05	CD-TMP I-SLN	PC, TMS,	DTX	High-pressure homogenization method	CD & TMP-1	MCF-7 cell, MCF-7/ADR cells	Significant increased antitumor efficacy with targeted drug delivery	[60]

Table 4.
 List of SLNs and their different ligand conjugated forms for breast cancer cell targeting.

List of SLNs and their different ligand conjugated form for breast cancer cell targeting have been summarized in **Table 4**.

7. Solid lipid nanoparticles for eye targeting

The eye is one of the delicate organs of human and one of the most delicate routes of drug delivery. However, the eye poses unique challenges relative to drug delivery due to the ocular anatomical and physiological constraints. SLNs are one of the promising targeted DDS for an eye. Numerous drugs such as antibiotics, plasmids, anti-inflammatory, and immunosuppressive agents were encapsulated in SLNs for the treatment of ophthalmic disorders.

7.1 Solid lipid nanoparticles for active eye targeting

Corneal neovascularization (CNV), a sight-threatening condition is caused due to various inflammatory settings including chemical injury. Single-stranded proline-modified short hairpin anti-angiopoietin-like protein 2 (ANGPTL2 RNA) interference molecules acts as potent angiogenic and pro-inflammatory factor and is used for the treatment of CNV [61]. Thus, ANGPTL2 RNA loaded SLNs were developed to deliver the interference molecule specifically to the retina. The single-stranded RNAi (pshRNA) loaded SLNs exhibit high stability *in vivo* and preliminary data suggest that pshRNA is less susceptible to degeneration due to RNase activity. The fluorescence-labeled developed SLNs eye drops penetrated all layers of cornea and expression of ANGPTL2mRNA was considerably inhibited in both epithelium and stroma. Further, the area of angiogenesis was remarkably decreased in the corneas by the SLNs drops as compared to the control group [62].

X-linked juvenile retinoschisis (XJR), a retinal degenerative disorder caused by mutation in the RS1 gene encoding a retinoschisin [63]. Among non-viral vectors, solid lipid nanoparticles (SLNs) represent one of the most effective lipid-based colloidal carriers, and for gene delivery to the posterior segment of the eye [64]. Plasmid (human RS1 gene) loaded SLNs were developed for the treatment of XJR diseases which showed significant improvement of the retinal structure with photoreceptor specific expression of the RS1 gene [65].

Tobramycin (TMC) is one of the most preferable drugs to treat vitreoretinal diseases, such as bacterial infections, endophthalmitis, cytomegalovirus retinitis (CMV), uveitis, proliferative vitreoretinopathy (PVR), diabetic retinopathy, age-related macular degeneration [66]. Thus TMC loaded mucoadhesive SLNs were developed which showed higher bioaccumulation of drugs in most of the ocular tissues and was able to penetrate into the retina. Moreover, it resulted in enhanced intraphagocytic antibiotic concentration in polymorphonuclear granulocytes and superior bactericidal activity against *Pseudomonas aeruginosa*. The developed SLNs showed good stability up to 12 months with no aggregation or precipitation phenomena, variations in zeta potential values or in amount of the drug encapsulated into the nanoparticles [67].

7.2 Solid lipid nanoparticles for passive eye targeting

7.2.1 Chitosan coated solid lipid nanoparticles

Indomethacin (IMC), a topical non-steroidal anti-inflammatory drug (NSAID) is used for ocular inflammatory disorders such as conjunctivitis, uveitis, cystoid macular edema, and anterior segment inflammation, including post-operative pain

following cataract surgery [68]. Chitosan (Cs) coated IMC loaded SLNs (IMC-Cs-SLN) were developed to deliver NSAID to the posterior segment of ocular tissues and for improving the pre-corneal residence time and transcorneal permeability characteristics. For surface modification of the developed SLNs, the chitosan was incorporated into the aqueous phase prior to preparation of the SLNs. The developed SLNs were stable in terms of drug loading, EE, and less drug expulsion during storage at 40°C for 90 days. The SLNs showed higher bioaccumulation of IMC in the ocular tissues. The IMC-Cs-SLN showed superior trans-membrane IMC permeation characteristics which were due to penetration enhancing properties of Cs [69].

7.2.2 Intercalated montmorillonite solid lipid nanoparticles

Betaxolol hydrochloride (BH) is widely used for the treatment of ocular hypertension and open-angle glaucoma in clinical therapeutics. However, it faces certain limitations like low bioavailability and pre-ocular retention, and some side effects.

Sl. no	SLN (Type)	Lipid(s)	Drugs	Preparation method	Target	Model	Comments	Ref.
01	SLN	DSGPC, CHO	ANGPTL2 RNA	Hydration method followed by extrusion	Retina	C57BL/6 mice	Inhibition of expression of ANGPTL2mRNA, Reduction in angiogenesis area	[62]
02	SLN	PRE	Human RS1 gene	Solvent emulsification followed by evaporation	Retina	661W, RS1h-deficient mouse	Improvement of the retinal structure	[65]
03	SLN	SA	TMC	Warm o/w microemulsion method	Aqueous humor	Albino rabbit	Superior bactericidal activity	[67]
04	Cs-SLN	GB	IMC	Hot homogenization	Posterior segment of ocular tissue	White albino Rabbits	Improved biodistribution of IMC at posterior segment	[69]
05	Mt-SLNs	PC, GMS	BH	Emulsion evaporation-low temperature solidification method	Cornea and Conjunctiva	Rabbit	Significantly reduced inflammation, No irritation	[70]
06	PEG-SLNs	COMP	KTZ	Emulsification followed by high pressure homogenizer	Upper posterior eye	ARPE-19 & RCE Cell line, Rat	Superior antifungal activity	[73]
07	Multifunctional SLNs	CP	BAI (Drug) C IR-780 (Diagnostic agent)	Modified solvent-diffusion method	Colorectal part	LoVo, CHO-K1	Imaging, Superior cytotoxicity	[75]
08	SIA-PEGylated SLN	GMS, OA	DXM	Solvent diffusion method	E-selectin receptor	HUVECs, ICR male Mice	Targeted delivery of DXM for ischemia-reperfusion-induced injury-induced AKI	[78]

Table 5.
List of SLNs and their different ligand conjugated forms for eye, colon and kidney targeting.

In order to overcome these limitations acid treated montmorillonite (Mt)- Betaxolol Hydrochloride (BH) nanocomposite encapsulated SLNs (Mt-BH-SLNs) were developed. An acid-treated montmorillonite (acid-Mt) was first intercalated with BH in the interlayers and this nanocomposite was encapsulated by SLNs. The developed Mt-BH-SLNs possess good stability. Long term irritation test reported that the (Mt-BH-SLNs) showed no damage for cornea and conjunctiva. The corneal hydration level of Mt-BH-SLNs was higher (78.25 ± 0.63)% indicating higher drug corneal permeability and absence of irritation to the cornea. Thus, Mt-BH-SLNs could be used for effective management of glaucoma [70].

7.2.3 Polyethylene glycol (PEG) conjugated (PEGylated) solid lipid nanoparticles

Ketoconazole (KTZ) is a broad spectrum antifungal agent, with high liposolubility [71] but a short ocular half-life (elimination half-life is 19 min in aqueous humor and 43 min in cornea) [72] and very poor solubility (0.04 mg/ml). Ketoconazole (KTZ) loaded PEGylated SLNs were developed for targeted delivery of KTZ to the posterior part of the eye for treatment of fungal infection. It showed higher bioavailability both in the aqueous and vitreous humor with significant antifungal potential. The *ex vivo* corneal permeation study revealed higher corneal permeability of the PEGylated KTZ-SLNs. The developed SLN was satisfying various parameters suitable for ocular delivery such as pH, osmolarity, stability, autoclavability, particle size, preservation against contamination. The SLNs were found to be stable in terms of entrapment efficiency and total drug content at 2–8°C for 12 months. Thus it could be helpful in the treatment of keratitis and endophthalmitis [73].

List of SLNs and their different ligand conjugated forms for eye targeting have been summarized in **Table 5**.

8. Solid lipid nanoparticles for passive colon targeting

Combination of nanocarriers and electroporation techniques is named as electropermeabilization which is commonly used for enhancing drug transport. The Cyanine-type IR 780 and Baicalein (BAI) co-encapsulated SLNs were developed for both imaging and therapy of colorectal carcinoma where cyanine-type IR 780 and baicalein (flavonoid derivative) were acting as a diagnostic agent (photosensitizer) and therapeutic cargo respectively. For preparation of SLNs the organic phase was prepared by dissolving IR-780, BAI, and melted lipid in dichloromethane. The organic phase was then added dropwise to hot aqueous phase containing surfactant under vigorous stirring. Supplementary material (flavonoids) facilitated in the reduction of dose and reduction in normal cell toxicity in cancer chemotherapy. The external electric field pulses applied in electroporation helped in increased of cell membrane permeability, either by generating transient pores or membrane electropermeabilization [74]. Electropermeabilization mediated administration of the developed SLNs showed cytoskeletal abnormalities more significantly than without electropermeabilization. The prepared SLNs particles were with good physical stability. With electroporation support, the developed SLNs showed increased p53 and manganese superoxide dismutase expression with significant higher cytotoxicity, thus validating their suitability for combined therapy and molecular imaging simultaneously [75].

List of SLNs and their different ligand conjugated form for colon targeting have been summarized in **Table 5**.

9. Solid lipid nanoparticles for kidney targeting

9.1 Solid lipid nanoparticles for passive kidney targeting

9.1.1 Polyethylene glycol (PEG) surface modified solid lipid nanoparticles

Icariin (IRN) is widely used as traditional Chinese medicine for the treatment of kidney diseases and reinforce yang. The PEG surface modified Icariin (IRN) loaded SLNs (PEG-IRN-SLNs) was developed for targeted delivery of IRN to the kidney and to improve the bioavailability. The SLN was prepared by high temperature melt-cool solidification method. Upon comparing with IRN solution it was revealed from the pharmacokinetic study that the biological half-life ($t_{1/2}$) and area under curve (AUC) of PEG-IRN-SLN was 7-fold and 4-fold higher. Biodistribution study revealed that IRN concentration in kidney tissues was significantly increased. Moreover, the relative target efficiency to kidney tissues was 79% and relative tissue exposure was 16.95. Thus the developed SLN could be helpful in the treatment of kidney diseases [76].

9.1.2 Sialic acid conjugated PEGylated solid lipid nanoparticles

E-selectin is a promising target for the site-specific delivery of anti-inflammatory agents. Several researchers have reported that sialic acid (SA)-mediated micelles could be specifically internalized by lipopolysaccharide (LPS)-activated human umbilical vein endothelial cells (HUVECs) via the specific binding between SA and E-selectin receptor [77]. Sialic acid (SIA) conjugated PEGylated dexamethasone (DXM) loaded SLNs (SIA-PEGylated-DXM-SLN) were developed to deliver DXM specifically to the kidney and to improve the therapeutic efficacy of DXM for renal ischemia–reperfusion injury (IRI)-induced acute renal injury. The Sialic acid (SIA) conjugated PEGylated DXM (SIA-PEG-DXM) was synthesized by adding PEG-DXM, dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP) into anhydrous dimethyl formamide (DMF) followed by addition of SIA into the solution. The resulting mixture was stirred for obtaining SIA-PEG-DXM. The crude product was purified by dialysis against deionized water for 2 days, followed by lyophilization. The developed SLNs potentially had good colloidal stability in human body. The study revealed that the apoptotic human umbilical vein endothelial cells (HUVECs) were significantly decreased. It indicated the suitability of SIA-PEGylated-SLNs for internalization by the inflamed vascular endothelial cells. Biodistribution study revealed higher renal accumulation of DXM (range 2.7- to 5.88-fold higher) after 6 h of intravenous administration. The Pharmacodynamic study revealed that higher blood biochemical indexes, histopathological changes, oxidative stress levels, and pro-inflammatory cytokines which indicated improved renal function by the influence of SIA-PEGylated DXM [64].

List of SLNs and their different ligand conjugated form targeting to the kidney have been summarized in **Table 5**.

10. Conclusion

Though drug targeting to a specific site in the body is an interesting approach, it is a highly challenging task. Despite that a large variety of smart nanocarriers have been developed for drug targeting in recent years, SLN has achieved a special status among them and can be employed for both passive as well as active targeting. These can be

employed for delivering not only the drug but also antibody, proteins, genes, imaging agents etc. and bring about increased cellular uptake at the targeted disease sites. Moreover, surface modification of SLNs through conjugation of various ligands on SLNs surfaces helped in enhancing its targeting efficacy in terms of cellular binding, uptake and intracellular transport to different cells as well as organs and ensure its greatest potentiality to combat wide ranges of diseases. However, the intrinsic complexity of biological environments strongly influences its functionality and often complicates their effective use for therapeutic treatments. Therefore, a deeper knowledge and understanding of the real interactions involved in the diseased tissues is fundamental for the development of therapeutic protocols of SLNs.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

Abbreviations

AM	alveolar macrophages
ANGPTL2 RNA	single-stranded proline-modified short hairpin anti-angiopoietin-like protein 2
AP-E	apolipoprotein E
ASGP	asialoglycoprotein
BAI	baicalein
BBR	berberine
BCL	baicalin
BH	betaxolol hydrochloride
CHO	cholesterol
CIR-780	cyanine-type IR-780
CMP	camptothecin
CO	cholesterol oleate
COMP	compritol 888 ATO
CP	cetyl palmitate
CRM	carmustine
c-SLN	cationic SLN
CSPT	cisplatin
Cs-SLN	chitosan coated SLNs
CUR	curcumin
CurB	curcumin B
DM	dimyristoyl
DMPC	1,2-dimyristoyl-sn-glycero-3-phospho-choline
DSPE	Distearoylphosphatidyl-ethanolamine
DSPEG	1,2-distearoyl-snglycero-3-phosphoethanolamine-N-[carboxy (polyethylene glycol)-2000]
DSGPC	1,2-distearoyl-sn-glycero-3-phosphocholine
DTX	docetaxel
DXM	dexamethasone
FA-PEG-SLN	folic acid-polyethylene glycol cross conjugated SLN
FB	<i>Ficus benjamina</i>
FR	folate receptor
F-SLN	fucose conjugated SLN
Ft-SLN	folate conjugated SLN
GB	glyceryl behenate

GEL	Gelucire®50/13
GL	glycerol
GMS	glyceryl monostearate
GS	glyceryl stearate
G-SLNs	galactosylated lipid conjugated SLNs
GT	glycerol trioleate
GTP	glyceryl tripalmitate
GTS	Glycerol tristearate
HSC	hepatic stellate cells
IMC	indomethacin
LDL	low density lipid
LfR	lactoferrin receptor
Lf-SLN	lactoferrin SLN
KTZ	ketoconazole
MIC	minimum inhibitory concentration
Mn (II) complex	[Mn ₂ (l (C ₆ H ₅) ₂ CHCOO) ₂ (bipy) ₄](bipy)(ClO ₄) ₂ complex
MR	mannose receptor
Msy-SLN	mannosylated SLN
Mt.	intercalated montmorillonite SLN
MTX	methotrexate
PA	palmitic acid
PC	phosphatidylcholine
PEG-SLN	PEGylated SLNs
PL	phospholipid
PL90NG	Phospholipon 90NG
PP	primaquine phosphate
PRE	Precirol ATO5
POPC	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine
PTX	paclitaxel
RIF	rifampicin
RFB	rifabutin
RSV	resveratrol
RLZ	riluzole
SA	stearic acid
SFB	sorafenib
SL	soya lecithin
SIA	sialic acid
siRNA	small interfering RNA
SD	Sprague-Dawley
SP	soybean phospholipid
SPC	soya phosphatidylcholine
STA	stearyl amine
TD	1-tetradecanol
TMC	tobramycin
TMP	temoporfin
TMP-I	trimethylphytosphingosine-iodide
TMS	trimyristin
TP	tripalmitate
TSN	tristearin
VIN	vinpocetine
WGA-SLN	wheat germ agglutinin conjugated SLN
3D7	asexual intraerythrocytic stage of <i>P. falciparum</i> laboratory strain (3D7)

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Author details

Bibhash Chandra Mohanta¹, Subas Chandra Dinda^{2*}, Narahari Narayan Palei³
and Jyotirmoy Deb⁴

1 Seemanta Institute of Pharmaceutical Sciences, Jharpokharia, Mayurbhanj,
Odisha, India

2 College of Pharmacy, Teerthanker Mahaveer University, Moradabad,
Uttar Pradesh, India

3 Sree Vidyanikethan College of Pharmacy, Tirupati, Andhra Pradesh, India

4 Department of Pharmacy, HUDA Group of Institution, Nagaon, Assam, India

*Address all correspondence to: subas.dinda@rediffmail.com

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