Iranian Journal of Veterinary Science and Technology

Received: 2018- Sep-26
Accepted after revision: 2018- Dec-12
Published online: 2019- Mar- 10

REVIEW ARTICLE

DOI: 10.22067/veterinary.v2i10.75569

# Lipid-based nanoparticles as novel drug delivery systems for antimicrobial agents

Ali Rassouli[a], Alwan Al-Qushawi[b]

[a]Department of Comparative BioScience, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran. [b]Faculty of Dentistry, Wasit University, Al Kūt, Iraq.

## ABSTRACT

Despite the development of novel drugs and technologies in combating the infectious diseases, they remain as a global health challenge. The use of conventional antimicrobial drugs are always associated with problems such as antimicrobial resistance, adverse effects, and inefficient drug delivery. In this regard, the unique physiochemical properties of the nanoparticles have led to increase in the researches on nanoparticles and their application as promising antimicrobial products. Lipid nanoparticles (LNPs) are new carrier systems developed as an alternative to traditional nanoparticle vehicles. The solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLCs), lipid-drug conjugates (LDCs), Lipid-core nanocapsules (LNCs) and lipid-polymer nanoparticles (LPNs) are carriers with a lipid matrix showing advantages for different applications due to the use of biodegradable, and biocompatible lipids. LNPs have exclusive properties owing to their ultra-small size and high surface area, thereby, they are able to increase drug targeting, treatment efficiency and reduce the toxicity of antimicrobial drugs. LNPs are often used as sustained release systems, and they also used for improving drug bioavailability. It has been found that the composition and structure of LNPs are two critical factors that may influence their pharmaceutical performance in different body organs. This review focuses on the development of LNP systems for antimicrobial drugs delivery and gives an overview on the modern LNP- based therapeutic strategies against the infections. The mechanism of action and advantages of these nanoparticles as antibacterial, antifungal, antiviral and anti-parasitic agents are highlighted in this review.

**Keywords**

*lipid nanoparticles; drug delivery; carrier systems; antimicrobial agents; infectious diseases*

**Abbreviations**

LNPs: Lipid nanoparticles
SLNs: solid lipid nanoparticles
NLC: nanostructured lipid carriers
LDCs: lipid-drug conjugates
LNCs: Lipid-core nanocapsules
LPNs: lipid-polymer nanoparticles



*Corresponding author:*
*Ali Rassouli*
*Tell/Fax: +98 21 66933222*
*Email: arasooli@ut.ac.ir*

## Introduction

An antimicrobial refers to an agent that kills or inhibits microorganisms by interfering with their growth [1]. Conventional antimicrobial therapy consists of using chemotherapeutic agents or antibiotics to treat the infectious diseases [2].With the commercial production of the first antibiotic penicillin in the late 1940s, use of the antimicrobial agents to treat the infectious diseases ranges from the topical ointments to intravenously injected solutions [3]. Infectious diseases, whether intracellular, extracellular, or biofilm-mediated infections, have always been a global problem causing millions of deaths each year [2].

Antimicrobial agents do suffer from a range of limitations, like narrow spectrum of activity, problems regarding the safety and tolerability, side effects and toxicity, and allergic reactions. Inefficient delivery of the drugs has been one of the major limitations of conventional antimicrobial therapy [2]. Another major limitation of antimicrobial therapy is the development of bacterial resistance to these agents by using different mechanisms. Some organisms are so refractory that they can only be treated with the experimental and potentially toxic drugs [4]. Also, intracellular infections remain difficult to treat because of the low antimicrobial activity inside the cells due to their difficult transport through the cell membranes [1, 5]. Moreover, the treatment of chronically infected conditions such as cystic fibrosis (CF) disease is another challenge in antimicrobial therapy because treating such conditions necessitates frequent intravenous administrations of high-dose antibiotics [4, 6].

One of the promising efforts to address this challenging and dynamic pattern of infectious diseases is the use of nanotechnology [2]. Because of their very small size, nanoparticles have much greater biological access, so they are more likely, than larger particles , to enter cells, tissues and organs [5]. Nanoparticles (NPs) are particulate dispersions, or solid particles with a size range of 10-1000 nm [2]. NPs usually have unique physicochemical, and biological properties which can be exploited for desired applications [7]. Rapid advances in the NPs production with uniform size, shape and composition have caused a revolution in the pharmaceutical sciences. These properties can be used to overcome some of the limitations of conventional antimicrobial agents and to be used as vehicles to carry these therapeutic agents [5, 8, 9]. The NPs drug delivery systems can improve the quality of antimicrobial therapy by decreasing their side effects, reducing the frequency of drug administration via prolongation of drug residence time, controllable uniform distribution in the target tissue, improved solubility, sustained and controlled release, and enhanced cellular internalization (Figure 1) [4,10].

Among the different nanoparticle carriers, the lipid nanoparticles (LNPs) represent important systems [11]. LNPs are useful for therapeutic purposes because of their special properties, including high surface to mass ratio and ability to bind and carry different compounds. LNPs can facilitate the dissolution of poorly water-soluble drugs, and increase drug absorption. Moreover, LNPs have good biocompatibility, lower cytotoxicity, good production scalability, as well as being able to modulate drug release, and to prevent the usage of organic solvents in the preparation process [12]. An essential advantage of LNPs in comparison to other lipid colloidal drug delivery systems such as liposomes and niosomes, is the high kinetic stability and rigid morphology [13].

In general, NPs can be classified into: (a) nanospheres, with a homogeneous structure, and (b) nanocapsules, with a core-shell structure. The performance of LNPs is greatly influenced by their composition. LNPs are generally composed of lipids, surfactants and co-surfactants. In most cases, LNPs are produced as dispersions and surface-tailored with surfactants to improve dispersion stability. Polymers are often used to form polymer-lipid cores or lipid-polymer core in the production of LNPs (Table 1) [13].

Due to the limitations accompanied with conventional antimicrobial therapy, this review focuses on the development of LNPs delivery systems for these chemotherapeutic agents. The current progress and challenges in synthesizing lipid nanoparticle platforms for delivering various antimicrobial, and employing nanotechnology as a new paradigm in controlling infectious diseases by reducing the amount, frequency of treatment, and thereby more patient compliance and less undesirable side effects of a given drug are also discussed.

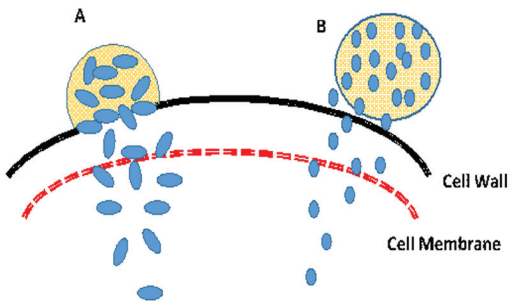


**Figure 1**
Cellular internalization of antimicrobial drug-lipid nanoparticles into microorganisms: (a) nanoparticles fuse with microbial cell wall or membrane and release the carried drugs; (b) nanoparticles bind to cell wall and serve as a drug depot to continuously release drug molecules. Redrawn from reference [1].

**Table 1**
Summary of lipid-based nanoparticle characteristics including solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLCs), lipid-drug conjugates (LDCs), lipid-core nanocapsules (LNCs) and lipid-polymer hybrid nanoparticles (LPNs).

| Lipid carrier | lipid composition | Structure & Assembly | Properties | Ref. |
|---|---|---|---|---|
| **SLN** | Solid lipids: pure triglycerides, glyceride mixtures, waxes (primarily saturated fatty acid chains) | Nanosphere: solid lipid with a surfactant coating | Hydrophobic in nature; used for different routes of administration; burst release more common; lower drug loading for hydrophilic compounds | [82] |
| **NLC** | Solid lipids and liquid lipids (oils): pure triglycerides, glyceride mixtures, with saturated and unsaturated fatty acid chains, waxes | Nanosphere: Blend of solid and liquid lipid phases with a surfactant coating | As 2nd-generation SLNs: better control of drug release, higher drug loading capacity | [82] |
| **LNCs** | A dispersion of lipids (medium chain triglycerides and fatty acids) with different surfactant/co-surfactants | Nanocapsule: Lipid core with polymeric shell | High capacity of lipid core for drug loading with protective envelope; more sustained drug release | [11 ,18, 64] |
| **LDCs** | Fatty acids/phospholipids conjugated to the drug molecule | Nanosphere | Drugs bind to lipids, enhance lipophilicity of hydrophilic drugs and cell membrane penetration | [12, 14, 83] |
| **LPNs** | Phospholipids | Nanocapsule: Polymer core with Lipid coat | Physical core stability due to polymer matrix; promising anti-biofilm activity | [6, 20] |

## *Types of LNPs*

### *Solid lipid nanoparticles (SLNs)*

SLNs are LNPs which were developed at the beginning of the 1990s as an alternative novel carrier system to liposomes, and polymeric nanoparticles. They are produced by replacing the liquid lipid of an emulsion by a solid lipid. The lipid particle matrix being solid at both room and body temperature. SLNs offer unique properties such as smaller size range of 50-1000 nm and larger surface area. These feautures are attractive for their ability to improve performance of pharmaceuticals. They are primarily composed of solid lipids from either physiological lipids or lipids generally regarded as safe status. SLNs possess a solid lipid core matrix that can solubilize lipophilic molecules, and this core is stabilized by surfactants [14, 15]. SLNs have potentially wide applications including parenteral delivery, ocular delivery, rectal delivery, oral delivery, topical delivery and vaccine delivery systems by improving bioavailability and controlled release characteristics [12]. In addition, SLNs can be used as an antimicrobial drug delivery platform (Table 2) [2]. However, the development of SLNs is impeded by some barriers. The most significant one is its low drug loading capacity for hydrophilic drugs. Secondly, burst release is more common for SLNs due to their open metrical structure (Figure 2A) [15].

### *Nanostructured lipid carriers (NLCs)*

This generation of LNPs consists of mixture of solid and liquid lipids with a special nanostructure. NLCs improve drug loading and firmly incorporate the drug during storage (Figure 2B). Therefore, the NLCs system minimizes or avoids some potential problems associated with SLNs [12, 14]. NLCs reduce burst release of drug and provide better control of drug release. The highest drug load could be achieved by mixing solid lipids with small amounts of liquid lipids (oils) which are called imperfections in the crystal [12, 16]. NLCs may find extensive application in topical drug delivery, oral and parenteral administration of cosmetic and pharmaceutical active ingredients (Table 3) [14].

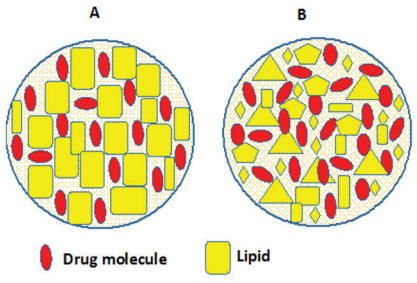


**Figure 2**
Structure of solid lipid nanoparticle (A) and nanostructured lipid carrier (B). Redrawn from reference [17].

**Table 2**
Properties of some of the solid lipid nanoparticles (SLNs) studied as drug delivery for antimicrobial drugs.

| Drug (Year) | Size (nm) | Lipid composition | Surfactant/ co-surfactant | (EE) (%) | Application/ Study | Ref. |
|---|---|---|---|---|---|---|
| **Econazole (2007)** | 139 ± 12.7 | Glyceropalmito-stea-rate | Tween 80 | 97-102 | Topical *in vivo* (hu-man) & *in vitro* (pig ear skin) | [33] |
| **Ciprofloxacin (2008)** | 73-98 | Stearic acid | Phosphatidyl-choline/ Sodium taurocholate | 37.8 ± 2.38 | *In vitro* release | [80] |
| **Ofloxacin (2011)** | 156 ± 7.5 | Palmitic acid | Poly vinyl alcohol | 41.4 ± 1.5 | Oral *in vitro* & *in vivo* (mice): PK, PD | [48] |
| **Amikacin (2013)** | 164 ± 7 | Cholestrol | Tween 80 | 89 ± 6 | Pulmonary & IV *in vivo* (rats) | [40] |
| **Erythromycin (2014)** | 153 ± 2.3 | Glycerylmono-stea-rate | Poloxamer 188/ soya lecithin | 88.4 ± 2.09 | *In vivo* (rats) | [45] |
| **Tilmicosin (2016)** | 186.3 ± 1.5 | Hydrogenated caster oil | Poly vinyl alcohol | 69.1 ± 2.8 | Oral *in vitro* & *in vivo* (chicken) | [64, 65] |

### *Lipid-core nanocapsules (LNCs)*

Nanocapsules are vesicular carriers constituted of an oil core surrounded by a polymeric wall [18]. The core acts as a liquid reservoir for several drugs, and the shell as a protective membrane. In particular, lipid nanocapsules, have special use for encapsulating and delivering hydrophobic drugs. Thanks to the drug protection and their controlled release, these kinds of nanoparticles provide an ideal solution for drug delivery, leading to selective toxicity, minimizing the serious side effects [19]. Recently, a new hybrid and promising lipid- nanocapsules were developed named lipid-core nanocapsules (LNCs), which are composed of a lipid core (containing a dispersion of sorbitan monostearate and medium chain triacylglyceride) and a polymer envelope (Table 4) (Figure 3) [11, 18]. The sustained release from those carriers could be a consequence of the variation of the core viscosity and the particle surface area [20].

### *Other lipid nanoparticles delivery systems*

Lipid drug conjugates (LDCs)-NPs is a special form of nanoparticles. A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process, and only highly potent hydrophilic drugs which are effective in low concentrations can be firmly incorporated in the solid lipid matrix [12, 21]. In order to overcome this limitation, LDCs-NPs with high drug loading capacities as much as 33% were developed. Such matrices may have potential applications in brain targeting of hydrophilic drugs in serious protozoan infections (Table 5) [12, 14].

Another kind of lipid nanocapsules has been recently developed that combines the advantages of colloidal particles and lipid delivery systems organized in an internal liquid or semi-liquid oil core, and an external lipid layer solid at room temperature. These have nearly the same particle size as SLNs, but they have a core-shell structure [8, 22]. Their structure mimics lipoproteins, while they have a hybrid structure between polymer nanocapsules and liposomes. These nanocapsules are composed of a medium chain triglyceride core of capric and caprylic acids known under the commercial name of Labrafac that is surrounded by a shell composed of lecithin and a surfactant called Solutol® HS, through incorporating hydrophilic and lipophilic surfactants (Figure 4) [23- 25].

Lipid-polymer hybrid nanoparticles (LPNs), where antibiotic-loaded polymeric nanoparticle core is coated with lipid layers (Figure 5), represent a promising anti-biofilm formulation as the hybrid nanoparticles possess physical robustness afforded by the polymer matrix, while at the same time they possess the high biofilm compatibility characteristics of

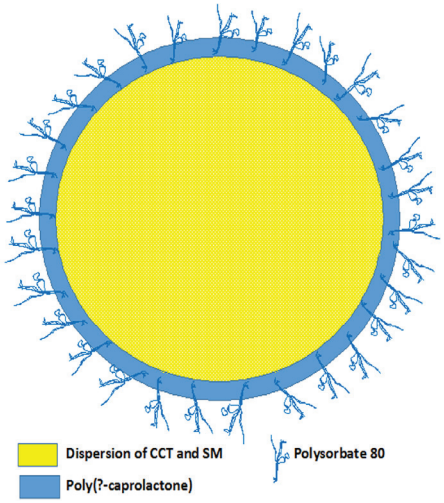


**Figure 3**
Illustrative model for lipid-core nanocapsules. Sorbitan monostearate (SM), caprylic/capric triglyceride (CCT). Redrawn from reference [18].

**Table 3**
Properties of some nanostructured lipid carriers (NLCs) studied as antimicrobial drug delivery system.

| Drug (Year) | Size (nm) | Lipid composition | Surfactant/co-surfactant | (EE)(%) | Application/ Study | Ref. |
|---|---|---|---|---|---|---|
| **Clotrimazole (2013)** | 210 ± 2.7 | Stearic acid, oleic acid | Tween 80, poloxamer 188, sodium lauryl sulfate, lecithin | 94 ± 3.6 | *In vitro* skin permeation (human cadaver) | [33] |
| **Miconazole (2013)** | >250 | Dynasan® 116, Miglyol® 812 | Poloxamer 188 | 80-98 | *In vitro* skin permeation (rat) | [80] |
| **Terbinafine (2015)** | 128 ± 4.5 | Glyceryl mono-stearate, Labrasol® | Pluronic F-127 | 63-84 | Dermal *in vitro* & *in vivo* (rat) | [48] |
| **Tilmicosin (2016)** | 149 ± 3.0 | Compritol® 888 ATO, sesame oil | Tween 80, poloxamer 407, | 86.3 ± 2.3 | Oral *in vitro* & *in vivo* (chicken) | [40] |

**Table 4**
Properties of some Lipid-core nanocapsules (LNCs) studies as chemotherapeutic drug delivery system.

| Drug (Year) | Size (nm) | Structure & Composition | | Surfactant/ cosurfactant | (EE) (%) | Application/ Study | Ref. |
|---|---|---|---|---|---|---|---|
| | | Shell (polymer) | Core (lipid) | | | | |
| **Clotrimazole (2014)** | 169 ± 15 | Coconut oil | Eudragit ® S 100 | Tween 80 | >99.9 | *In vitro* release & *in vitro* antifungal activity | [32] |
| **Tilmicosin (2016)** | 85.0 ± 1.0 | Coconut oil | Eudragit® S 100 | Span 80 Tween 80 | 94.3 ± 2.0 | Oral<br>*In vitro* release & *in vivo* (chicken), PK | [64, 65] |
| **Praziquantel (2018)** | 50.8 ± 0.1 | Labrafac® Oleic acid | Kolliphor® HS 15 | Miltefosine Span 80 | 99.8 ± 0.8 | Oral *in vitro* & *in vivo* (mice, rat) PD & PK | [81] |

Eudragit ® S 100: Methacrylic Acid - Methyl Methacrylate Copolymer (1:1); Labrafac® lipophil WL 1349: Caprylic-capric acid triglycerides; Kolliphor® HS 15: a mixture of free polyethylene glycol and polyethylene glycol (15)-hydroxystearate; Miltefosine: 1-hexadecylphosphocholine; Span 80: Sorbitan mono-oleate

liposomes. The small nanoparticle size enables them to penetrate the sputum mesh, which has an average spacing of 100-400nm, to reach embedded biofilm colonies resulting in higher anti-biofilm efficacy [6, 20].

## *Applications of LNPs as drug delivery systems*

Applications with regard to routes of administration are discussed below.

### LNPs as topical delivery system

Topical infections of skin are among the most widespread diseases, therefore, percutaneous therapy is a good choice for the treatment of these pathologies because of self-administration, patient compliance and lower systemic adverse effects which would result into reducing possible toxicity of the drug [27, 28]. Stratum corneum is the main barrier in percutaneous absorption of the topically applied drugs [29].

Many approaches have been used to increase the passage of the poorly skin-partitioned drug molecules through this barrier. One of the interesting features of the LNPs for topical use is related to their proper semisolid consistency [30]. The advantages of using LNPs to deliver antimicrobial agents to superficial infections have been well documented [1, 9]. Unique properties of LNPs make them a promising antimicrobial drug delivery platform. Although emulsion has the problem of low viscosity, which results in less retention time, LNPs can be used in the formulations with increased viscosity. Occlusive compounds affect the skin hydration, penetration of compounds into the skin and retention of water content of the skin that lead to stratum corneum swelling and better drug permeation. LNPs have small particle size and film forming properties, which make it the best candidate for enhancement of bioavailability of the encapsulated material after topical applications (Table 6) [4, 26, 29, 31].

Azole antimycotic drugs are extremely water-insoluble, therefore, it is difficult to deliver these drugs to infected sites [1]. Clotrimazole is used topically in the treatment of vulvo-vaginitis caused by *Candida albicans*. However, this treatment is generally associated with mucosal irritation, and low residence time at the vaginal cavity. Taking all into account, clotrimazole-lipid core nanocapsules with Eudragit (RS100), as a cationic polymer, was developed for the vaginal

**Table 5**
Properties of some lipid-drugs conjugate nanoparticles (LDCs) studied as antimicrobial drug delivery systems [83].

| Drug conjugate | Lipid used | Possible type of Linkage | Advantages | Ref. |
|---|---|---|---|---|
| **Cephalosporin (1994)** | Lipidic and glycolipidic amino acids | Lipidic amino acids and peptides conjugation. | Enhanced oral bioavailability. Such conjugation enhances the lipophilicity and oral uptake of drug which intensifies the amount of drug in blood and at the site of action. | [75] |
| **Diminazine diaceturate (2002)** | Stearic acid, oleic acid | Ionic bond due to protonation of amide bond | High drug loading (33%, wt/wt). It seems that the formulated LDCs avoid the hepatic uptake by plasma protein adsorption pattern. It targets specific site with prolonged drug release. A possibility of increased uptake of diaminazene by LDL receptor at the blood-brain barrier. | [76] |
| **Acyclovir (2012)** | Ricinoleic acid, 12- Hydroxy stearic acid | Ester | Higher absorption and higher cellular accumulation. Biotinylated lipids of acyclovir possess enhanced affinity towards SMVT. These pro-drugs appear to be potential therapy for oral and ocular herpes virus infections because of higher expression of SMVT on intestinal and corneal epithelial cells. | [77] |
| **Isoniazid (INH) (2012)** | Phospholipon®100H, stearic acid and palmitic acid | Lipopeptide | Improved cellular uptake and site-specific delivery of INH. The affinity and penetration of lipopeptide into mycolic acid-containing lipid monolayer were higher compared to phospholipid. | [78] |
| **Rifampicin (2014)** | Lipoid® S- 75 | Hydrogen bonding | Higher aqueous solubility. Enhanced bioavailability | [79] |

LDL: low-density lipoprotein; SMVT: sodium-dependent multivitamin transporter; Phospholipon®100H: a hydrogenated soy lecithin; Lipoid® S- 75: Soybean lecithin; Miltefosine: 1-hexadecylphosphocholine; Span 80: Sorbitan mono-oleate

delivery [32].

Sanna et al. (2007) investigated the topical delivery of econazole nitrate using its SLN formulation [33]. *In vivo* studies demonstrated that SLNs promoted the skin penetration of econazole nitrate and improved drug diffusion into the deeper skin layers after 3 h of application compared to conventional econazole nitrate. In addition, they demonstrated that permeation profiles of econazole nitrate from LNPs were influenced not only by the lipid content but also by the particle size [34]. Due to poor cutaneous permeability, miconazole nitrate (MN) presents a problem by topical application [30]. In this connection, Bhalekar et al. (2009) and Sanap and Mohanta (2013) studied the MN-SLNs and MN-NLCs. There was an increased uptake of miconazole when enclosed in LNPs and used by topical application [30, 35].

Castro et al. (2011) demonstrated that retinoic acid-SLNs reduced the retinoic acid-induced skin irritation in comparison to those of conventional formulations, but without reducing the therapeutic efficiency of retinoic acid [36]. In addition, acitretin, a retinoid widely used for the treatment of psoriasis, a chronic skin disorder in adults, was recently included in NLCs [37].

## LNPs as pulmonary delivery system

The use of aminoglycosides can be limited because of their adverse effects and low oral pharmacokinetic properties due to their polarity. Aminoglycosides are used for the treatment of severe pulmonary infections like cystic fibrosis (CF) [38, 39]. CF is characterized by extremely high viscosity secretions from exocrine glands in the airways. The increased viscosity of mucus leads to a reduced clearance of microorganisms from the respiratory tract and results in chronic bacterial infection of the airways. Amikacin is an aminoglycoside that is used for the treatment of CF infections [40].

The distribution of amikacin-SLNs after pulmonary delivery was studied by Videira et al. (2002). Radio-labelled amikacin was loaded in cholesterol solid lipid and after *in vitro* optimization, the desired SLNs and free drug were administered through pulmonary and intravenous routes to male rats. It seems that pulmonary delivery of SLNs may improve patients' compliance due to reduction of drug side effects in kidneys and prolongation of drug dosing intervals due to the sustained drug release property of SLNs [41]. As reported by Videira et al. (2002) a significant uptake of the radio-labeled SLNs was shown in the lymphatics after inhalation and a high rate of distribution was

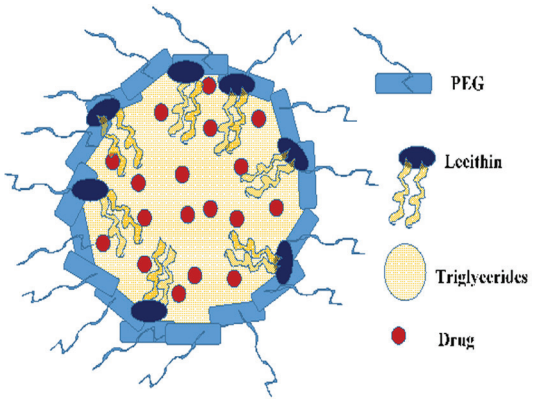


**Figure 4**
Schematic representation of lipid nanocapsules. Solutol ® HS 15, a mixture of free polyethylene glycol and polyethylene glycol (15)-hydroxystearate (PEG); Labrafac®, Caprylic-capric acid triglycerides (Triglycerides). Redrawn from reference [25].

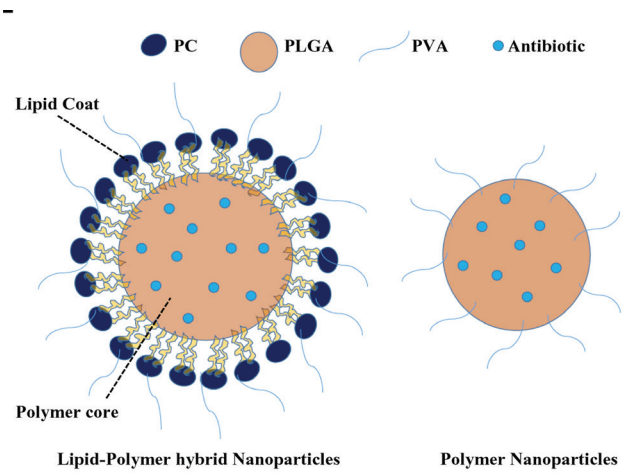


**Figure 5**
Schematic representation of lipid-polymer hybrid nanoparticles (LPNs) and their non-hybrid polymer nanoparticle counterparts. PC: phosphatidylcholine; PLGA: poly lactic-co-glycolic acid; PVA: poly vinyl alcohol. Redrawn from reference [6].

seen in lymph nodes. Consequently, the use of amikacin-SLNs seems promising for enhanced effects of this drug in CF as inhaled nanoparticles which can reduce the dose frequency and improve the pharmacologic index of the drug. Furthermore, Bargoni et al. (2001) showed that tobramycin-SLNs were concentrated in lungs and concluded that this increased concentration might help treating pulmonary infections [42].

### LNPs as an oral delivery system

Bioavailability of oral drugs are always limited by their poor solubility and dissolution rate, degradation in the GIT, the trans-membrane absorption barrier and the efflux mediated by transporters such as P-gp (Figure 6) [15, 46]. The development of composite formulation methods helps to improve the BA of oral drugs. Normally, the presence of lipids in the GIT induces secretion of gastric lipases, pancreatic lipases and co-lipases. In addition, the secretion of biliary lipids, bile salts and cholesterol are stimulated, yielding the formation of mixed micelles, which associate to solubilized drugs. Lipid-based formulations can be applied to influence the absorption of pharmaceuticals via various mechanisms, such as modifying the release of active ingredients, improving their BA, stimulating the lymphatic drug transport, interacting with enterocyte-based transport processes and reducing unwanted drug side effects. In addition, LNPs can protect encapsulated drugs against enzymatic degradation in GIT [47, 48].

The following factors can also enhance the absorption of drugs: the reduction in particle size that results in significant increase in the surface area of the particles, and makes a sufficient and steady drug absorption in GIT. In addition, bioadhesion of LNPs to the gut wall due to the increased surface area seems to prolong the residence time of LNPs and enhance their close contact. The oral BA of retinoic acid was increased by 2.16 folds when the particle size of SLNs decreased from 328 nm to 89 nm. In addition, digestion of triglycerides by lipase produces surface-active mono- and diacylglycerols, which in turn induces secretion of endogenous bile salts, and facilitates drug absorption. Furthermore, LNPs can enhance lymphatic delivery of drugs contributing to the overall BA. The uptake by M-cells and lymphatic transport of intact LNPs plays an important role in the GIT absorption profiles [15]

The absorption of tobramycin by intestinal cells is poor because of P-gp and an ATP-dependent drug efflux pump. In contrast, tobramycin-SLNs can significantly suppress the P-gp efflux pump as they penetrate the intestinal linings through endocytosis rather than passive diffusion [1, 4]. The AUC value of praziquantel-SLNs after oral administration in rats was 4.1-fold higher than that obtained with a praziquantel tablet [47]. In another study, praziquantel-SLNs increased drug BA by 14.9-fold and prolonged its systemic circulation. An initial burst release was observed in drug release study followed by a sustained release of the SLNs [24].

There are also other evidence for improved drug absorption by using SLNs. Ofloxacin-SLNs improved the dissolution rate leading to a shorter Tmax and higher Cmax of ofloxacin. In addition, SLN may increase drug residence time in GIT because of more adhesion to the GIT wall or entrance to the intervillar spaces owing to their small particle size [48]. A re-

**Table 6**
Applications and advantages of LNPs as topical antimicrobial drug delivery systems.

| Formulation | Drug | Application | Advantage | Ref. |
|---|---|---|---|---|
| **LNCs with Eudragit (RS100)** | Clotrimazole | To treat vulvo-vaginitis caused by Candida albicans | Inhibited Candida at lower concentration<br>Internalized more by fungal cells<br>Increased antifungal efficiency | [32] |
| **Stearic acid based NLCs** | Clotrimazole | *In vitro* skin penetration and *in vivo* skin hydration | A greater quantity of drug remained localized in the skin with lesser amount penetrating into the target site *ex vivo* | [29] |
| **SLNs** | Econazole nitrate | *Ex vivo* drug permeation using porcine skin | econazole nitrate-SLNs with a diameter of 150 nm increased drug diffusion rate into deeper skin layer | [1] |
| **SLNs** | Miconazole nitrate | Topical application<br>*Ex vivo* drug skin permeation | Increased uptake of miconazole in skin<br>Sustained drug release over 24 h period<br>In tape stripping experiments, a 10-fold greater retention of the drug | [35, 43] |
| **NLCs- based gel** | Miconazole nitrate (MN) | Topical application | MN-NLCs successfully incorporated into hydrogel for topical application<br>*In vitro* and skin permeation data provides sustained release of MN | [30] |
| **Chitosan- SLNs** | Retinoic acid | Anti-inflammatory and antimicrobial efficacy | High encapsulation efficiency<br>High physical stability<br>High antibacterial activity against *P. acnes* and *S. aureus* | [44] |
| **NLCs-based gel** | Acitretin | *In vitro* studies in human cadaver skin<br>Clinical studies to treat psoriasis | Higher deposition of acitretin was found in human cadaver skin<br>An improvement of clinical responses and reduction of local side effects | [27] |
| **SLNs** | Erythromycin | As a second-line topical treatment for acne | Exhibited a biphasic pattern with the burst release at the initial stage and sustained release subsequently which could be therapeutically desired | [45] |

cent study aimed to improve the oral BA of curcumin by incorporating curcumin in SLNs. Average particle size and total drug content of the SLNs were 134.6 nm and 92%, respectively. SLN formulation prolonged *in vitro* drug release and improved the oral bioavailability of curcumin (Table 7) [24].

## Lipid nanoparticles for the ocular delivery

Ocular drug delivery remains challenging because of the anatomy, physiology and biochemistry of the eye, which renders this organ impervious to foreign substances. Challenges for the ocular delivery of a drug are due to different characteristics of the layers of the cornea, sclera, retina, choroid as well as conjunctivae blood flow, lymphatic clearance and tear [26, 49]. Basically, ocular infections are treated by using topical application of antibiotics in the form of eye drops. About 90% of the dose applied topically through such solutions is lost due to pre-corneal losses (lacrimation and drainage) which lead to poor aqueous availability, so frequent dosing are required to achieve an adequate drug level and therapeutic effect [49].

An ocular delivery system should provide extended contact time and increased penetration of drug from tear phase to eye. Lipophilic drugs are permeable to cornea but formulations of these lipophilic drugs are problematic. Colloidal dosage forms provide the ability to overcome blood-ocular barriers, and efflux-related issues associated with the parent drug. Tobramycin loaded as an ion pair with hexadecyl phosphate in SLNs at a concentration of 0.3% was administered in rabbit eye and aqueous humor concentration of tobramycin analyzed up to 6 h, showed better results than solution of the same concentration of tobramycin. SLNs have the advantage of high viscosity to increase retention time, controlled release kinetics, and corneal permeability [26].

SLN formulations are also promising means for prolonged ciprofloxacin release, particularly in ocular infections via local delivery [4]. Pavankumarreddy et al. (2014) used levofloxacin loaded SLNs to evaluate its antimicrobial activity against *S. aureus*. The developed formulations were stable, non-irritant, and suitable for sustained release with better antibacterial actions [49].

### LNPs for increasing drug uptake at the blood-brain barrier (BBB)

The delivery of drugs to the brain is still a great challenge for treating brain related diseases, because hydrophilic drugs cannot cross the BBB. The BBB comprises cerebrovascular endothelial cells, which are very tightly connected to each other and supported by glial cells.

One approach to overcome the problem of the impermeability of the BBB was to enhance the fluidity of brain blood vessel membranes by using drug carriers [50]. It was used for treatment of the second stage of human African trypanosomiasis characterized by the presence of parasites (*T. bruceigambiense* and *T. rhodesiense*) in the central nervous system. Nowadays, clinical therapy of trypanosomiasis shows problems of drug bioavailability and toxicity as well as drug resistance. No drug can be given orally, all drugs have to be administered intravenous. Up to now no successful treatment has been found and diamidines (e.g. diminazene, pentamidine) do not cross the BBB due to their polarity [50].

As shown in Table 3, to overcome the low drug loading capacity of SLNs (especially for hydrophilic drugs), lipid-drug conjugate nanoparticles (LDC-NP) were developed by using polysorbate 80 as stabilizer and surface modifier. They possess a drug loading capacity of up to 33% of diminazene [26, 50]. LDC-Diminazene nanoparticles studied on the brain of trypanosomiasis-infected mice provided increasing uptake via the BBB and needed a lower dose with reduced side effects [50, 76].

## *Applications with regard to the pathogenic agent*

### LNPs as drug delivery system for tuberculosis

Tuberculosis (TB) results in more than eight million new cases and two million deaths annually. Although potentially curative treatments are available, it remains the principal cause of preventable deaths in the world today [51]. LNPs-antimicrobial drug delivery system can be more useful for the treatment of TB by decreasing the dosing frequency and improving the patient compliance [31]. LNPs facilitate the delivery of antitubercular drugs to lungs and to the lymphatic systems. They can provide a sustained release of the loaded antimicrobial, and effectively eliminate the infections at lymphatic sites [31]. Some studies have revealed the ability of SLNs to bypass P-gp pump, which is one of the mechanisms of multidrug-resistance [10].

Although rifampin (RIF) remains one of the first-line drugs in therapy of TB, many mycobacteria have emerged resistant against it. Two mechanisms are responsible for the drug resistance of mycobacteria: the impermeability of the mycobacterial cell wall and the active multidrug efflux pumps. SLN formulation can manipulate both of them to increase the efficacy. Efforts have been made to achieve formulations of RIF-SLNs with the ideal size suitable for intravenous administration, with highest encapsulation efficiency and improved penetration of the bacterial cell wall. It has been suggested that improved penetration is due to their small size and hydrophobic nature of SLNs which is similar to gram negative bacterial cell wall. In addition, SLNs can decrease the frequency of drug administration [10]. TB infection can spread from lungs to the lymphatic system. Therefore, drug delivery to macrophages is of crucial importance in this case. SLNs can aid the delivery of RIF to lungs as well as to the lymphatic system (Figure 7). When the SLNs enter the lungs, alveolar macrophages phagocyte them and transfer drug to the lymphoid tissues [10, 52].

Pandey et al (2003) developed RIF, isoniazid and pyrazinamide-SLNs and tested against tuberculosis in experimentally-infected mice [53]. Following a single oral administration to mice, SLNs maintained therapeutic drug concentrations in plasma for 8 days as compared to conventional drugs, which were cleared within 1-2 days. In infected mice, 5 oral doses of drug-loaded SLNs at every 10th day were sufficient to completely suppress the bacterial load in the lungs/spleen whereas conventional drug required administration of 46 daily oral doses to get the same effect [4]. Streptomycin-SLNs can also be used as an effective antitubercular agent by overcoming the limitation of its use to not more than 2-3 months [39].

### LNPs as delivery system for antimalarial agents

Malaria is the most common parasitic disease that causes morbidity and mortality in the world. Currently, the treatment of choice for malaria is based on the combination of an artemisinin (ART)-type compound with another drug. This combination with different mechanisms of action can ensure high cure rates and prevent the drug resistance. In fact, these combination therapies may reduce the impact of ART-induced dormancy (or quiescence) of a subpopulation of the ring stage parasites, a mechanism that allows the parasites to survive under the pressure of high doses of ART. Moreover, other reasons including cost, pharmacokinetic mismatch, resistance, cross-resistance and side effects due to the co-administrated drug may also lead to treatment failure [54].

The design of an antimalarial drug is affected by the route of administration. For instance, the intravenous route is the preferred route in cerebral malaria, while in acute malaria, the oral route is preferable. The large particle sizes even up to 640 nm are useful to be

**Table 7**
Applications and advantages of some solid lipid nanoparticles (SLNs) as oral drug delivery systems.

| Formulation | Drug | Application | Advantage | Ref. |
|---|---|---|---|---|
| **SLNs** | Tobramycin | To use orally against *P. aeruginosa* infections in the GI tract of CF patients | Penetrate the intestinal linings through endocytosis rather than passive diffusion<br>Release tobramycin payloads inside the cells | [1] |
| **SLNs- Fatty acid** | Enrofloxacin | To improve oral BA | Increased the BA<br>Extended the mean residence time of enrofloxacin by several-fold | [48] |
| **SLNs** | Vinpocetine | To improve oral BA | Increased dissolution<br>Increased oral BA by 322% | [15] |
| **SLNs** | Praziquantel | To improve oral BA in rats | Oral BA was 4.1-fold higher than that of praziquantel tablet<br>Increased oral BA by 322%<br>Mean residence time of the drug enhanced about two-folds | [47] |
| SLNs | Praziquantel | To improve oral BA and prolong drug systemic circulation | Increased drug BA in mice by 14.9-fold<br>The mean residence times of the drug were extended from 7.6 to 95.9 h | [24] |
| SLNs | Ofloxacin | To improve drug dissolution rate and its level in GIT fluids | Shorter Tmax and higher Cmax for drug<br>Increased its residence time in the GI tract | [48] |
| **SLNs** | Curcumin | To improve drug PK parameters following oral administration. | Prolonged *in vitro* drug release (up to 7 days) mainly by diffusion mechanism<br>Improved oral BA | [24] |

CF: cystic fibrosis; BA: bioavailability; PK: pharmacokinetic

used as targeted delivery system because erythrocytes are roughly 10 times bigger than them (averaged 6 microns in size). In fact, antimalarial drug carriers in this size range can be used for targeting the plasmodial schizonts and merozoites or their organelles, since the diameter of these blood forms (generally about 1μm) is significantly higher than the particle size [55].

ART, an antimalarial drug, has very poor solubility. ART-NLCs (Nanoject) enhanced its antimalarial activity, when used parenterally. Nanoject showed a significantly higher survival rate (60%) after 31 days as compared to the conventional formulation which showed no survival (100% mortality) [26].

Chloroquine (CQ) was the mainstay of antimalarial agents for years. Resistance to CQ increased in the recent years with the appearance of many resistant strain of *Plasmodium falciparum*. Antimalarial drug combinations have been used to solve this problem. The replacement of CQ with the new successful and expensive artemisinin-based combination therapies has serious economic implications [55]. The extents of accumulation of the drug in vacuoles of chloroquine-sensitive and resistant strains are different which suggests the involvement of drug efflux (P-gp transport) mechanisms [56, 57].

In malaria therapy, chlorpheniramine or promethazine is commonly co-administered with CQ to combat itching, a major adverse effects of CQ. The ability of LNPs to evade P-gp transport has also been exploited in cancer chemotherapy. Therefore, it makes sense to apply a combined approach by using the nanodelivery system and the phenomenon of P-gp inhibition. This is called co-encapsulation, meaning that the two drugs are trapped in a nanoparticle matrix [58].

Co-encapsulation of CQ and chlorpheniramine in a lipid matrix was investigated. Chlorpheniramine has a much lower BA than CQ and so its pharmacokinetics may be more favorably modified by nanodelivery than that of CQ. Clinical evidence for superiority of CQ-chlorpheniramine combination were based on overcoming drug resistance, due to possible effects on P-gp mediated drug efflux. Therefore, SLNs co-encapsulated CQ and chlorpheniramine can be prepared to desired particle size, smaller than the diameter of both human capillary systems and red blood cells and merozoites, by the hot homogenization- dilution method [55].

### LNPs for antiviral agents

Aji Alex et al. (2011) enhanced oral bioavailability of lopinavir (Lo), a protease inhibitor used for the treatment of HIV infections by 2.13-fold and 4.91-fold after oral and intraduodenal administration of Lo-SLNs, respectively [58]. Stavudine (D4T) is a pyrimi-

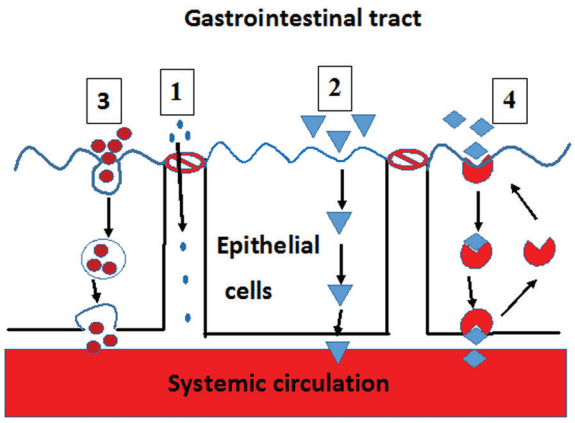


**Figure 6**
A schematic representation of drug absorption pathways 1) Paracellular transport and intercellular transport of drugs or solutes across the epithelial cells of the gastrointestinal tract into the systemic circulation; 2) Transcellular passive diffusion; 3) Transcellular endocytosis; 4) Carrier-mediated transport processes. Redrawn from reference [46].

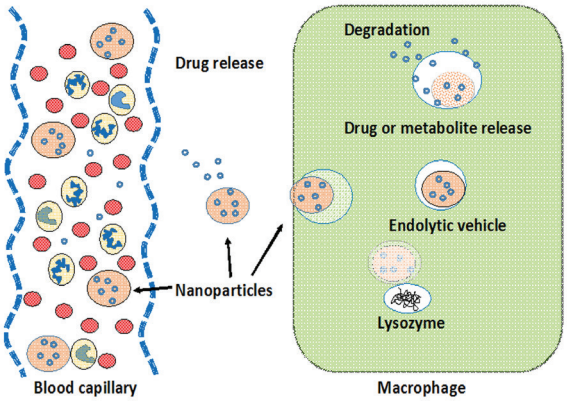


**Figure 7**
The proposed mechanism by which nanoparticle-loaded drugs can be released in infected macrophages during antitubercular therapy. Redrawn from reference [52].

dine nucleoside analog and inhibitor for the duplication of HIV, but with short residence time in plasma. Delavirdine (DLV) is a reverse transcriptase inhibitor with high plasma protein binding (98%). Saquinavir (SQV), the first protease inhibitor used against HIV, is a P-glycoprotein (efflux protein) substrate and liable to be pumped out from the brain parenchyma [59]. SLNs with core of Compritol 888 ATO, tri-palmitin, and cacao butter were formulated for encapsulation of D4T, DLV, and SQV. The dissolution kinetics showed that the cumulative of drugs released from SLNs was in the order of D4T > DLV > SQV. The complex lipid compositions in SLNs act as the drug reservoir and can improve the bioavailability of these drugs [60, 61].

## *LNPS for loading different antibacterial agents*

Ciprofloxacin HCl (CIP), a water-soluble drug, was selected to be formulated in SLNs. Cetylpalmitate used as the lipid core and polysorbate 80 as the surfactant. The antibacterial activity of CIP-SLNs against *S. aureus* and *P. aeruginosa* increased compared to CIP solution while drug-free (blank) SLNs showed no antibacterial effect [62].

Tilmicosin (TLM)-SLNs suspensions with different particle sizes (about 900, 450 and 150 nm) were formulated with different polyvinyl alcohol surfactant levels. Suspensions of smaller-sized particles (150 nm) showed faster initial release, much lower minimum inhibitory concentrations (MIC) and more acute toxicity in mice relative to suspensions of larger-sized particles, due to faster drug release. The TLM released from the TLM-SLNs suspensions with the smaller-sized particles had the same MIC and MBC values as that of the standard TLM, demonstrating that the preparation and release processes did not change the antibacterial activity of the TLM [63].

In study by Al-Qushawi et al (2016), using different lipid nanoparticles to load with tilmicosin, the results showed that TLM can be effectively loaded in LNPs formulations especially TLM-LNCs and TLM-NLCs. In microbiological tests, *S. aureus* was about 4 times more sensitive than *E. coli* to TLM-LNPs with MIC ranges of 0.5-1.0 and 2-4 µg/ml, respectively, and among them, the TLM-LNCs exhibited the best antibacterial activities [64]. The PK study also indicated that the LNPs improved TLM bioavailability and PK parameters especially by LNCs formulation, so these LNPs could be considered as promising delivery systems for TLM and suggest more efficient medications compared to the conventional TLM. The relative bioavailability of TLM-SLNs, TLM-NLCs and TLM-LNCs were 2.51, 4.31 and 6.69 times more than conventional TLM, respectively [65].

## *Other application of LNPs*

### LNPs for reduction of antimicrobial drug toxicities

SLNs of amikacin were designed for pulmonary delivery to reduce the dose or its dosing intervals, leading to the reduction of its toxicities especially in long-term treatment. Therefore, lower doses of amikacin in SLNs can clear the infection with less adverse effects and more safety. It was suggested that the more potent effect of amikacin-SLNs could be due to easier diffusion of LNPs into the cellular membrane of *P. aeruginosa* as the lipid character of the cholesterol used in their formulation is similar to the cell wall

of the bacteria. It may be concluded that this carrier could help with better transfer of aminoglycosides into the site of their action and possibly reduce the required dose and consequently decrease the untoward side effects [38].

In addition, the small particle size of the SLNs is a contributing factor in enhancing diffusion of drug into the bacterial cell [38]. The *in vitro* analyses of the cytotoxicity of different tilmicosin-SLNs suspensions showed that none of them altered BHK-21 tissue cell proliferation at concentrations up to 32 µg/ml. At higher concentrations (64-512 µg/ml of tilmicosin), all suspensions showed similar concentration-dependent cytotoxic activity. This could be due to the low inherent cytotoxicity of native tilmicosin since the main differences among the suspensions were found in their drug release speed [63].

**LNPs as a delivery system for antimicrobial agents from herbal extracts**

Nowadays, herbal remedies are more appealing in the treatment of different types of diseases, including bacterial and fungal infections. There are many medicinal plant extracts which are used for the treatment of microbial infections due to the presence of certain active chemical constituents like tannins, which are effectively fight against wide range of microbes [66]. Herbal remedies are considered as the safest therapeutic agents due to less frequent side effects such as local irritation, contact dermatitis, photosensitivity, itching and redness of the skin [67].

Modern pharmacological research has revealed that essential oils are the primary effective components in frankincense and myrrh oil (FMO) which exhibits a broad spectrum of antimicrobial activities. The poorly water-soluble drug FMO was efficiently encapsulated into SLNs. The evaporation release study of the formulation showed that SLN incorporation could reduce the evaporation loss of FMO components to a desirable degree. Hence, the prepared SLNs could be used as drug carriers for hydrophobic oil drugs extracted from traditional Chinese medicines [68].

The essential oil extracts of *N. sativa* was also shown to have antimicrobial effects. It was shown that it was possible to formulate *N. sativa* with good properties with SLNs by using mixed lipids to lower the SLNs crystallinity and overcome the problem of drug expulsion encountered with the use of high purity lipids in the formulation of SLNs and NLCs [69].

Lacatusu et al. (2012) found that NLCs might have complementary effects with regard to antimicrobial activity [66]. Carotene-NLCs were found to be effective against resistant *E. coli* bacteria. This antimicrobial activity was mainly correlated with the natural oil used and β-carotene concentration. In a recent study to evaluate the antimicrobial activity of methanolic extract of *Abutilon indicum* (MEAI)-SLNs against pathogens that can cause diabetic foot and urinary tract infection, it was shown that MEAI-SLNs was effective against these microorganisms due to the vicinity of tannins [67].

Acne is caused by *Propionibacterium acne* (*P. acne*) microorganisms, which live in deep layers of skin within follicles and pores. *P. acne* bacteria use sebum, cellular debris and metabolic by-products as their primary nutrient sources. Elevated production of sebum by hyperactive sebaceous glands or blockage of the follicle can facilitate *P. acne* bacteria to grow [70]. Treatment of acne with antimicrobial agents requires a long-term therapy, which sometimes results in failure. There are concerns that the development of resistance by *P. acne* may be associated with the development of resistance by other organisms, such as *S. aureus* and *S. pneumoniae*. Thus, alternative approaches for the antimicrobial treatment of acne are needed [45]. Neem oil is used in the treatment of acne. It contains strong antibacterial agents such as Margolone and Mahmoodin which are very similar to the ingredients found in common anti-acne products. Neem oil-SLN formulation was applied for the treatment of acne by using different concentrations of lecithin. Neem oil-SLNs with more lecithin content exhibited sustained effect and produced more antibacterial action against *P. acne* [70].

**LNPs for delivery of microorganism-derived sources of antimicrobial agents**

Nisin, a polypeptide is produced by *Lactococcus lactis* strains and belongs to the lantibiotic family. Nisin as a natural antimicrobial agent is active against a wide variety of gram-positive bacteria, and is used as a preservative in heat processed and low pH foods. The mode of action of nisin on vegetative cells involves the formation of pores in the cytoplasmic membrane leading to the efflux of cytoplasmic components. However, nisin has limited stability and it is rapidly exhausted from the foods due to its interactions with the food components, such as proteins and lipids, inactivation by enzymatic degradation, or uneven distribution of nisin molecules within the food matrix. Slow release nisin-SLNs protects its effects in food environment and prolongs its biological activity. Nisin is released from the SLNs gradually up to 25 days. The antibacterial activity of nisin-SLNs against *Listeria monocytogenes* and *Lactobacillus plantarum* was evident for up to 20 and 15 days, respectively, compared to only one and three days, respectively, for free nisin [71].

**LNPs for anti-biofilm agents**

Biofilm is a adhesive community of bacterial

cells enclosed by a self-secreted matrix of extracellular polymeric substances. Biofilm is the predominant mode of growth of *P. aeruginosa* bacteria as it renders them less susceptible (10-1000 fold) to antibiotics compared to the planktonic forms [72]. In this regard, lipid-polymer hybrid nanoparticles (LPNs), where antibiotic-loaded polymeric nanoparticle core is coated with lipid layers, represent a promising anti-biofilm formulation as the hybrid nanoparticles possess physical robustness afforded by the polymer matrix. Moreover, owing to their robustness, LPNs can withstand the physical transformation from their aqueous suspension state into the pharmaceutical solid dosage form, hence enabling their delivery by dry powder inhaler, which is widely regarded as much more effective than nebulization [73].

Levofloxacin (LEV), a fluoroquinolone antibiotic has been found to be highly effective against *P. aeruginosa* biofilm cells. LEV-LPNs which are composed of biodegradable and biocompatible poly (lactic-co-glycolic acid) (PLGA) and phosphatidylcholine, in which they were employed as the polymer and lipid models, respectively. They have been found to exhibit higher antibacterial efficacy against *P. aeruginosa* biofilm cells than their non-hybrid PLGA nanoparticle counterparts. The higher antibacterial efficacy, however, is not observed against planktonic cells that are steadily shed from the biofilm matrix, which consequently rules out lipid-induced enhancement of the antibiotic activity as the factor responsible for the high anti-biofilm efficacy of LPNs. Increased biofilm cell detachment into the planktonic state might be induced by biofilm-adsorbed nanoparticles, but it seems not to be the cause for the higher biofilm eradication rate either. Furthermore, the impact of antibiotic exposure levels on the biofilm eradication rate has been found to be minimal, hence ruling out the more sustained antibiotic release rate in the LPNs as the factor contributing to the higher anti-biofilm efficacy. Hence, it is thought that the presence of lipid may have enhanced the antibiotic diffusion into the biofilm matrix resulting in more effective biofilm cell eradications [6].

### LNPs with biopolymer

Tretinoin (TRE) is an analog of vitamin A used in the topical treatment of various skin diseases. Its use is highly restricted by its skin irritation and chemical instability. Chitosan is a biopolymer with extensive applications in pharmaceutical products. Its bioadhesive property and antibacterial activities are useful in the treatment of skin diseases such as acne and it can be used in combination with SLNs. TRE-SLNs showed no *in vitro* antibacterial activity against the bacteria tested (*P. acnes* and *Staphylococcus aureus*) but the SLNs-chitosan-TRE inhibited the activity of these bacteria at low concentrations. The SLNs-chitosan-TRE showed an antibacterial activity against bacteria involved in the acne, which can increase the therapeutic efficacy of TRE in the topical treatment of this disease [44].

Onychomycosis is a fungal infection that is responsible for nail diseases. This infection is caused mainly by *Trichophyton rubrum*. Human nail is composed of more than 80 layers of dead cells. Thus, it is hard to induce therapeutic drug concentration of terbinafine in the skin and nail. It has low fungicidal concentrations. However, 40% of the oral dose is lost with first-pass metabolism. SLNs were formulated with a chitosan based gel to obtain a topical dosage form with a semi-solid consistency. This hydrogel formulation renders an occlusive film with special affinity for the stratum corneum. Bio-adhesive properties and antimicrobial activities of chitosan may contribute to the efficacy of this formulation. The network of gel formulation stops the polymorphic SLN transitions, thus, enhances the stability of SLNs, the functionality of excipients, drug loading, and decreases the quantity of lipid content and reduces the cost of the formulation [28].

## Conclusion

For more than a half century antimicrobials have been saving a great number of lives caused by diverse infectious agents. Many antimicrobial drugs are suffering from a range of limitations such as their low water-solubility, narrow spectrum of activity, rapid degradation and clearance, low safety and tolerability. Insufficient delivery of the drugs has also been one of the major limitations of conventional antimicrobial therapy, as well as the development of bacterial resistance, and chronic lung biofilm infection. Their antimicrobial activities against intracellular microbes are also severely limited by poor membrane transport ability.

Because of their very small size, nanoparticles (NPs) have much greater biological availability, and are more likely to enter the cells, tissues and organs in comparison to larger particles. Rapid advances in the nanoparticle production with uniform size, shape and composition have caused a revolution in the pharmaceutical sciences and industry. These properties can be used to overcome some of the limitations of conventional antimicrobial agents. The NPs drug delivery systems can improve the quality of antimicrobial treatment by decreasing side effects, reducing the frequency of drug administration via prolongation of drug residence time, controllable uniform distribution in the target tissue, improved solubility, sustained and controlled release, enhanced cellular internalization and improving pharmacokinetic parameters and drug safety.

Extensive studies have demonstrated that lipid nanoparticles (LNPs) such as solid lipid nanoparti-

cles (SLN), nanostructured lipid carriers (NLC), lipid-drug conjugates (LDC), Lipid-core nanocapsules (LNCs) and lipid-polymer nanoparticles (LPNs) are able to overcome these issues and facilitate antimicrobial delivery to infection sites. While most of these nanoparticle-based antimicrobial drug delivery systems are currently in preclinical development, some have been approved for clinical use. With the ongoing efforts in this field, there is no doubt that nanoparticle-based drug delivery systems will continue to improve treatment of bacterial infections, especially in life-threatening diseases such as staphylococcal infections and tuberculosis.

## Acknowledgment

Authors wish to thank Mr. Gh.R. Shams for his help in redrawing of the figures.

## Author Contributions

Wrote the first draft: A.A, Changed the structure of the first draft, thoroughly revised and submitted: A.R.

## Conflict of Interest

The authors declare that they have no competing interests.

## References

1. Zhang L, Pornpattanangkul D, Hu CMJ and Huang CM. Development of nanoparticles for antimicrobial drug delivery. Current Medicinal Chemistry. 2010; 17:585-594.

2. Ranghar S, Sirohi P, Verma P and Agarwal V. Nanoparticle-based drug delivery systems: promising approaches against infections. Braz. Arch. Biol. Technol. 2014; 57(2):209-222.

3. Abed N and Couvreur P. Nanocarriers for antibiotics: A promising solution to treat intracellular bacterial infections. Int. J. Antimicrobial. 2014; 43:485-496.

4. Huh AJ and Kwon YJ. Nanoantibiotics: A new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J. Controlled Release. 2011; 156:128-145.

5. Troncarelli MZ, Brandão HM, Gern JC, Guimarães AS and Langoni H. Nanotechnology and antimicrobials in veterinary medicine. Microbial pathogens and strategies for combating them: Sci. Tech. education. (A. Méndez-Vilas, Ed.). 2013; 543-556.

6. Cheow WS, Chang MW and Hadinoto K. The roles of lipid in antibiofilm efficacy of lipid-polymer hybrid nanoparticles encapsulating antibiotics. Colloids and Surfaces A: Physicochem. Eng. Aspects. 2011; 389:158-165.

7. Feynman R. There's plenty of room at the bottom. Science. 1991; 254:1300-1301.

8. Battaglia L and Gallarate M. Lipid nanoparticles: state of the art, new preparation methods and challenges in drug delivery. Expert. Opin. Drug Deliv. 2012; 9(5):497-508.

9. Westendorf AM. Applications of nanoparticles for treating cutaneous infection. J. Invest. Dermat. 2013; 133:1133-1135.

10. Aboutaleb E, Noori M, Gandomi N, Atyabi F, Fazeli MR., Jamalifar H and Dinarvand R. Improved antimycobacterial activity of rifampin using solid lipid nanoparticles. International Nano Letters. 2012; 2:33-40.

11.Yurgel VC, Oliveira CP, Karine R, Begnini KR, Schultze E, Thurow H, Leon PMM, Dellagostin OA, Campos VF, Beck RCR, Collares T, Pohlmann AR and Seixas FK. Methotrexate diethyl ester-loaded lipid-core nanocapsules in aqueous solution increased antineoplastic effects in resistant breast cancer cell line. Int. J. Nanomed. 2014; 9:1583-1591.

12. Attama AA, Momoh MA and Builders PF. Lipid nanoparticulate drug delivery systems: a revolution in dosage form design and development. In: Recent Advances in Novel Drug Carrier Systems. 2012; 107-140.

[13. Shah R, Eldrige D, Palombo E and Harding I. Composition and structure. In: lipid nanoparticles: production, characterization and stability. Springer Briefs in Pharmaceut. Sci. Drug Develop. 2015; 319-10710-3.

14. Nair R, Kumar KSA, Priya KV and Sevukarajan M. Recent advances in solid lipid nanoparticle-based drug delivery systems. J. Biomed. Sci. and Res. 2011; 3(2):368-384.

15. Qi J, Lu Y and Wu W. Absorption, disposition and pharmacokinetics of solid lipid nanoparticles. Current Drug Metabolism. 2012; 13:418-428.

16.Dandagi PM, Dessai GA, Gadad ABB and Desai VB. Formulation and evaluation of nanostructured lipid carrier (NLC) of lornoxicam. Int. J. Pharm. Pharm. Sci. 2014; 6(2):0975-1491.

17. Pardeike J, Hommoss A and Muller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2009; 366(1-2):170-84.

18. Venturinia CG, Jagerb E, Oliveira CP, Bernardi A, Battastini AMO, Guterres SS and Pohlmann AR. Formulation of lipid core nanocapsules. Colloids and Surfaces A: Physicochem. Eng. Aspects. 2011; 375: 200-208.

19. Sánchez-Moreno P, Ortega-Vinuesa JL, Martín-Rodríguez A, Boulaiz H, Marchal-Corrales JA and Peula-García JM. Characterization of different functionalized lipidic nanocapsules as potential drug carriers. Int. J. Mol. Sci. 2012; 13:2405-2424.

20. Cattania VB, Fiel LA, Jager A, Jager E, Colome LM and Uchoa F. Lipid-core nanocapsules restrained the indomethacin ethyl ester hydrolysis in the gastrointestinal lumen and wall acting as mucoadhesive reservoirs. Europ. J. Pharm. Sci. 2010; 39:116-124.

21. Wissing SA, Kayser O and Muller RH. Solid lipid nanoparticles for parenteral drug delivery. Adv. Drug Del. Rev. 2004; 56, 1257-1272.

22.Ramadan A, Lagarce F, Tessier-Marteau A, Thomas O, Legras P, Macchi L, Saulnier P and Benoit JP. Oral fondaparinux: use of lipid nanocapsules as nanocarriers and in vivo pharmacokinetic study. Int. J. Nanomed. 2011; 6:2941-2951.

23. Varshosaz J, Hajhashemi V and Soltanzadeh S. Lipid nanocapsule-based gels for enhancement of transdermal delivery of ketorolac tromethamine. J. Drug Del. 2011; 571272.

24. Das S and Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS Pharm. Sci.Tech. 2011; 12(1): 62-76.

25. Huynh NT, Passirani C, Saulnier P and Benoit JP. Lipid nano-

capsules: A new platform for nanomedicine. Int J Pharmaceut. 2009; 379: 201-209.

26. Kumar S and Randhawa JK. High melting lipid based approach for drug delivery: Solid lipid nanoparticles. Materials Sci. Eng. 2013; 33: 1842-1852.

27. Puglia C and Bonina F. Lipid nanoparticles as novel delivery systems for cosmetics and dermal pharmaceuticals. Expert Opin. Drug Deliv. 2012; 9(4): 429-441.

28. Tiwari S, Mistry P and Patel V. SLNs based on co-processed lipids for topical delivery of terbinafine hydrochloride. J. Pharm. Drug Develop. 2014; 2(4): 404-411.

29. Shekhawat PB. Preparation and evaluation of clotrimazole nanostructured lipid carrier for topical delivery. Int. J. Pharm. Bio. Sci. 2013; 4(1):407- 416.

30. Sanap GS and Mohanta GP. Design and evaluation of miconazole nitrate loaded nanostructured lipid carriers (NLC) for improving the antifungal therapy. J. Applied Pharm. Sci. 2013; 3(1), 46-54.

31. Sarathchandiran, I. A Review on nanotechnology in solid lipid nanoparticles. I. J. P. D. T. 2012; 2(1):45-61.

32. Santosa SS, Lorenzonia A, Pegoraroa NS, Denardib LB, Sydney H, Alves SH, Schaffazicka SR and Cruza L. Formulation and in vitro evaluation of coconut oil-core cationic nanocapsules intended for vaginal delivery of clotrimazole. Colloids and Surfaces B. Biointerfaces. 2014; 116: 270-276.

33. Sanna V, Gavini E and Cossu M. Solid lipid nanoparticles (SLN) as carriers for the topical delivery of econazole nitrate: in-vitro characterization, ex-vivo and in-vivo studies. J. Pharm. Pharmacol. 2007; 59:1057-64.

34. Passerini N, Gavini E and Albertini B. Evaluation of solid lipid microparticles produced by spray congealing for topical application of econazole nitrate. J. Pharm. Pharmacol. 2009; 61:559-67.

35. Bhalekar MR, Pokharkar V and Madgulkar A. Preparation and evaluation of miconazole nitrate-loaded solid lipid nanoparticles for topical delivery. AAPS Pharm. Sci. Tech. 2009; 10:289-96.

36. Castro GA, Oliveira CA and Mahecha GA. Comedolytic effect and reduced skin irritation of a new formulation of all-trans retinoic acid-loaded solid lipid nanoparticles for topical treatment of acne. Arch. Dermatol. Res. 2011; 303:513-20.

37. Agrawal Y, Petkar KC and Sawant KK. Development, evaluation and clinical studies of acitretin loaded nanostructured lipid carriers for topical treatment of psoriasis. Int J Pharm. 2010; 401:93-102.

38. Ghaffari S, Varshosaz J, Saadat A and Atyabi F. Stability and antimicrobial effect of amikacin-loaded solid lipid nanoparticles. Int. J. Nanomed. 2011; 6:35-43.

39. Kaur IP and Verma MK. Exploring solid lipid nanoparticles for intranasal administration of streptomycin. Int. J. Pharma. 2011; 1(2):110-117.

40. Varshosaz J, Ghaffari S, Mirshojaei S.F, Jafarian A, Atyabi F, Kobarfard F and Azarmi S. Biodistribution of amikacin solid lipid nanoparticles after pulmonary delivery. Bio. Med. Res. Int. 2013; 136859.

41. Videira MF, Botelho Santos AC, Gouveia LF, Pedroso De Lima JJ and Almeida AJ. Lymphatic uptake of pulmonary delivered radiolabelled solid lipid nanoparticles. J. Drug Targeting. 2002; 10(8): 607–613.

42. Bargoni A, Cavalli R, Zara GP, Fundaro A, Caputo O and Gasco, MR. Transmucosal transport of tobramycin incorporated in solid lipid nanoparticles (SLN) after duodenal administration to rats. Part II—tissue distribution. Pharmacol Res. 2001; 43(5): 497–502.

43. Jain S, Jain S and Khare P. Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. Drug Deliv. 2010; 17:443-51.

44. Ridolfi DM, Marcato PD, Justo GZ, Cordid L, Machadob D and Duran N. Chitosan-solid lipid nanoparticles as carriers for topical delivery of tretinoin. Colloids and Surfaces B: Biointerfaces. 2012; 93:36-40.

45. Sahu AK, Kumar T and Jain V. Formulation optimization of erythromycin solid lipid nanocarrier using response surface methodology. Bio Med. Res. Int. 2014; 689391.

46. Salama NN, Eddington ND and Fasano A. Tight junction modulation and its relationship to drug delivery. Adv. Drug Deliv. Rev. 2006; 58:15-28.

47. Fricker G, Kromp, T, Wendel A, Blume A, Zirkel J, Rebmann H,Setzer C, Quinkert RO, Martin F and Müller-Goymann C. Phospholipids and lipid-based formulations in oral drug delivery. Pharm Res. 2010; 27:1469-1486.

48. Xie S, Zhu L, Dong Z, Wang Y, Wang X, and Zhou WZ. Preparation and evaluation of ofloxacin-loaded palmitic acid solid lipid nanoparticles. Intl. J. Nanomed. 2011; 6: 547-555.

49. Pavankumarreddy A, Parthiban1 S, Vikneswari A and Senthilkumar GP. Evaluation of potential antimicrobial activity of levofloxacin loaded solid lipid nanoparticles. Asian J. Res. Biol. Pharm. Sci. 2014; 2(3):99-111.

50. Olbrich C, Gessner A, Schroder W, Kayser O and Muller RH. Lipid-drug conjugate nanoparticles of the hydrophilic drug Diminazene-cytotoxicity testing and mouse serum adsorption. J. Cont.Rel. 2004; 96:425-435.

51. Gelperina S, Kisich K, Iseman MD and Heifets L. The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis. Am. J. Resp. Critical Care Med. 2005; 172: 1487-90.

52. Ranjita S, Loaye1 AS and Khalil M. Present Status of Nanoparticle Research for Treatment of Tuberculosis. J. Pharm. Pharmaceut. Sci. 2011; 14(1) 100 -116.

53. Pandey R, Sharma A, Zahoor A, Sharma S, Khuller GK and Prasad B. Poly (DL-lactide-coglycolide) nanoparticle-based inhalable sustained drug delivery system for experimental tuberculosis. J. Antimicrob. Chemother. 2003; 52: 981-986.

54. Memvanga PB, Coco R and Préat V. An oral malaria therapy: Curcumin-loaded lipid-based drug delivery systems combined with β-arteether. J. Cont. Rel. 2013; 172:904-913.

55. Nzekwea IT, Azodo VI, Agubata CO, Naicker B, Okore VO and Esimone CO. Preliminary formulation and characterization of solid lipid nanoparticles containing chloroquine and a P-glycoprotein inhibitor: Influences of lipid-surfactant ratios. J. Chem. Pharm. Res. 2015; 7(2):932-939.

56. Spoelstra EC, Dekker H, Schuurhuis GJ, Broxterman HJ and Lankelma J. P-glycoprotein drug efflux pump involved in the mechanisms of intrinsic drug resistance in various colon cancer cell line. Biochem. Pharmacol. 1991; 41(3):349-359.

57. Wang B, Goh WL, Zhang Q, Chang A, Liu XY, Tan TM and Lee H. In-vitro cytotoxicity of stealth liposome co-encapsulation doxorubicin and verapamil on doxorubicin– resistant

tumor cells. Biol. Pharm. Bull. 2005; 28(5): 822-828.

58. Aji Alex MR, Chacko AJ and Jose S. Lopinavir loaded solid lipid nanoparticles (SLN) for intestinal lymphatic targeting. Eur J Pharm Sci. 2011; 42:11-18.

59. Williams GC and Sinko PJ. Oral absorption of the HIV protease inhibitors: a current update. Adv. Drug Deliv. Rev. 199; 39: 211-238.

60. Kuo YC and Chung CY. Solid lipid nanoparticles comprising internal Compritol 888 ATO, tripalmitin and cacao butter for encapsulating and releasing stavudine, delavirdine and saquinavir. Colloids and Surfaces B: Biointerfaces. 2011; 88:682- 690.

61. Harde H, Das M and Jain S. Solid lipid nanoparticles: an oral bioavailability enhancer vehicle. Expert Opinion on Drug Delivery. 2011; 8(11):1407-1424.

62. Gandomi N, Atyabi F, Fazeli M, Farbood E and Dinarvand R. Solid lipid nanoparticles of ciprofloxacin hydrochloride with enhanced antibacterial activity. J. Nanosci. lett. 2012; 2:21-25.

63. Chen X, Wang T, Lu M, Zhu L, Wang Y and Zhou W. Preparation and evaluation of tilmicosin-loaded hydrogenated castor oil nanoparticle suspensions of different particle sizes. Intl. J. Nanomed. 2014; 9:2655-2664.

64. Al-Qushawi A, Rassouli A, Atyabi F, Peighambari SM, Esfandyari-Manesh M, Shams GR and Yazdani A. Preparation and characterization of three tilmicosin-loaded lipid nanoparticles: physicochemical properties and in-vitro antibacterial activities. Iranian J Pharmaceut Res. 2016; 15 (4): 663-676.

65. Rassouli A, Al-Qushawi A, Atyabi F, Peighambari SM, Esfandyari-Manesh M and Shams GR. Pharmacokinetics and bioavailability of three promising tilmicosin-loaded lipid nanoparticles in comparison with tilmicosin phosphate following oral administration in broiler chickens. Turk J Vet Anim Sci. 2016; 40: 540-547.

66. Lacatusu I, Badea N, Ovidiu O, Bojin, D and Meghea A. Highly antioxidant carotene-lipid nanocarriers: synthesis and antibacterial activity. J. Nanopart. Res. 2012; 14(6):902-917.

67. Rajesh J, Lakshmi SM, Thamizhvanan K and Viswasanthi T. Formulation, characterization and evaluation of methanolic extract of Abutilon indicum loaded solid lipid nanoparticles against microorganisms causing diabetic foot and urinary tract infection. J. global trends in pharm. sci. 2012; 5(4):2093-2102.

68. Shi F, Zhao JH, Liu Y, Wang Z, Zhang YT and Feng NP. Preparation and characterization of solid lipid nanoparticles loaded with frankincense and myrrh oil. Int. J. Nanomed.

2012;7:2033-2043.

69. Alhaj NA, Shamsudin MN, Alipiah NM, Zamri HF, Bustamam A, Ibrahim S andAbdullah R. Characterization of Nigella Sativa L. essential oil-loaded solid lipid nanoparticles. Am. J. Pharm. Toxi. 2010; 5(1):52-57.

70. Vijayan V, Aafreen S, Sakthivel S and Reddy KR. Formulation and characterization of solid lipid nanoparticles loaded Neem oil for topical treatment of acne. J. Acute Dis. 2013; 282-286.

71. Prombutara P, Kulwatthanasal Y, Supaka N, Sramala I and Chareonpornwattana S. Production of nisin-loaded solid lipid nanoparticles for sustained antimicrobial activity. Food Control. 2012; 24:184-190.

72. Davies D. Understanding biofilm resistance to antibacterial agents. Nat. Rev. Drug Discov. 2003; 2:114-122.

73. Labiris NRC, Holbrook AM, Chrystyn H, Macleod SM and Newhouse MT. Dry powder versus intravenous and nebulized gentamicin in cystic fibrosis and bronchiectasis-A pilot study. Am. J. Resp. Crit. Care. 1999; 160:1711-1716.

74. Gaba B, Fazil M, Khan S, Ali A, Baboota S and Ali J. Nanostructured lipid carrier system for topical delivery of terbinafine hydrochloride. Bulletin of Faculty of Pharmacy, Cairo University. 2015; 53: 147–159.

75. Toth I, Hughes RA, Dekany G, Hillery AM and Ward P. Synthesis and oral uptake studies of lipidic and glyco-lipidic conjugates of β- lactam antibiotics. Liebigs Annalen Der Chemie. 1994; 7:685–8.

76. Olbrich C, Gessner A, Kayser O and Mueller RH. Lipid drug conjugate nanoparticles as novel carrier system for the hydrophilic antitrypanosomal drug diminazene aceturate. J. Drug Target. 2002; 10(5):387–96.

77.Vadlapudia AD, Vadlapatlaa RK, Kwatrab D, Earlaa R, Samantaa SK, Pala D and Mitra AK. Targeted lipid based drug conjugates: a novel strategy for drug delivery. Int. J. Pharm. 2012; 434: 315–324.

78. Penzesa CB, Schnoller D, Horvati K and Kiss E. Membrane affinity of antituberculosis drug conjugate using lipid monolayer containing mycolic acid. Colloids Surf A Physicochem Eng Asp. 2012; 413(5): 142–8.

79. Singh C, Bhatt TD, Gill MS and Suresh S. Novel rifampicin- phospholipid complex for tubercular therapy: synthesis, physicochemical characterization and in- vivo evaluation. Int. J Pharm. 2014; 460 (1–2): 220–227.

80. Jain D and Banerjee R. Comparison of ciprofloxacin hydrochloride-loaded protein, lipid, and chitosan nanoparticles for drug delivery. J. Biomed. Materials Res. Part B: Appl. Biomaterials. 2008; 105-112.

81. Amarah RO, Ramadan AA, El-Moslemany RM, Eissa MM, El-Azzouni MZ and El-Khoragui LK. Praziquantel–lipid nanocapsules: an oral nanotherapeutic with potential Schistosoma mansoni tegumental targeting. Intl. J. Nanomed. 2018; 13: 4493-4505.

82. Puri A, Loomis K, Smith B, Lee JH, Yavlovich A, Heldman E and Blumenthal R. Lipid-Based Nanoparticles as Pharmaceutical Drug Carriers: From Concepts to Clinic. Crit. Rev. Ther. Drug Carrier Syst. 2009; 26(6): 523–580.

83. Banerjee S and Kundu A. Lipid-drug conjugates: a potential nanocarrier system for oral drug delivery applications. DARU J. Pharmaceut. Sci. 2018; 26: 65–75.