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Review Article

Theme: Lipid-Based Drug Delivery Strategies for Oral Drug Delivery
Guest Editor: Sanyog Jain

Lipid-Based Nanocarriers for Lymphatic Transportation

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Abstract. The effectiveness of any drug is dependent on to various factors like drug solubility, bioavailability, selection of appropriate delivery system, and proper route of administration. The oral route for the delivery of drugs is undoubtedly the most convenient, safest and has been widely used from past few decades for the effective delivery of drugs. However, despite of the numerous advantages that oral route offers, it often suffers certain limitations like low bioavailability due to poor water solubility as well as poor permeability of drugs, degradation of the drug in the physiological pH of the stomach, hepatic first-pass metabolism, *etc.* The researchers have been continuously working extensively to surmount and address appropriately the inherent drawbacks of the oral drug delivery. The constant and continuous efforts have led to the development of lipid-based nano drug delivery system to overcome the aforesaid associated challenges of the oral delivery through lymphatic transportation. The use of lymphatic route has demonstrated its critical and crucial role in overcoming the problem associated and related to low bioavailability of poorly water-soluble and poorly permeable drugs by bypassing intestinal absorption and possible first-pass metabolism. The current review summarizes the bonafide perks of using the lipid-based nanocarriers for the delivery of drugs using the lymphatic route. The lipid-based nanocarriers seem to be a promising delivery system which can be optimized and further explored as an alternative to the conventional dosage forms for the enhancement of oral bioavailability of drugs, with better patient compliance, minimum side effect, and improved the overall quality of life.

KEY WORDS: Lipid-based nanocarriers; lymphatic system; bioavailability; oral route.

INTRODUCTION

The oral route is often considered as one of the most convenient and safest routes of drug administration with better patient compliance when compared to the parenteral route. Nevertheless, despite various advantages of the oral route, the drug delivery often faces several drawbacks like low bioavailability of drug due to poor aqueous solubility or poor permeability, instability of drug within physiological pH of the stomach, hepatic first-pass metabolism, *etc.* However, the formulations have reportedly been formulated and optimized in order to avoid the aforesaid drawbacks (1).

The lymphatic system is one of the crucial systems that help to maintain the homeostasis by transporting the extracellular fluid. The system consists of the vessels that run in parallel throughout the body along the side of the blood circulatory system. The lymphatic system is primarily involved in maintaining the water balance within the body by reabsorbing the extracellular fluid that has been leaked from the interstitial space (2). The lymphatic system not only plays a central role in the immune cell transportation to the lymph nodes but also in the absorption of water-insoluble vitamins, fatty acids and cholesterol esters, *etc.* (3). One of the major advantages of using the lymphatic system is the avoidance of the first-pass metabolism and thus drugs undergoing extensive hepatic metabolism resulting in lower bioavailability can be given in systems which favor their lymphatic transportation. The lymphatic system can be used for the transportation of drug used in the treatment of cancer, human immunodeficiency virus, and various diagnostic agents (4), more effectively if they are primarily associated with lymphatics (Fig. 1).

Lipid-based nanocarriers or nanosystems have been extensively utilized for the improvement of bioavailability of drugs administered orally. However, using conventional dosage forms the enhanced bioavailability of poorly water-

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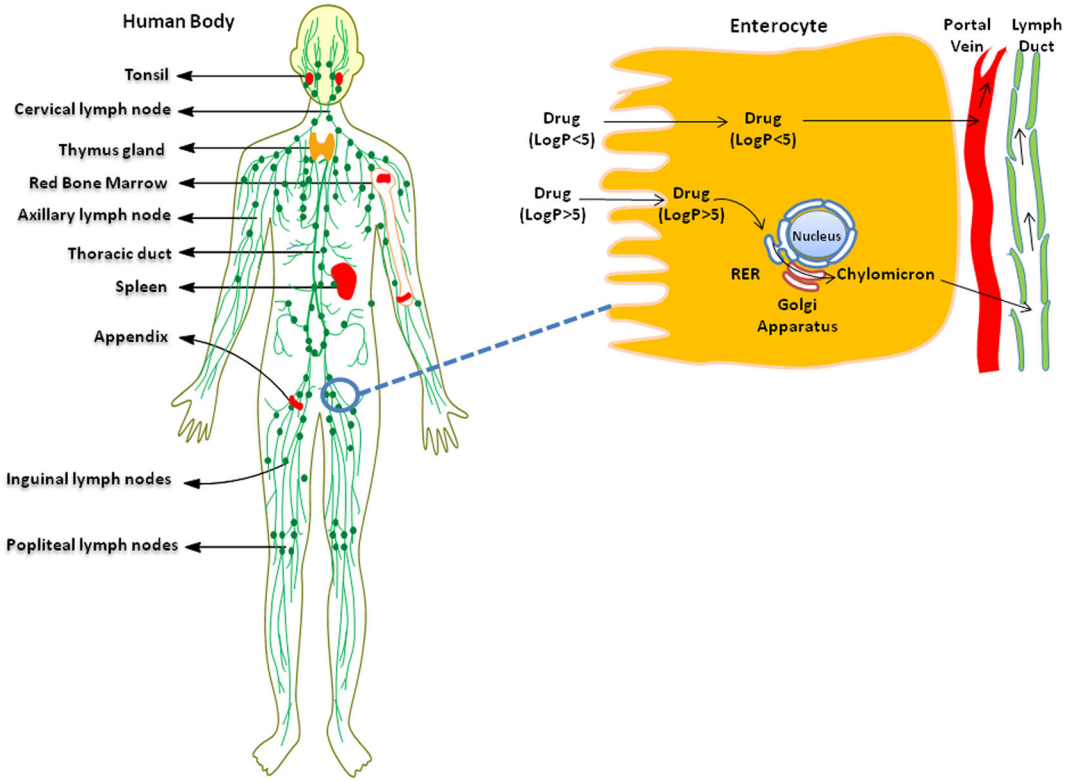

Fig. 1. Lymphatic system: anatomy and physiology and lymphatic transport of drugs

soluble drugs given orally is totally dependent on the absorption of the drug from the intestine. The factors which govern the use of nanocarriers as an effective drug carrier are solubility enhancement, GIT transit time, internalization by intestinal mucosa, *etc.* (5).

In the recent past, numerous nanosystem(s)/nanocarrier(s) (Fig. 2) such as liposomes, solid lipid nanoparticles, nano lipid carriers, lipid nanocapsules, niosomes, self-microemulsifying system, and solid self-emulsifying systems have already been reported for their potential and employability for the delivery of drugs *via* lymphatic system and diverse routes such as subcutaneous route, intraperitoneal route, intradermal route, pulmonary route, intrapleural, submucosal injection, *etc.* However, among all the available nanosystems, the systems which are based on lipid are better performing and hence preferred for lymphatic delivery of drugs (6). Lipid-based nanocarriers are favored over conventional dosage forms because they offer considerably improved oral bioavailability, with least variation in plasma profile and owing to superior and wide range availability of biocompatible lipoid additives, *etc.* (7).

These lipid-based nanosystems are helpful in enhancing the bioavailability of the drugs on account of absorption and transportation through lymphatic route. Lipophilic drugs can be incorporated in the lipid nanocarriers for the administration through the oral route. The lipid-based nanocarriers administered through oral route get transformed into or assembled in the core of a group of lipoproteins referred to as chylomicrons, which are then sampled by enterocytes from the intestine and presented to lymphatic transport system *via* mesenteric lymph (6).

MECHANISM OF LYMPHATIC UPTAKE

The absorption of the drug from the intestinal lymphatic system is quite a complex process and can be described as follows. The enterocytes in the intestinal tract are surrounded by lamina propria and thus have abundant supply of both blood and lymph. The orally administered drug can be absorbed through either blood capillaries or lymph capillaries for entry into systemic circulation (Fig. 3). The drug absorbed

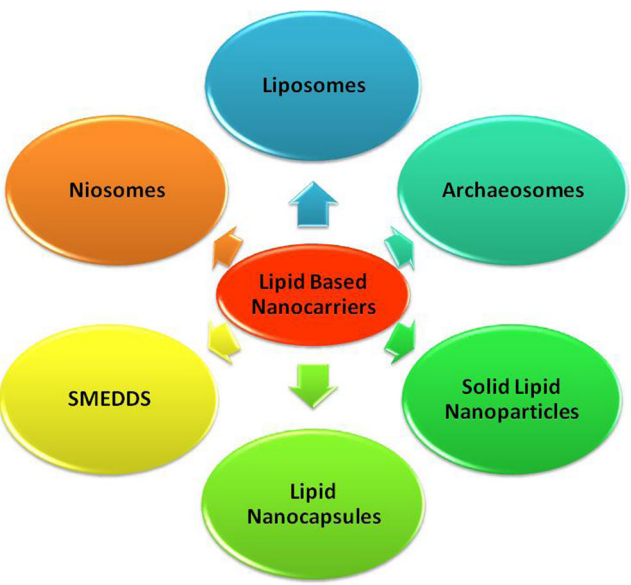

Fig. 2. Classification of lipid-based nanocarriers

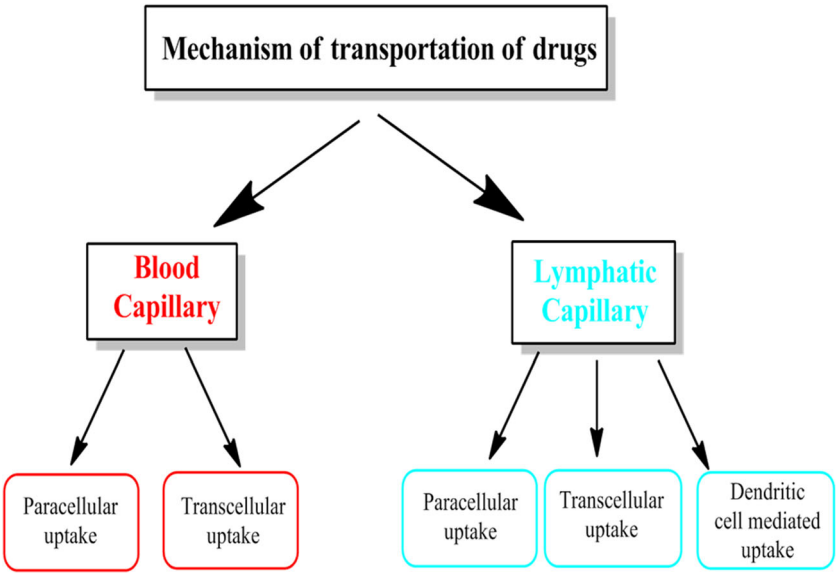

Fig. 3. Mechanism of transportation of drugs

into blood capillaries is transported into portal blood because the rate of flow of fluid is comparatively 500 times higher in portal blood than the intestinal lymph. However, the absorption of drug(s) with high molecular weight is restricted to lymphatic capillaries which are more permeable as compared to blood capillaries for absorption. These high molecular weight drug(s) bind or get accumulated in the core of the lipoproteins which aid to the entry and movement through and across the enterocytes. The diffusion of the drug-loaded chylomicrons across the endothelium is regulated by the size of such lipoproteins (8).

Lymphatic uptake of drugs follows three pathways. The first path involves the passage of the macromolecules from the highly permeable porous wall of the lymphatic system. The transfusion of macromolecules and large conjugates can be possibly enhanced with the use of absorption enhancer. The second path includes through of Peyer's patches due to the presence of lymphoid follicles in the gut tissues. The third path includes the transcellular absorption, paracellular transport, cytochrome P450 inhibition through intestinal walls, *etc.* (3) (Fig. 4). The underlying mechanism of lymphatic transport of lipid-based drugs/nanocarrier(s) is shown in Fig. 5.

STRATEGIES TO ENHANCE LYMPHATIC TRANSPORTATION OF DRUGS USING LIPID-BASED NANOCARRIERS

The lymphatic route of drug delivery is mainly used for the enhancement of oral bioavailability. The success of the delivery system depends on certain strategies which will promote the uptake of lipid-based nanocarriers by lymphatic route. The enhancement of lymphatic transport could be achieved either by making changes in the physicochemical properties of the nanocarriers like size (less than 100 nm), molecular weight (between 10 and 16 kD), surface charge (negatively charged > positively charged > neutral), lipophilicity (partition coefficient, *i.e.*, LogP greater than 5), use of lipophilic polymers like polystyrene, PMMA, *etc.* (solubility higher than 50 mg/ml in triglycerides), with the use of penetration enhancer (bile salts) or by using the formulation approaches like use of prodrugs [*e.g.*, palmitoyl propanolol hydrochloride (9)], making requisite modification on to the surface of nanocarriers with the use of ligands (lectins), PEG, biotin, *etc.* (10) (Fig. 6).

LIPID-BASED NANOCARRIERS

A wide number of nanocarriers have been explored for the lymphatic delivery of drugs like liposomes, archaeosomes, niosomes, solid lipid nanoparticle (SLN), *etc.* Some of them are discussed in the subsequent sections.

Liposomes

Liposomes are spherical vesicles of lipid that consists of one or more layers of phospholipid and cholesterol similar to the constitution of cell membranes. They can also be defined as the lipid bilayer system consisting of a hydrophilic core of size ranging from few nanometers to micrometers. Due to their lipid constitution, the lipophilic drugs can be incorporated into the lipid bilayer and the hydrophilic drug can be encapsulated and kept well protected within the formulated liposomes. Liposomes are widely used as a carrier for both lipophilic as well as hydrophilic molecules in pharmaceutical and cosmetic industries (11). The encapsulated drug(s) can be protected from degradation upon administration from harsh physiological pH of the stomach as well as from enzymatic degradation. The liposome can stimulate the formation of chylomicrons in enterocytes or can be combined with bile salts to form a mixed micellar structure thereby promoting the transportation of drug into the lymphatic system (12). Transportation of drugs using liposomes not only improves the absorption of the drug but also reduces the chances of toxicity through altered pharmacokinetic parameters. However, the delivery of drugs from oral liposomes may face stability issues in the GI conditions which can be overcome by making certain alterations in lipid compositions, including a coating of polymer, formulation of proliposomes and double

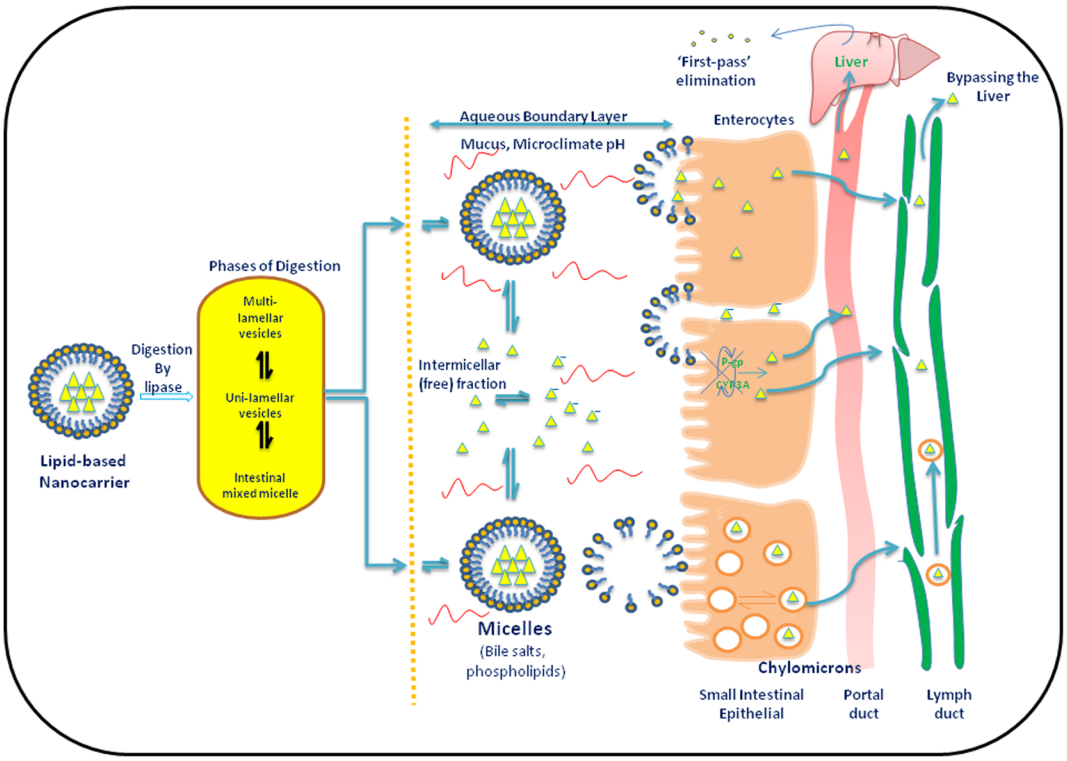

Fig. 4. Pathways involved in the lymphatic uptake of lipid-based formulations

liposomes, *etc.* The liposomes can be employed as an effective alternative for drug administration through routes such as the subcutaneous route, intestinal route, and pulmonary for lymphatic transport (5). Various modifications have been employed in conventional liposomes during the last decade for their effective delivery to and through the lymphatic system. Ye *et al.* have prepared 7-ethyl-10-hydroxycamptothecin containing nanoliposomes (SN-38-Lips) with the aim of enhancing lymphatic targeting following administration through the subcutaneous route using Borneol (S-BO) as a penetration enhancer. The lymphatic pharmacokinetics studies were performed in KM rats. The results of SN-38 nanoliposomes administration in

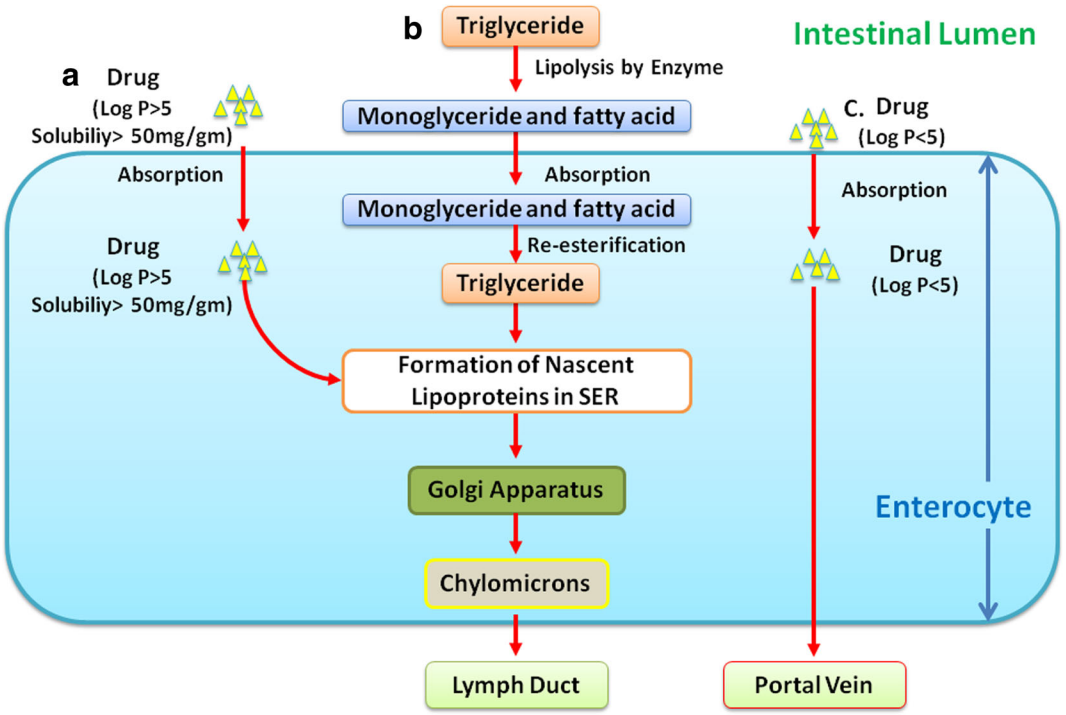

Fig. 5. Mechanism of lymphatic transport of lipid-based drugs/nanocarriers

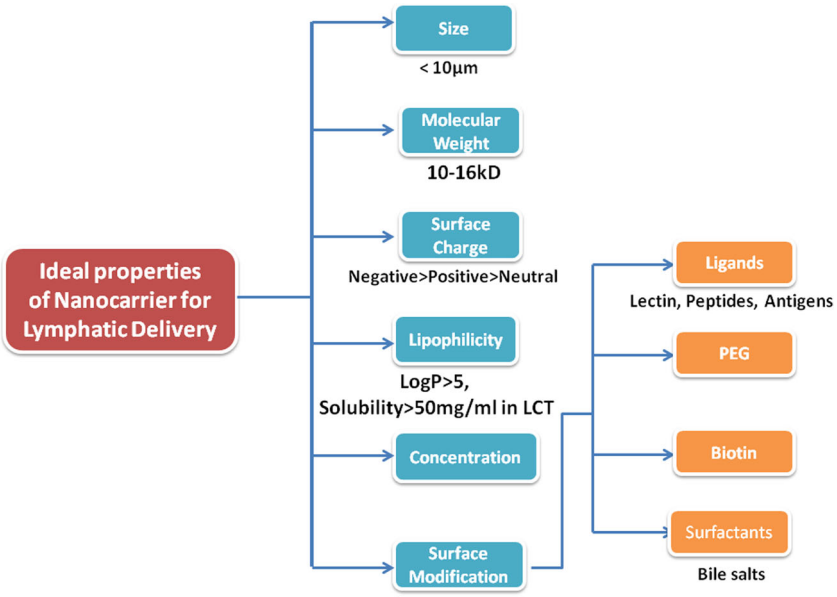

Fig. 6. Ideal properties of lipid-based nanocarriers requisite for lymphatic transportation of drugs

combination with 2 mg/ml of Borneol showed a significant increase in the lymphatic uptake and retention in popliteal, iliac, and renal lymph nodes (13). In another study, a modified form of the liposome, *i.e.*, proliposomes, containing lipophilic drug ritonavir has been formulated by Narayan *et al.* with the aim of promoting their targeting towards CD4+ T cells found in the lymphatic systems. The proliposomes were synthesized by using lipid thin film hydration technique and the suspension obtained was further lyophilized in the presence of a cryoprotectant, *i.e.*, mannitol. The prepared proliposomes were surface modified using biotin in order to improve their specificity towards the lymphatic tissues. The *in vivo* pharmacokinetic and biodistribution studies performed in Wistar rats revealed an increase in the extent of absorption of biotinylated liposomes by nearly 2 folds as compared to that of conventional liposomes. The AUC for the proliposomes was found to be much higher in the spleen and thymus compared to that in the plasma which indicated that the developed formulations could not only enhance the bioavailability but possessed target specificity as well in contrast to the pure drug (14). Another derivative of the liposomes, *i.e.*, bile salt liposomes (containing SGC, STC, or SDC), has been formulated by Niu *et al.* in order to enhance the oral absorption and bioavailability of insulin. The bile salt liposomes containing rhINS were prepared using the reverse phase evaporation method and the *in vivo* studies performed in male Wistar rats showed higher accumulation of rhINS as compared to that of conventional liposomes. The results from the studies also suggested that the bile salt liposomes could protect the rhINS from enzymatic degradation in GIT and also showed better biocompatibility, faster uptake as well as better rhINS transport when cultured with Caco-2 cells (15).

Archaeosomes

Archaeosomes word is the amalgamation of two words, *i.e.*, archaea and liposomes. These are basically liposomes consisting of membrane derived from one or two or a combination of more than two archeaobacterial diethers (archaeol) or tetraether (caldarchaeol) lipids (16) (Fig. 7). Archaeosomes are found to be noticeably stable against harsh environments like excessively low or acidic pH, the elevated temperature of more than 80 degrees (hyperthermophile), effects of biles and lipases, *etc.* Due to these reasons, the archeaosomes are also known as extremophiles (17). Archaeosomes are prepared using the reported procedure such as thin film, freeze-thawing, extrusion, reverse phase evaporation at any temperature and can encapsulate thermally stable compounds due to their hyperthermophilic nature, also they can prevent the oxidative degradation of the compounds (18). The *in vivo* and *in vitro* studies showed the absence of any sign of toxicity when tested on mice (16). Archaeosomes are reported to have an immune-adjuvant effect and can be used as an effective carrier for vaccines to provoke both humoral and cellular immune response against specific antigens (5). It is also reported that the administration of archaeosomes is well tolerated in murine models and quite safe (19). Li *et al.* (20) studied the pharmacodynamics of insulin-encapsulated archaeosomes in diabetic mice following

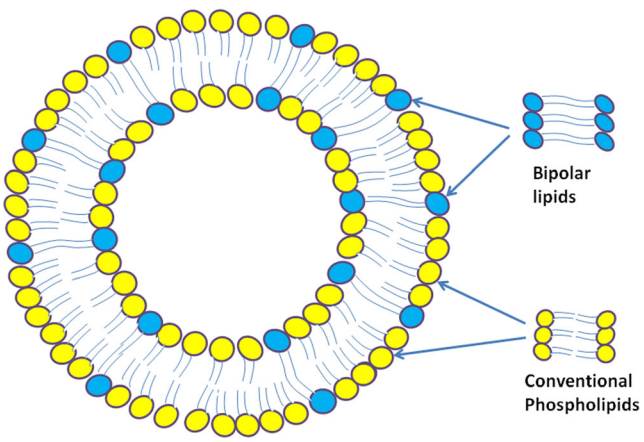

Fig. 7. Schematic representation of structure of archaeosomes

oral administration. Archaeosomes made of polar lipid fraction were stable in simulated GIT conditions and were also capable of controlling blood levels of glucose more precisely comparative to conventional liposomes. In another study by the same group, archaeosome-loaded ovalbumin antigen elicited an elevated systemic IgG response as well as mucosal IgA response, in addition to antigen-specific CD81 T cell proliferation. These data indicate that archaeosomes are prospective carriers and adjuvants for effective oral immunization (21).

Solid Lipid Nanoparticle

Drawbacks in the conventional dosage form lead to the development of an alternative effective novel approach for the delivery of drug with minimum side effects and maximum therapeutic potential. One such approach is the delivery of drug with the help of lipid-based nanosized particulate carriers which remain solid in the body as well as room temperature (Fig. 8). These solid lipid nanoparticles offer copious advantages over the conventional dosage forms such as physical stability and chemical stability, enhanced bioavailability, biocompatibility, sustained and prolonged drug release, enhanced uptake being particulates by Peyer's patches, and protection of drug from degradation (4). Solid lipid nanoparticles not only have the advantage of increased lymphatic uptake but it can also aid in reducing the activity of enzyme cytochrome P450 on the drugs as well it also improves the permeability of the drug through intestinal wall by reducing the P-glycoprotein efflux transport activity (22). Furthermore, the nanosize of the solid lipid nanoparticles facilitates the uptake of the substrate across the intestinal wall (23). SLNs utilized the perks both contributory of nanoscience and lipid science, thus can be used as an effective alternative to the already available therapeutic options (24).

SLNs are made up of triglyceride(s), their polar heads assemble themselves to form a polar crown towards the aqueous phase similar to that of chylomicrons (Fig. 5). Thus these self-assemblage characteristics of SLNs will promote their lymphatic transport as well as the absorption of drugs *via* or through enterocytes and intestinal epithelial cells (25).

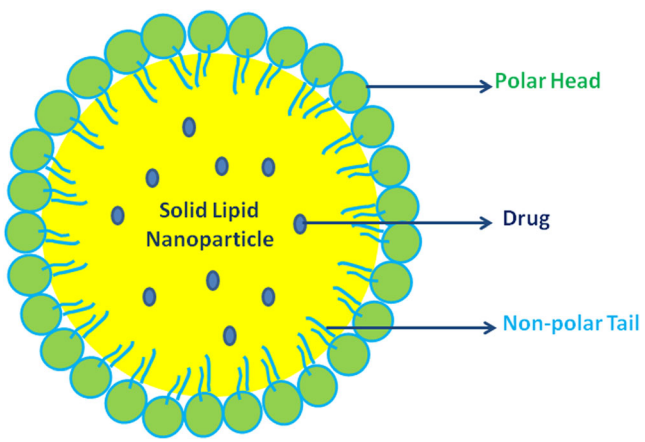

Fig. 8. Schematic representation of structure of solid lipid nanoparticles

Solid lipid nanoparticles have been reported to enhance the oral bioavailability of many drugs. Dudhipala *et al.* (26) formulated Capecitabine loaded solid lipid nanoparticles by microemulsion technique and demonstrated better anticancer activity in colon cancer induced by 1,2-dimethylhydrazine and also resulted in a marked increase in the oral bioavailability of Capecitabine by 2.76 folds as compared to that of suspension containing the same drug. Similarly, Desai *et al.* (27) have prepared the lipid nanoparticles of a lipophilic antiviral drug Darunavir using hydrogenated castor oil to overcome the problems like low oral bioavailability (nearly 37%) and low availability of the formulation to the target biocompartment, *i.e.*, the lymphoid system. The nanoparticles were prepared by using high-pressure homogenization and their *in vivo* pharmacokinetic studies performed in rats. The results showed a tremendous increase in relative bioavailability as well as an increase in trans GI barrier permeability by 4 folds as compared to the suspension formulation of Darunavir. In the similar manner, some researchers during the last few years have developed the solid lipid nanoparticles with the aim of enhancing the oral bioavailability and improved lymphatic uptake of some antiretroviral drugs such as Efavirenz (28), Lopinavir (22), Ritonavir (23), Curcumin (29), and Imatinib mesylate (30) (Table I). Nooli *et al.* (40) formulated solid lipid nanoparticles of Olmesartan medoxomil (OLM) for the delivery of a drug by the oral route. OLM has a poor oral bioavailability limiting to about 28% due to various reasons like efflux by P-glycoprotein, hepatic first-pass metabolism, and low aqueous solubility. The solid lipid nanoparticles containing OLM were prepared by emulsification and solvent evaporation methods. The data from the pharmacokinetic studies performed in rats revealed that on administering OLM in the form of oral suspension and SLN there was an increase in the relative bioavailability by 2.32 times in case of SLN. In another study, Zhao *et al.* (41) used solid lipid nanoparticles as a carrier for the encapsulation and delivery of a bioactive flavonoid Hydroxysafflor yellow A (HSYA) to overcome the problem of low systemic absorption and hence low bioavailability following the oral administration. The injection formulation is already available for clinical use; however, to avoid the inconvenience caused to the patients, there has been a critical requirement of the development of an effective oral formulation. Hence in an attempt, an oral formulation was developed based on solid lipid nanoparticles by warm microemulsion technique. The optimized HSYA solid lipid nanoparticles, on oral administration in rats, demonstrated an increase in systemic bioavailability by 3.97 fold. In another study, Mishra *et al.* (42) formulated Praziquantel loaded solid lipid nanoparticles for targeting the lymphatic system following oral administration. The perusal of the outcome of researches made in the last few years suggests that the solid lipid nanoparticles could be a promising carrier for the enhancement of oral bioavailability and improved lymphatic targeting of the poorly water-soluble drug(s).

Nanostructured Lipid Carriers

Solid lipid nanoparticles are made up of lipids that exist in a solid state at physiological temperature. SLNs offer

several advantages like improved oral bioavailability, biocompatibility, prevention of drug from degradation in the physiological pH of the stomach, controlled drug release and stability, *etc.* However, the delivery of the drugs with the help of SLN has certain limitations like limited drug loading efficiency, the release of the drug during storage, *etc.* This necessitates the development of formulation which will reduce the inherent drawbacks of the SLNs and deliver a drug with an enhanced bioavailability. One such system is NLCs or nanostructured lipid carriers with a distinctive structural composition based on liquid lipids and solid lipids in different parts (43). NLCs matrix comprises of a mixture of solid and liquid lipids which enable them to accumulate more drug, thereby improving the drug loading efficiency as well as preventing the loss of drug on account of release during the storage. The delivery of drugs that have been attempted by researchers in the last few years is discussed in Table I.

Lipid Nanocapsules

Lipid nanocapsules are nanosized vesicular bodies composed of both lipophilic and hydrophilic components encapsulated within a polymeric coating or membrane (Fig. 9) and were firstly synthesized by Couvreur and his coworkers (44). Nanocapsules can be used for improving the transport of the drug across biological membranes, for preferential uptake by the cell, modified biodistribution of the drug, *etc.* Depending on the type of core, the lipid nanocapsules can be used as a reservoir for both lipophilic as well as a hydrophilic core contents in the form of liquid or solid or molecular dispersion which will protect the drug from external harsh environmental factors (45). Nanocapsules are also reported to contain the drug or the active substance anchored chemically onto the surface or placed in the polymeric membrane. The polymeric coating will prevent the drug from degradation in the harsh physiological pH of the stomach as well as it can also be used to improve the biodistribution of nanocarrier by enabling subsequent modification of surface charge on the polymeric layer. Furthermore, the encapsulation of drug within nanocapsule will decrease the P-gp mediated efflux and the lipid nature of the nanocapsule will further accentuate the lymphatic transportation (46).

Various methods used for the production of nanocapsules include nanoprecipitation, layer by layer coating, double emulsification, polymer coating and emulsion coacervation, emulsion evaporation, *etc.* (47). The prepared nanocapsules can be characterized further for the various parameters such as average (mean) particle size, zeta potential, dispersion pH, shell thickness of the formulated nanocapsules, drug entrapment or encapsulation efficiency, cumulative drug release from the nanocapsules, and stability (48).

Varshosaz *et al.* prepared the lipid nanocapsules (LNCs) of efavirenz (EFV) by the phase-inversion temperature method and assessed various formulation parameters using Box-Behnken design. The LNCs were prepared using labrafac and solutol HS 15 and the optimized formulation showed an increased *ex vivo* intestinal permeation of EFV as compared to that of suspension of EFV. Thus, it can be concluded that an optimized formulation could be used for improved oral delivery of EFV (49). Peltier *et al.* reported enhancement of oral bioavailability of Paclitaxel upon administration through the oral route using lipid nanocapsule as a carrier (50). Thus from the studies, it can be concluded that lipid nanocapsules can be used as a potential carrier for the enhancement of oral bioavailability of drugs.

Self-Microemulsifying Drug Delivery Systems

It has been accepted that the drug delivery systems which are based on lipids have shown to play a crucial role in the enhancement of bioavailability of lipophilic drugs by overcoming the physiological barriers despite low dissolution rates (51). Self-microemulsifying drug delivery systems (SMEDDS or SEDDS) are microemulsions of size ranging between 100 and 200 nm composed of oils of natural or synthetic origin, surfactants (solid or liquid), and with alternatively one or more hydrophilic solvents/cosolvents/surfactants (52). The SMEDDS form a thermodynamically stable system and constituted by the isotropic mixture/blend of drug, oil, and surfactant. SEDDS or SMEDDS are usually administered in hard or soft gelatin capsules which upon oral administration undergo self-emulsification due to agitation within the GIT resulting into formation of microemulsion (o/w) or tiny oil droplets with the large surface area. The system not only facilitates the permeation of drug across the biological membrane but it also protects the drug from enzymatic hydrolysis in GIT and it bypasses the first-pass metabolism as well (53). SMEDDS are comparatively easy to prepare and are proven to be effective in improving the solubility as well as the bioavailability of poorly water-soluble drugs. The enhancement of bioavailability is due to the digestion of lipids present in the biliary and pancreatic secretions. These enzymes act on the interface of the o/w emulsion to form micelles leading to solubilization of the drug and their enhanced uptake by the lymphatic pathways (54). SMEDDS have gained popularity and emerged as a promising system for the delivery of drugs with poor aqueous solubility. The drug release from SMEDDS is relatively reproducible and is independent of the physiology and absence or presence of the food in the GIT (55).

Wang *et al.* (52) formulated the self-microemulsifying drug delivery system of silymarin and demonstrated that there is a remarkable enhancement in the relative bioavailability of silymarin by 1.88 and 48.82 folds as compared to when the same drug is delivered in the form of PEG 400 suspension and solution. Similarly, Zhang *et al.* (56) reported a remarkable increase in the oral bioavailability of Oridonin by 2.2 fold when it was delivered using SMEDDS as compared to that of suspension of Oridonin. Shen *et al.* (57) reported a significant increase in the bioavailability of the Atorvastatin SMEDDS capsules as compared to a tablet administered through the oral route. Cui *et al.* (58) developed SMEDDS of Curcumin for the improvement of its solubility and oral absorption as an effective probable alternative to conventionally available formulations given orally. Pokale *et al.* (55) formulated SMEDDS containing DRV (Darunavir) using Imwitor 988 as oil for lymphatic transport and the *in vivo* studies demonstrated a marked increase in solubility

Table I. Lipid-Based Nanocarriers for Lymphatic Transport

Nanosystem	Composition	Drug	Size (nm)	Targeted organ/ disease	Cell line/animal model	Remarks	References
Nano-liposome	Labrasol, EPC, cholesterol, Tween 80	Carvedilol	79.8	–	Male Wistar rats	The pharmacokinetics data showed a marked increase in the oral bioavailability by 2.3 fold	(31)
Solid lipid nanoparticles	Compritol 888 ATO, Pluronic F68	Imatinib mesylate	190	–	Rat	The pharmacokinetic studies revealed an increase in bioavailability of Imatinib mesylate by 1.9 fold and an increase in lymphatic transport by 4.6 fold	(30)
Solid lipid nanoparticles	Glyceryl monostearate, chitosan, stearylamine, Poloxamer 188, soya lecithin	Curcumin	182.0 ± 6.7	–	Sprague-Dawley rats	The optimized formulation showed an increase in relative bioavailability and lymphatic uptake of Curcumin	(29)
Solid lipid nanoparticles	Compritol 888 ATO (glyceryl behenate)	Ritonavir	323.35 ± 24.56	Intestinal lymphatic vessels	Wistar rats	The Cmax and Tmax of SLNs containing ritonavir were found to be significantly high in spleen and thymus as compared to pure drug	(23)
Solid lipid nanoparticles	Compritol 888 ATO (glyceryl behenate), Gelucire 44/14, soya lecithin, Poloxamer 188	Efavirenz	168.92 ± 31.16	HIV reservoirs	Sprague-Dawley rats	The results showed an increase in the bioavailability and enhanced targeted delivery of the drug to HIV reservoirs	(28)
Solid lipid nanoparticle	Compritol 888 ATO (glyceryl behenate), Pluronic F 127, mannitol	Lopinavir	230 ± 5.6	–	Male Wistar rats	The results from the pharmacokinetic studies showed an elevation in the mean plasma concentration of Lo_SLN by 2.13 fold	(22)
Nanostructured lipid carrier	Glyceryl monostearate, tripalmitate, Pluronic F-68	Olanzapine	158.5	–		The prepared NLCs containing Olanzapine showed an increase in Tmax by 5.26 fold as compared to that of oral suspension	(32)
Nanostructured lipid carrier	Glyceryl monocaprylate, glycerol dibehenate	Tacrolimus	98 ± 7.52	–	Albino Wistar rats	The result from the pharmacokinetic studies showed a marked enhancement in the relative bioavailability by 7.2 folds and an increase in the lymphatic distribution by 19.25 folds as compared to that of an oral suspension of Tacrolimus	(33)
Nanostructured lipid carrier	Cetyl palmitate, Gelucire, Comprotol 888, tripalmitin	Carvedilol	165.11–204.54	–	Wistar rats	The data from the *in vivo* absorption studies showed a significant increase in bioavailability of CAR-NLCs as	(34)

Table I. (continued)

Nanosystem	Composition	Drug	Size (nm)	Targeted organ/ disease	Cell line/animal model	Remarks	References
						compared to CAR-S (solution)	
Lipid nanocapsule	Kolliphor HS15, Labrafac	Gemcitabine	53–68	–	Swiss mice	The pharmacokinetic data showed lipid nanocapsule containing Gemcitabine was able to target the mediastinal lymph nodes and to combat the metastases locally.	(35)
Nanoemulsion	Castor Oil, Labrasol, PEG400, Labrafil M 1944	Berberine hydrochloride	–	–	Male Sprague-Dawley rats	The data obtained from the pharmacokinetic studies showed an increase in the AUC, Cmax, and Tmax by 4.4, 1.6, and 4.3 fold, respectively as compared to Berberine hydrochloride suspension	(36)
Self-nanoemulsifying oily formulations	Maisine, Transcutol HP	Lopinavir	53.16	HIV reservoir	Rats	The pharmacokinetic data showed a significant increase in the oral bioavailability of Lopinavir	(37)
Self-nanoemulsifying drug delivery system	Labrafil, olive oil, Lauroglycol FCC, Labrasol, and Transcutol P	Trans-resveratrol	56.73		Rats	The data from the pharmacokinetic studies showed a marked increase in the permeability through the intestine	(38)
Self-nanoemulsifying drug delivery system	Kolliphor HS-15, propylene glycol, MCT	Bruceine D	18.03 ± 0.59		Rats	The pharmacokinetic studies showed a significant increase in the plasma drug concentration of drug when administered in SNEDDS as compared to Bruceine suspension	(39)

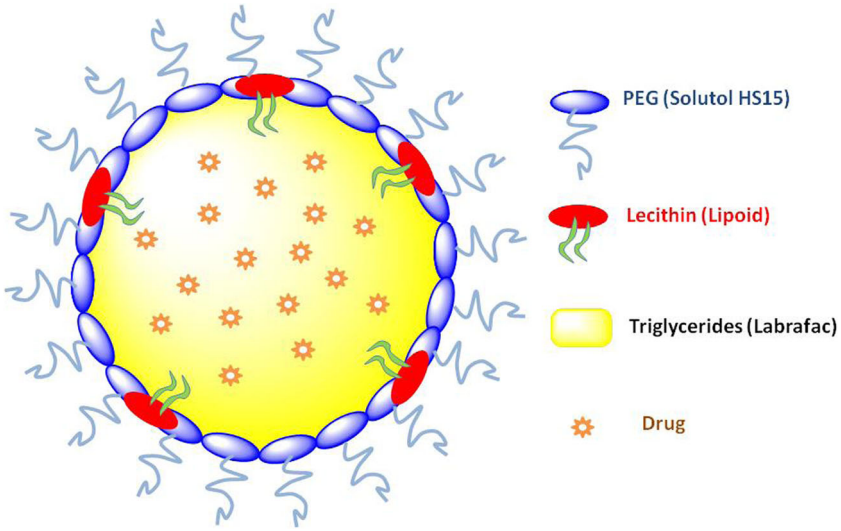

Fig. 9. Schematic representation of structure of lipid nanocapsule

as well as the bioavailability of the drug administered in DRVs in comparison to the marketed tablet of the same.

Self-Nanoemulsifying Drug Delivery Systems

Another lipid-based formulation which can promote the rate of absorption of the poorly water-soluble drug is self-nanoemulsifying drug delivery systems (SNEDDs). These SNEDDs are basically an anhydrous form of nanoemulsions composed of a uniform mixture of the drug with oil, surfactants, and co-surfactants. SNEDDs is one of the carriers which is reported to enhance the bioavailability and lymphatic transport of drugs by minimalizing the metabolism of lipophilic drugs by cytochrome P-450 found in abundance in the enterocytes (38) Few examples of the SNEDDs formulated with the aim of enhancing oral bioavailability by lymphatic route are given in Table I.

Nanoemulsion

Another effective alternative approach for the improvement of oral bioavailability is by the use of nanoemulsions. The nanoemulsions can be defined as a biphasic system consisting of nanosized globules in the size range between 30 and 500 nm. Nanoemulsions are thermodynamically stable dosage form composed of oil, water, surfactant, or co-surfactants and the dispersion might appear as a transparent or translucent depending on its composition (59). Nanoemulsions offer an advantage of rapid onset time as it does not require any extra time to form dispersion like the existing SEDDS. Nanoemulsions can be used as potential delivery system for the enhancement of oral bioavailability by encouraging the solubilization of the drug within the GIT, enhancing the GIT retention, and stimulating the lymphatic uptake by reducing the efflux activity by P-glycoprotein and promoting the permeability of the intestinal wall (60). Nanoemulsions for the lymphatic transport and enhancement of oral bioavailability of drugs have been explored by researchers and some of the recent researches and their outcomes are listed in Table I.

Microemulsions

Microemulsions are thermodynamically stable, biphasic system containing the droplet of oil/water in the size range of 10–100 nm and are known to enhance the lymphatic absorption of drugs (61). Microemulsions can be utilized for the improvement of oral bioavailability of poorly soluble drugs with the aid of lymphatic transportation. Modified or altered microemulsions, *i.e.*, SMEDDS, have already been discussed earlier in this review and are proved to enhance the lymphatic uptake of the drugs and their oral bioavailability.

Polymer-Lipid Hybrid Nanoparticles

Polymer-lipid hybrid nanoparticles have been developed with an aim to overcome the inadequacies of lipid-based nanoparticles and polymer nanoparticles. These possess the properties of both polymer nanoparticles and lipid nanoparticles. The polymer is responsible for controlling the release of the drug from the nanosystem whereas the lipid enhances the penetration across the biological membrane as well as the entrapment efficiency of drugs (62).

The term hybrid is used because the system comprises three major components, *i.e.*, polymer, lipid, and drug. Some researchers have reported the enhancement of oral bioavailability by improved lymphatic transport of the drugs. Wang *et al.* formulated polymer-lipid hybrid nanoparticles containing cabazitaxel and the data from the *in vivo* studies showed a marked enhancement in the oral bioavailability of cabazitaxel by 56.6%. The formulation also showed an increase in the inhibition of tumor growth when tested in a subcutaneous H22 liver cancer model (63).

Niosomes

Niosomes are the novel carriers prepared using non-ionic surfactants which self-assemble to form a vesicle and were reported by a cosmetic industry for the first time in the 1970s (64). Niosomes are non-ionic surfactant vesicles made up of polyoxyethylene, polyglycerol, crown ether, hydrophilic amphiphiles, and hydrophobic alkyl groups (64). Due to their inherent

Table II. Patents on Lipid Nanocarriers for Lymphatic Transport

Patent number	Kind code	Nanocarrier	Title of patent	Application/ publication date	Significance	Reference
US20170333362	A1	Solid lipid particle	Stable solid lipid particle composition for improved bioavailability of lipophilic compounds for age-related diseases	2017-11-23	The patent provides information for the delivery of lipophilic drugs or compounds specifically for age-related diseases	(69)
CN103405752	A	Solid lipid nanoparticle	Oral thymosin alpha-1 solid lipid nanoparticle absorption preparation and preparing method thereof	2013-11-27	The patent application involves the formulation of solid lipid nanoparticle for oral absorption of Thymosin alpha 1	(70)
CN101129375	B	Solid lipid nanoparticle	Vinorelbine solid lipid nano granule, freeze drying formulated product and method of preparing the same	2010-12-22	The patent focuses on the method of preparation of Vinorelbine solid lipid nanoparticles for the improvement of its anticancer reactivity	(71)
CN101926779	A	Solid lipid nanoparticle	Gemcitabine solid lipid nanospheres, preparation method thereof and use thereof	2010-12-29	The invention relates to the formulation of solid lipid nanoparticles of anti-tumor agent gemcitabine with the aim of promoting clinical application range	(72)
CN104055733	B	SMEDDS	Indirubin one kind SMEDDS its preparation method	2017-07-18	The patent focuses on the development of SMEDDs system containing Indirubin with the aim of reducing the number of doses to achieve prolong time and to enhance better patient compliance	(73)
CN105640886	A	SMEDDS	Sirolimus self-microemulsion preparation and preparation method thereof	2016-06-08	The patent aims in improving the solubility and dissolution rate of Sirolimus, providing high yield, a low-cost formulation which can be prepared with ease by large-scale industrial production and provide subsequent economic benefits	(74)
CN102008471	B	SMEDDS	Lacidipine self-microemulsifying soft capsules and preparation method thereof	2012-12-19	The present invention involves the formulation of SMEDDS soft capsules containing Lacidipine for the enhancement of its oral bioavailability by absorption through lymphatic route	(75)
WO2012033478	A1	SEDDS	An improved oral dosage form of tetrahydrocannabinol and a method of avoiding and/or suppressing hepatic first-pass metabolism *via* targeted chylomicron/lipoprotein delivery	2012-03-15	The invention aims in providing a better delivery system or pharmaceutical formulation for enhancing the bioavailability, minimizing the gastric irritation and the effective delivery of the dronabinol or A^9-THC through an alternative pathway, *i.e.*, *via* lymphatic transport	(76)

advantages over liposomes such as improved chemical stability, low production cost, *etc.*, the niosomes are preferred more as a novel drug delivery system for the drugs. The niosomal system may enhance the bioavailability of poorly water-soluble drugs by promoting the absorption of the drug in GIT *via* transcytosis through intestinal lymphatic tissue (65). Similarly, Jain *et al.* reported a marked increase in lymph concentration of rifampicin by 46.2% when the drug is administered in a niosomal formulation as compared to plain rifampicin (66). The niosomal formulations have also been reported by Jain *et al.*, for the lymphatic delivery of encapsulated Methotrexate for the enhancement of its bioavailability (67). Arzani *et al.* have prepared the three niosomal formulations of Carvedilol, *viz* plain niosomes, bile salt-enriched niosomes, and charged niosomes, and studied their effect on the relative bioavailability. They reported that the relative bioavailability of the bile salt-enriched niosomes was

found to be enhanced by approximately 1.84 folds whereas the relative bioavailability of the charged niosomes (positively charged and negatively charged) were found to be 2.3 and 1.7 folds higher than that of the suspension formulations (68).

The lymphatic transportation of drugs with the aid of nanocarriers has been continuously explored. A number of patents are granted/applied for, which will enable the availability of formulations in the market and help the patients to retrieve the benefits associated. Table II summarizes the list of some of the patents applied/granted in the field of nanocarrier for lymphatic transportations.

CONCLUSION

The lymphatic system plays a significant role in the progression of various deleterious diseases and thus delivery systems which have affinity towards the lymphatic uptake could be used effectively for targeted delivery of medicaments or drugs. The use of lipid-based nanocarriers will improve the lymphatic uptake of the drugs. The lipid-based nanocarriers are able to provide numerous advantages for the effective delivery of drugs with poor water solubility, poor permeability, prevention from enzymatic degradation, effective targeted delivery, and subsequent enhancement in the uptake of the drugs from lymphatic route resulting into better bioavailability. Hence, by utilizing the advantages of the lipid-based nanocarriers, the administration of the drugs by the oral route and its inherent benefits can be maximized.

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