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Review Article

Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages

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Abstract

During the recent years, more attentions have been focused on lipid base drug delivery system to overcome some limitations of conventional formulations. Among these delivery systems solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are promising delivery systems due to the ease of manufacturing processes, scale up capability, biocompatibility, and also biodegradability of formulation constituents and many other advantages which could be related to specific route of administration or nature of the materials are to be loaded to these delivery systems. The aim of this article is to review the advantages and limitations of these delivery systems based on the route of administration and to emphasis the effectiveness of such formulations.

Keywords: Drug delivery systems; Nanoparticles; Nanostructured lipid carriers (NLCs); Routes of administration; Solid lipid nanoparticles (SLNs).

CONTENTS

1.INTRODUCTION

Lipid nanoparticles as drug delivery systems were considered from the beginning of the 19th century by professor R. H. Müller from Germany and Professor M. Gascon from Italy (1,2). These nanoparticles are manufactured from solid or mixture of solid and liquid lipids and stabilized by emulsifiers.

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Lipids used in these nanoparticles are biocompatible and completely tolerated by the body like triglycerides, fatty acids, steroids, and waxes. In addition, using combination of emulsifiers could stabilize the formulations more efficiently. Lipid nanoparticles have many advantages in comparison to other particulate systems such as the ease of large-scale production (3), biocompatible and biodegradable nature of the materials (4), low toxicity potential (5), possibility of controlled and modified drug release (6), drug solubility enhancement and the possibility of both hydrophilic and lipophilic drug incorporation. Lipid nanoparticles are different from micro-emulsions, which are clear thermodynamically stable dispersion of oil and water that are stabilized by surfactants and cosurfactants (7,8). The most important parameters in lipid nanoparticles characterization are particle size and size distribution, zeta potential, polymorphism, degree of crystallinity, drug loading, entrapment efficiency, and drug release. There are three different types of lipid nanoparticles: homogenous drug-lipid matrix, drug enriched core and drug enriched shell. Drug release from lipid nanoparticles is mostly dependent on the matrix type and location of drug in matrix formulation; for example in the third type, drug release from the nanocarriers shows more sustained release profile. The composition of lipid matrix, surfactant concentration and manufacturing parameters, such as temperature and stirring rate, can also affect drug release profiles. Probably the most important reasons of using lipid nanoparticles, as a suitable alternative of previous polymeric nanoparticles, are the ease of large-scale production and their low toxicity potential (1).

2. TYPES OF LIPID NANOPARTICLES

Solid lipid nanoparticles (SLNs) are the first generation of lipid-based nanocarriers that are formulated from lipids, which are solid in the body temperature and stabilized by emulsifiers (1). SLNs have submicron (less than 1000 nm) sizes (9). They have numerous advantages such as drug protection against harsh environmental situations, ease of large scale production using high pressure homogenization technique, biocompatibility, and biodegradability (10). SLNs have also some disadvantages; because of their perfect crystalline structure, they have low drug loading efficiency (10) and the possibility of drug expulsion due to the crystallization process during the storage conditions. Another drawback is initial burst release (11) which usually occurs with these formulations. In SLNs drug molecules orients between the fatty acid chains or glycerides and during the storage periods and polymorphic changes in solid lipid structures there is a tendency to expulsion of previously dissolved drug in SLNs. Fig. 1 illustrates the actual place of drug orientation in SLNs and nanostructured lipid carriers (NLCs) schematically.

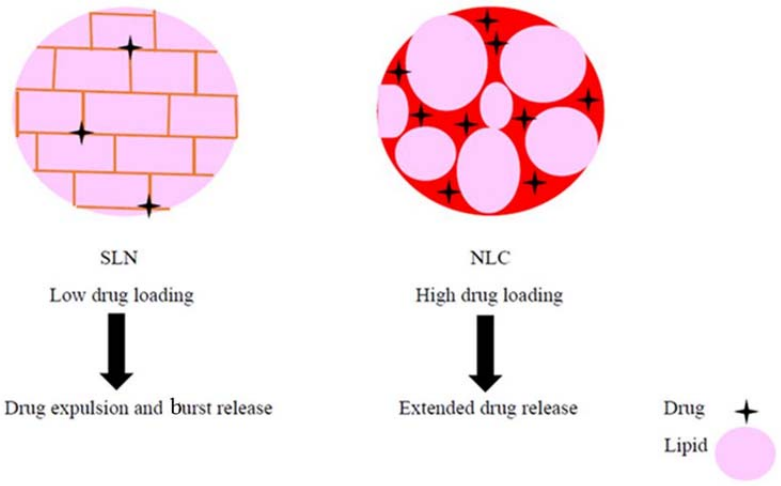

Fig. 1. Schematic view of the solid lipid nanoparticle (SLN) and nanostructured lipid carriers (NLCs) showing the drug location within the lipid matrix.

NLCs are second generation of lipid-based nanocarriers formed from mixture of solid and liquid lipids and have unstructured-matrix due to the different moieties of the constituents of NLCs (2). NLCs were designed in order to overcome the SLNs limitations. NLCs have higher drug loading capacity because of imperfect crystal structure and could avoid drug expulsion by avoiding lipid crystallization during the manufacturing and storage periods. Due to the presence of liquid lipids in NLCs formulation expulsion of loaded drug after formulation and during the storage period is minimized. NLCs also can increase drug solubility in lipid matrix and they can show more controllable release profiles in comparison to SLNs (12). Although NLCs are solid in nature even in body temperature but they have low melting point than SLNs and due to their unstructured nature and imperfection in their crystalline behaviors provide more space for drug dissolution and payload in liquid part of the NLCs. In this regard, loading capacity in NLCs are more than SLNs. Previous researches also confirm on less susceptibility of NLCs than SLNs to gelation during the preparation and storage period, which is another advantage of NLCs, NLCs can facilitate separation of nanoparticle from the rest of the medium and dosage form preparation for parenteral administration (2,12).

3. METHODS OF LIPID NANO-PARTICLES PREPARATION

Lipid nanoparticles could be prepared by different methods such as hot and cold high pressure homogenization (13,14), solvent emulsification/evaporation (15), microemulsion formation technique (16), and ultrasonic solvent emulsification (3). Large-scale productions of lipid nanoparticles are mainly obtained by high pressure homogenization technique.

3.1. High pressure homogenization technique

3.1.1. Hot high pressure homogenization

In this method, lipid phase is heated up to 90 °C, then the hot lipid phase is dispersed in aqueous phase containing surfactants with same temperature. The pre-emulsion is homogenized at 90 °C under 3 cycles of high pressure homogenizer at 5×10^7 Pa. Finally, the obtained oil in water emulsion is cooled down to room temperature to solidify SLNs or NLCs (17).

3.1.2. Cold high pressure homogenization

In this method, the melted lipid phase is cooled to solidify and then ground to form lipid microparticles. Obtained lipid microparticles are dispersed in cool aqueous phase containing surfactants to form pre-suspension. Then the pre-suspension is homogenized under 5 cycles of high pressure homogenizer at room temperature and pressure of 1.5×10^8 Pa (18).

3.2. Solvent emulsification/evaporation technique

In this method, lipid phase is dissolved in an organic solvent such as acetone (organic phase). Then the organic phase is added to the aqueous phase (surfactant solution in water) under continuous stirring at 70-80 °C. The stirring will be continued until the organic phase is completely evaporated. Then obtained nanoemulsion is cooled (below 5 °C) to solidify lipid nanoparticles (15).

3.3. Microemulsion formation technique

In this method, lipids are melted at appropriate temperature and aqueous phase containing surfactants are heated up to same temperature. Then the hot aqueous phase will be added to the melted lipids under stirring at the same temperature. The hot oil in water microemulsion is dispersed in cold water at 1:50 ratio to solidify lipid nanoparticles (19).

3.4. Ultrasonic solvent emulsification technique

In this method, lipid phase is dissolved in an organic solvent such as dichloromethane and heated up to 50 °C. Then, aqueous phase containing surfactants and emulsifiers is heated up to the same temperature. After partial evaporation of dichloromethane, the aqueous phase is added to the organic phase under stirring at 50 °C. Obtained emulsion is sonicated for appropriate time and finally cooled in an ice bath to solidify lipid nanoparticles (3).

4. LIPID NANOPARTICLES APPLICATIONS AND DIFFERENT ROUTES OF ADMINISTRATION

Numerous articles are reviewed and the results are categorized according to the routes of drug administration to six topics of topical, oral, parenteral, ocular, lung and brain delivery as shown in Table 1.

4.1. Topical route of administration

Skin related diseases are very common around the world. The major limitations for treatment of these diseases are low drug efficacy because of poor skin penetration or skin permeation of drugs from the most conventional formulations. Stratum corneum of epidermis is the major skin barrier and it should be bypassed through changing the penetration pathway from transcellular to paracellular or follicles. Lipid nanoparticles such as SLNs and NLCs have been developed to increase skin penetration or permeation. These particulate formulations are manufactured by mixing SLNs or NLCs with conventional formulations. They could be directly prepared in a one-step process which produce drug-loaded SLNs or NLCs. Lipid nanoparticles have so many advantages for topical drug delivery such as biocompatibility and biodegradability, controlled and extended drug release profile, close contact and strong skin adhesion, skin hydration and film formation in order to increase skin and dermal penetration (Table 2) (27,29,35,36, 40).

Table 1. Different loaded active compound and routes of administration of lipid nanoparticles.

	Route of administration	First author	Year(s)	Reference(s)	Loaded drug
1	**Topical**	Garazi Gainza	2014	(20)	RhEGF
		Carla Vitorino	2014	(21)	Olanzapine and simvastatin
		Garazi Gainza	2015	(22)	rhEGF
		Jana Pardeike	2009	(18)	-
		Petra O. Nnamani	2014	(23)	Artemether
		Jun-Hyung Park	2015	(24)	DH-I-180-3
		Mara Ferreira	2016	(25)	Methotrexate
		Amit K. Jain	2014	(26)	Adapalene
		Dhruv Butani	2016	(27)	Amphotericin B
		Silke B. Lohan	2015	(28)	Coenzyme Q10
		Jin Chen	2017	(29)	Resveratrol and Vitamin E and EGCG
		Volkhard Jenning	2000	(30)	Vitamin A
		Jana Štecová	2007	(31)	Cyproterone acetate
		Melike Üner	2014	(32)	Loratadine
		Mahesh L. Bikkad	2014	(33)	Halobetasol propionate
		Ponwanit Charoenputtakhun	2013	(34)	Retinoic acid
		Eline Desmet	2016	(35)	-
		Andreas Lauterbach	2015	(36)	-
		RAINER H. MÜLLER	2014	(37)	-
		Ümİt Gönüllü	2014	(38)	Lornoxicam
		Hamed Hamishehkar	2014	(39)	Caffeine
		Joana Marto	2017	(40)	N-Acetyl-D-Glucosamine
		Carmelo Puglia	2012, 2014, 2016	(41-43)	Caffeine, sesamol
		Veerawat Teeranachaideekul	2017	(44)	Capsaicin

Table 1. (Continued)

	Route of administration	First author	Year(s)	Reference(s)	Loaded drug
2	**Oral**	R.H. M¨uller	2006	(45)	Cyclosporine
		Yaowaporn Sangsen	2015	(46)	Oxyresveratrol
		Chun-Yang Zhuang	2010	(47)	Vinpocetine
		Mingzhu Shangguan	2015	(48)	Silymarin
		Yongtai Zhang	2016	(49)	*trans*-Ferulic acid
		Anuj Garg	2017	(50)	Lumefantrine
		Marzia Cirri	2017	(51)	Hydrochlorothiazide
		Jingjing Luan	2015	(52)	Baicalin
		A.I. Mendes	2013	(53)	Miconazole
		Nisharani S. Ranpise	2014	(54)	Lercanidipine hydrochloride
		Punna Rao Ravi	2014	(55)	Raloxifene
		Arpana Patil-Gadhe	2014	(56)	Montelukast
		L.M.D. Gonçalves	2016	(57)	Glibenclamide
		Deepti Pandita	2014	(58)	Resveratrol
		Preshita P. Desai	2012	(59)	-
		Ana Beloqui	2013	(60)	-
		Mansi K Shah	2017	(61)	-
		Marc Muchow	2008	(62)	-
		Sara Nunes	2017	(63)	Phenolic Compounds
		Shasha Rao	2016	(64)	-
3	**Ocular**	Antonio Leonardi	2014	(65)	-
		Anthony A. Attama	2008	(66)	Diclofenac sodium
		Xiang Li	2008	(67)	Ibuprofen
		Qiuhua Luo	2011	(68)	Flurbiprofen
		J. Araújo	2009, 2010	(69,70)	Triamcinolone acetonide
		Joana F. Fangueiro	2014	(71)	-
		Sai Prachetan Balguri	2016, 2017	(72,73)	Ciprofloxacin, indomethacin
		Patrizia Chetoni	2016	(74)	Tobramycin
		E. Sánchez-López	2017 (part I, II)	(75,76)	-
		Dandan Liu	2017	(77)	Coumarin
		Hugo Almeida	2014	(78)	-
		Lígia M. Andrade	2016	(79)	Voriconazole
		Ebru Bas¸aran	2010	(80)	Cyclosporine-A
		Luigi Battaglia	2016	(81)	-
		Ali Seyfoddin	2010	(82)	-
		Eliana B. Souto	2010	(83)	Anti-Inflammatory Drugs
4	**Parenteral**	S.A. Wissing	2004	(84)	-
		António J. Almeida	2007	(85)	Peptides and proteins
		Ho Lun Wong	2007	(86)	Anticancer drugs
		Ghaith Hommoss	2017	(87)	Tetrahydrocannabinol
		Rainer H. Muller	2004	(88)	Biotech drugs
		Chong-Kook Kim	2010	(89)	Itraconazole
		Ketki Bhise	2017	(90)	Polyphenols
		Lejiao Jia	2010	(91)	Silybin
		Donghua Liu	2011	(92)	Docetaxel
		Jingjing Luan	2014	(93)	-
		Medha D. Joshi	2009	(94)	Amoitone B

Table 1. (Continued)

	Route of administration	First author	Year(s)	Reference(s)	Loaded drug
		Elham Ajorlou	2017	(95)	-
		Samuel V. Mussi	2013	(96)	Doxorubicin and DHA
		Akhayacatra Chinsriwongkul	2011	(97)	all-*trans* retinoic acid (ATRA)
		Miaojing Wu	2015	(98)	Vincristine and temozolomide
		Susana Martins	2007	(99)	Peptides and proteins
		Omer Salman Qureshi	2017	(100)	Docetaxel
		Alam Zeb	2017	(101)	Itraconazole
		Sara Ahmadnia	2013	(102)	Albendazole sulfoxide
5	**Pulmonary**	David Cipolla	2014	(103)	-
		Oleh Taratula	2013	(104)	Doxorubicin or paclitaxel and siRNA
		J. Pardeike	2011	(105)	Itraconazole
		Arpana Patil-Gadhe	2014, 2016	(106,107)	Montelukast, rosuvastatin
		Alberto Hidalgo	2015	(108)	-
		Ram R. Patlolla	2010	(109)	Celecoxib
		Noha Nafee	2014	(110)	Quorum sensing inhibitors
		M. Paranjpe	2014	(111)	Sildenafil
		María Moreno-Sastre	2016	(112)	Tobramycin
		Yun Zhao	2017	(113)	Yuxingcao
		Shaimaa Makled	2017	(114)	Phosphodiesterase-5-inhibitor
		Germán A. Islan	2016	(115)	Levofloxacin and DNase
		S. Weber	2014	(116)	-
		Jana Pardeike	2016	(117)	Itraconazole
		Prabhjot Kaur	2014	(118)	Paclitaxel
		Mukta Paranjpe	2014	(119)	-
6	**Brain delivery**	Indu Pal Kaur	2008	(120)	-
		R. Dal Magro	2017	(121)	-
		Paolo Blasi	2007, 2011, 2013	(122-125)	-
		Lucia Gastaldi	2014	(126)	-
		Lucia Montenegro	2011	(127)	Idebenone
		Sonal Patel	2011	(128)	Risperidone
		Giovanni Tosi	2016	(129)	-

Table 2. Lipid nanoparticles advantages and disadvantages as topical drug delivery systems.

Advantages	Disadvantages/limitations
✓ Increased skin penetration and/or skin permeation (18, 25)	× Restricted transdermal drug delivery
✓ Biocompatible and biodegradable nature (24)	× Loss of high amounts of drug (2)
✓ Accumulation and film formation which promote skin hydration (26)	× Lack of robust controlled drug release (36)
✓ Easy and scalable production process (32)	
✓ Increased drug solubility and longer skin deposition (act as drug reservoir) (25)	
✓ Avoid systemic absorption and side effects in dermal drug delivery purpose (36)	
✓ Possibility of specific follicular targeting (36)	
✓ Good stability during storage period (39)	

4.2. Oral route

Oral drug administration is the most common route of drug delivery system because of the highest patient compliance. Low oral bioavailability due to limited drug solubility and/or high hepatic first pass effect are the most important limitations in oral drug delivery that should be overcome. Nanoparticle-based drug delivery systems were considered as suitable delivery system to increase oral bioavailability. Lipid nanoparticles such as SLNs and NLCs have the advantage of sustained drug release capability to maintain a constant plasma levels. In addition, nanoparticles with higher specific surface area and higher saturation solubility have more rapid dissolution rate that can accelerate the onset of drugs action. Other major barriers in oral drug delivery are p-glycoprotein efflux pumps and chemical or enzymatic degradation. Recent researches have shown that some specific lipids or surfactants, which are used in lipid nanoparticles, are capable of inhibiting p-glycoprotein efflux pumps. Drug-loaded lipid nanoparticles could reduce chemical or enzymatic degradation of the drugs which are embedded in a lipid matrix. Lipid nanoparticles could promote lymphatic transport and can bypass the liver and avoid hepatic first pass effect (50-52,130,131). Lipid nanoparticles advantages and disadvantages for oral route are listed in Table 3.

4.3. Ocular administration

Ocular drug delivery has many limitations and remains challenging because of specific physiological and anatomical features of the eyes. Eyes are a very complex and sophisticated organ and have several barriers that should be overcome in order to reach specific ocular tissue. Novel drug delivery systems such as lipid nanoparticles were considered to overcome these barriers and improve ocular tissue bioavailability. Topical application is the most common route of drug delivery to the anterior segment of the eyes. This route of administration has many advantages and is the choice for superficial ocular diseases. Major barriers in this pathway are corneal epithelium, blood ocular barrier, conjunctival blood flow, and tear drainage. Lipid nanoparticles which are used as ocular drug delivery systems are capable of passing blood ocular barrier, obtain sustained and controlled drug release, protect drugs from lacrimal enzymes and prolong drug deposition and residence time in eyes. Treatment of ocular diseases, which involve posterior segment of the eyes, is very difficult. There are different ways to target posterior segment of the eyes.

Topical route is not a suitable way to target intraocular tissues; other routes that are used for this purpose are transscleral delivery (subconjunctival and retrobulbar injection), intravitreal route, subretinal injection, etc. Most of these ways are invasive, so novel drug delivery systems such as lipid nanoparticles could be an appropriate alternative. Gene therapy for the purpose of retinal targeting in retinal diseases was also considered using non-viral vectors gene delivery including SLNs and NLCs (73-76,81). A brief list of advantages and disadvantages of this route of administration are listed in Table 4.

Table 3. Lipid nanoparticles advantages and disadvantages as oral drug delivery systems.

Advantages	Disadvantages/limitations
✓ Improving oral bioavailability (45)	× Lipid dispersions contain high amounts of water (60)
✓ Reducing hepatic first pass metabolism (46)	× Drug expulsion during storage (60)
✓ By passing p-glycoprotein efflux pumps (47)	× Limited loading capacity for hydrophilic drugs (49)
✓ Protecting drug from intra-enterocyte metabolism (132)	× Polymorphic transition (58)
✓ Low variation in oral absorption (50)	× Particle size growth during storage time (64)
✓ Preventing undesired plasma peak (62)	× Gelation of lipid dispersions (131)
✓ Modulated and controlled drug release (63)	
✓ Increasing AUC and MRT values (49)	
✓ Shorter onset of action and longer duration time (51,57)	

Table 4. Lipid nanoparticles advantages and disadvantages as ocular drug delivery systems.

Advantages	Disadvantages/limitations
✓ High encapsulation efficiency (66) ✓ High ocular permeation (67) ✓ Appropriate pharmacokinetic properties (74) ✓ Sustained and controlled release (75) ✓ Enhancing drug corneal permeability (76) ✓ Enhancing drug pre-corneal retention time (73) ✓ Increasing ocular bioavailability and distribution (69) ✓ Preventing ocular toxicity (78) ✓ Positively charged lipid nanoparticles have longer ocular retention time because of close contact with negative mucous (80) ✓ Good stability and biocompatibility (79) ✓ Maintaining sufficient drug levels in aqueous humor, vitreous humor and retina (81)	× Initial burst release from SLNs (66) × Low drug loading capacity (74) × Not extended clinical trials have been recently done for these formulation and most of the studies were just *in vitro* assessment (76) × Lipid nanoparticles toxicity on retinal cells have not been studied completely yet (82) × Although lipid nanoparticles are biocompatible, but particle size, charge, exposure time and drug concentration are also important factors in retinal toxicity

Table 5. Lipid nanoparticles advantages and disadvantages as parenteral drug delivery systems.

Advantages	Disadvantages/limitations
✓ Scale up feasibility (84) ✓ Long physical stability (84) ✓ Controlled and sustained drug release (90) ✓ Three to five-fold increment in drug plasma peaks (84) ✓ Lower clearance rate and smaller volume of distribution (95) ✓ Limited side effects (94) ✓ Good potential as vaccine adjuvants (94) ✓ Specific accumulation in Kupffer cells for targeted liver delivery in liver diseases (84) ✓ Longer drug circulation time (133) ✓ Lower cytotoxicity (84) ✓ Improving drug bioavailability (133) ✓ Enhancing drug permeability and retention in tumor tissues (EPR) (90)	× Drug burst release by erosion mechanism (84) × Lack of wide clinical studies (86) × Low drug payload for hydrophilic drugs (134) × Drug expulsion (84) × Reticuloendothelial system (RES) clearance for systemic cytotoxic drug delivery (135) × Accumulation of lipid in liver and spleen may cause pathological alteration specially with Compritol-containing SLNs (136) × EPR is a very heterogeneous phenomenon and could vary significantly from animal model to human or from one patient to another

SLN, solid lipid nanoparticle.

4.4. Parenteral administration

Nanomedicine and nanotechnology play an important role in improving the parenteral drug delivery. Lipid nanoparticles advantages and disadvantages as parenteral drug delivery systems are listed in Table 5. The most important advantages of lipid nanoparticles for this purpose are ease of scale up production, biocompatible and biodegradable nature of the formulation constituents, controlled and modified drug release pattern, preventing drug degradation and maintaining more constant serum levels of drugs. Drug-loaded lipid nanoparticles may be injected intravenously, subcutaneously, intramuscularly, and directlyto target organs. Drug release from lipid nanoparticles may occur via erosion (such as enzymatic degradation) or via diffusion which could support a sustained drug release. Recent researches have confirmed the capability of lipid nanoparticles in peptide and protein incorporation. In this context, SLNs are not suitable carrier due to limited drug loading capacity but NLCs are appropriate alternative. In this method peptides and proteins can be protected from harsh environmental conditions (92,93,97,100).

4.5. Pulmonary delivery

Pulmonary drug delivery is a relatively new approach, which has many advantages. It is a non-invasive route of drug delivery for both local and systemic administration. By this direct delivery system, drug dosage may be decreased and consequently drug adverse effects would be reduced. Direct drug inhalation can also accelerate onset of action. High drug accumulation in target site is another advantage of such administration route. Large surface area of pulmonary system and thin alveolar epithelium could guarantee high drug permeability. Lipid microparticles

were used as delivery systems for lung targeting. These particulate systems showed good results such as drug bioavailability enhancement in comparison with conventional formulations. Lipid nanoparticles including SLNs and NLCs have been considered for pulmonary delivery. They have the advantage of sustaining drug release, biocompatibility and biodegradablity, lower toxicity and better stability in comparison with previously designed particulate systems. Pulmonary delivery of drug-loaded nanoparticles would result in high local concentration and can reduce systemic adverse effects. Also nanoparticles can achieve higher bioavailability for systemic delivery purposes. Lipid nanoparticles used in lung drug delivery, like other routes of administration, have the advantage of sustained drug delivery (103,114,117,118). Some of the most important advantages and limitations of this route of administration are listed in Table 6.

4.6. Brain delivery

Drug delivery to the brain is one of the most important challenges in pharmaceutical sciences because of the presence of blood brain barrier (BBB). Nanoparticles with the advantage of small particle size and high drug encapsulation efficiency have been considered for specific targeting of brain tissues. Since nanoparticles can bypass reticuloendothelial system (RES), they are suitable as brain drug delivery systems. Two major obstacles in brain drug delivery are limited penetration of drugs across BBB and efflux of transported drugs from brain to blood circulation. Lipid nanoparticles such as SLNs and NLCs are one of the colloidal drug delivery systems that have been utilized to overcome these barriers. Lipid nanoparticles advantages and limitations as brain drug delivery systems are listed in Table 7. Lipid nanoparticles have the advantage of increasing drug retention time in blood of brain capillaries and inducing a drug gradient from blood to brain tissues, opening tight junctions to facilitate passage from BBB and transcytosis of drug-loaded lipid nanoparticles through the endothelium layer. Lipid nanoparticles are suitable for incorporating both lipophilic and hydrophilic drugs which could be administered via different routes (120-129). Previous researches emphasized on significant effect of surfactant suitability for brain drug delivery. Appropriate surfactants could be chosen according to their HLB and packing parameter. For site-specific brain drug delivery, polysorbates especially polysorbate 80, has shown best results. In addition, results showed that positively charged lipid nanoparticles induce better drug accumulation in the brain (123).

Table 6. Lipid nanoparticles advantages and disadvantages as pulmonary drug delivery systems.

Advantages	Disadvantages/limitations
✓ Better biopharmaceutical properties (103)	× No human safety data available
✓ Sustained drug release (105)	× Change in drug release profile because of lipase degradation in some lipid matrix compositions (103)
✓ Obtaining high local concentration (106)	
✓ Obtaining better bioavailability (108)	× Burst drug release from these nanocarriers may induce toxic effects (137)
✓ Prolong drug residence time in lung (109)	
✓ Potential in lung cancer treatment by loading chemotherapeutic drugs in lipid nanoparticles (118)	× Macrophage drug clearance (rapid clearance) (108)
✓ Potential gene delivery of cationic SLNs	× Not suitable for deep lung delivery because of their small particle size so they should be encapsulate in lipid microparticles (106)
✓ Prevention of adverse drug effects (119)	
✓ Good storage stability (103)	× Agglomeration, clotting and fragmentation of lipid nanoparticles during nebulization (111)
✓ Low toxicity (105)	
✓ Increasing patient compliance (112)	× Loss of loaded drug during nebulization (116)
✓ Bypassing hepatic first pass metabolism (106)	
✓ Mucoadhesiveness (114)	
✓ Long dosing intervals (112)	
✓ Preventing premature degradation of peptides and proteins in pulmonary systemic drug delivery purposes (116)	

SLN, solid lipid nanoparticle.

Table 7. Lipid nanoparticles advantages and disadvantages as brain drug delivery systems

Advantages	Disadvantages/limitations
✓ Significant increase in brain uptake of drugs (123) ✓ Biocompatibility, biodegradability and low cytotoxicity (121) ✓ Bypassing blood brain barrier (129) ✓ Enhancing drug retention time in brain (123) ✓ Opening tight junctions (129) ✓ Increasing brain bioavailability by polysorbate 80-coated lipid nanoparticles (123) ✓ Inhibition of efflux system (especially P-gp) (129) ✓ Controlled drug release (122) ✓ Long storage stability (125) ✓ Non-invasive brain drug delivery (129) ✓ Possibility of both hydrophilic and lipophilic drug encapsulation (120) ✓ Possibility of administration via different routes for brain targeted delivery (121) ✓ Possibility of site specific brain targeting by SLN-apolipoprotein E (121) ✓ Achieving highest drug concentration in the brain using lipid nanoparticles with particle size less than 100 nm (121, 123)	× The possibility of the detection of lipid nanoparticles by reticuloendothelial system (RES) cells (123) × Rapid clearance of IV administered drug-loaded SLNs from systemic circulation (121)

P-gp, permeability glycoprotein; SLN, solid lipid nanoparticle; IV, intravenous.

5. COMMERCIALLY AVAILABLE PRODUCTS FROM LIPID NANO-PARTICLES IN MARKET

Today, most of the commercially available products from lipid nanoparticles are cosmetic products such as Cutanova Cream Nano Repair Q10, Intensive Serum Nano Repair Q10, Cutanova Cream Nano Vital Q10, SURMER Crème Legère Nano-Protection, SURMER Crème Riche Nano-Restructurante, SURMER Elixir du Beauté Nano-Vitalisant, SURMER Masque Crème Nano-Hydratant, NanoLipid Restore CLR, NanoLipid Q10 CLR, NanoLipid Basic CLR, NanoLipid Repair CLR, IOPE SuperVital cream, serum, eye cream, extra moist softener and extra moist emulsion, NLC Deep Effect Eye Serum, NLC Deep Effect Repair Cream, NLC Deep Effect Reconstruction Cream, NLC Deep Effect Reconstruction Serum, Regenerations Creme Intensiv Scholl, Swiss Cellular White Illuminating Eye Essence, Swiss Cellular White Intensive Ampoules, SURMER Creme Contour Des Yeux Nano-Remodelante, Olivenöl Anti Falten Pflegekonzentrat, Olivenöl Augenpflegebalsam (18).

6. CONCLUSION

lipid nanoparticles are novel drug deivery systems which have many advantages over other colloidal and polymeric nanocarriers. The most important advantages of lipid carriers are their biocompatibility, biodegradability, ease of scalability, and controlled and modified release patterns. Among these two types of lipid nanoparticles (SLN and NLC), NLCs as a second generation of lipid nanoparticles, has shown better results for the purpose of targeted drug delivery and nowadays are more considered for different routes of administration. Lipid nanoparticles are suitable carriers for both hydrophilic and lipophilic drugs. They can be administered by different routes such as topical, oral, parenteral, ocular, pulmonary, brain drug delivery. These nanoparticles for each routes of administration have its own advantages and also limitations that should be considered. Lipid nanoaprticles are promising drug delivery systems for delivery of various pharmaceutically important active ingredients from small molecule to protein and gene in early future.

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