Trends in Analytical Chemistry 77 (2016) 100–108

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

journal homepage: www.elsevier.com/locate/trac

# Solid lipid-based nanocarriers as efficient targeted drug and gene delivery systems

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ARTICLE INFO

*Keywords:*
Lipid-based nanocarriers
Solid lipid nanoparticles
Nanostructured lipid carriers
Drug and gene delivery
Co-delivery

ABSTRACT

Most of the active pharmaceutical ingredients are often prone to display low bioavailability, biological degradation and inadvertent intrinsic side effects. To circumvent such obstacles, the expansion of efficient and novel drug carrier system is of increasing importance in terms of their efficient applicability through different administration routes such as dermal, oral, topical, parenteral and pulmonary. To pursue such aims, as an effective strategy, targeted delivery of drugs/genes to specific tissues/cells has widely been investigated. Accordingly, colloidal delivery of nanosystems such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, niosomes and transfersomes have materialized great means towards improved targeted delivery of drug/gene cargoes. The potential advantages of solid lipid-based nanocarriers applications over other nanoparticles (NPs) are because of their high biocompatibility, higher drug loading capacity and scalability. In this study, we review the utility of various targeted solid lipid-based nanocarriers and discuss their applications in drug and gene delivery systems.



**Contents**



## 1. Introduction

Lipid-based nanocarriers were shown to have great potential for delivery of drugs and genes. Lipidic nanoparticles (NPs) offer noticeable plausibility towards development of new therapeutics, in large part due to their straightforwardness in formulation process as well as unique size dependent properties. Their pronounced capability for encapsulation of drugs/nucleic acids together with simplicity in surface functionalization make them very attractive nanosystems (NSs) for the targeted delivery of drugs/genes, which can be administered through dermal, oral, topical, parenteral and pulmonary routes [1–4]. Compared to other drug delivery system (DDS), lipidic NPs combine several advantages such as controlled-release of encapsulated/incorporated drugs/genes, negligible toxicity, high biocompatibility and suitable protection of active compounds [5–7]. Further, because of their nanoscaled size properties, the lipid-based nanocarriers display enhanced encapsulation/incorporation potential [8].

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http://dx.doi.org/10.1016/j.trac.2015.12.016
0165-9936/

The most important roles of lipid-based formulations seem to be the effective delivery of the sparingly water soluble/insoluble drugs [9], even though they have been used for minimizing inadvertent side effects and maximizing specific delivery of the active agents. Further, it should be pointed out that the application of lipid-based formulations have largely been based on the nature and type of the active ingredients, the route of delivery and the biological characteristics of target tissue/cells.

Overall, nanoscale lipid-based DDSs hold great capacity for the targeted delivery of cargo molecules to the target tissues/cells in a controlled-release and site-specific manner, at which point these DDSs have been the center of attention to a large number of pharmaceutical/biomedical researchers and many pharmaceutical industries [10]. Technically, lipid-based DDSs include solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, niosomes and transfersomes. To the best of our knowledge, this review article will be one of the first of its kind studies that discuss comprehensively the targeted delivery of drugs/genes using nanoscale lipid-based DDSs. Therefore, the aim of this work is to provide an inclusive overview on the lipid-based nanoformulations used for the targeted delivery of drugs/genes as well as their pharmacological benefits.

## 2. Advantages and disadvantages of lipid-based NSs

Lipid-based nanocarriers possess interesting nanoscale properties necessary for the specific delivery of drug molecules. They display distinctive features such as large surface to mass ratio, capability for modifications and conjugations and potential for encapsulation of drug molecules. In fact, inherent limitations of slow dissolution of poorly water soluble drugs can easily be resolved by formulating them as lipidic NSs that can facilitate the solubilization process while offering high drug loading, long-term shelf stability and easy scale up potentials [11,12]. These nanoscaled DDSs, like any other DDS, may suffer from some deficits such as variable loading efficiency. Further, in some methods of production, application of surfactants and/or co-surfactants in high concentrations is not plausible. Possible undesired aggregation of NPs and inevitable growth of particles and the unpredictable tendency for gelation seem to be some other shortcomings of the lipid-based NSs [11].

### 2.1. SLNs

SLNs were established as alternative lipid-based NSs such as emulsions, micelles, liposomes and polymeric NPs. Nonetheless, in comparison with the polymeric NPs (in particular synthetic non-biodegradable polymeric NPs), biocompatible lipids such as Compritol®888 ATO, Precirol® ATO5, cetyl alcohol, cetylpalmitate, glyceryl monostearate, trimyristin/Dynasan®114, tristearin/Dynasan®118, stearic acid, Imwitor®900 used in formulation of SLNs appear to be well tolerated physiologically when administered *in vivo*. They may also be prepared without using toxic organic solvents [1,12]. Moreover, under optimized conditions, incorporation of lipophilic or hydrophilic drugs into SLNs and their protection are seemingly possible, which may meet most of the requirements for an optimum particulate nanocarrier system [13]. As noted previously, the main drawbacks of SLNs appear to be their inherent low-drug incorporation, which is in part due to the crystalline structure of the solid lipid together with tendency towards undesired aggregation and/or gelation and unexpected dynamics of polymorphic transitions [8,12,14–17].

### 2.2. NLCs

NLCs are a new generation of SLNs which comprise of a mixture of solid and semisolid/liquid lipids, and possess a nanometer size range [8,18]. NLCs improve the loading of drug molecules while retaining them firmly during the storage period. These nanostructures appear not to have any significant problem(s) associated with SLNs. They possess (a) higher water content than that of SLN dispersions, (b) lower drug payload and drug expulsion during storage and (c) enhanced long-term physical stability of the suspension [18]. Owing to the production procedure and the composition of the lipids used in nanoformulation, various types of NLCs can be attained for different purposes. In order to avoid the expulsion of incorporated compound(s) during storage and to increase the payload of active compounds, lipid matrix should be in the form of nanostructured particulates. Under some circumstances, the composition of formulation can be devised for the triggered- and/or controlled-release of incorporated drug/gene molecules from the NLCs [18,19].

### 2.3. Lipid-drug conjugate (LDC) NPs

At times, the loading capacity of SLNs is not sufficient for the encapsulation of hydrophilic drugs, in large part because of the low solubility of hydrophilic substances into lipidic phase and crystalline structure of the lipid matrix. Therefore, transformation of the hydrophilic drugs into water-insoluble drugs can be achieved through lipid-drug bioconjugates through grafting the carboxylic groups of the fatty acids (e.g., stearic acid, oleic acid) with the functional groups (e.g., amine group) of drug molecules [20,21]. To pursue such aim, the hydrophilic drug molecules are covalently conjugated to the desired lipid molecules and then the lipid-drug bioconjugates are prepared by melting the conjugate and exerting high pressure homogenization after pre-dispersion in hot surfactant solution processing – a method similar to preparation of SLNs [22]. Due to the high drug loading capacity of lipid-drug conjugates in comparison with SLNs, significantly higher drug molecules can be delivered into the target cells using profoundly lower amount of the lipid-drug conjugate NPs, which results in maximal delivery of drugs with minimal side effects [21].

## 3. Targeted delivery of drugs and genes by lipid-based NSs

Targeted delivery of drugs and genes has been implemented for the selective accumulations of cargo molecules in specific cells/tissue. Of these, targeted therapy of cancer seems to provide promising outcomes towards maximized efficacy with minimized side effects and hopefully much more personalized nanomedicines. As matter of fact, the key challenge in cancer therapy is to engineer drug and gene delivery systems capable of specifically targeting the cancerous cells solely but not the normal healthy cells/tissues. As a general rule in cancer therapy, the higher efficacy with the lower side effects can result in the more effective treatment modality and improved clinical outcomes. This might be achievable by efficient delivery of anticancer agents into the tumor microenvironment (TME) and subsequently tumor cells [23,24], while the formulated NPs must go through several physiological and biological barriers. These NSs must be able (a) to remain stable in the blood as long as they reach into TME, (b) to escape from the reticuloendothelial system (RES) clearance, (c) to accumulate in TME through irregular tumor vasculature, (d) to penetrate into the tumor interstitial fluid of TME with high pressure, and (e) to reach the target site and to interact with the target cells specifically [25,26]. To explicitly target the cancer cells, the lipidic NPs must be armed with the ligands that show high binding affinity to the related biomarker(s), through which they can efficiently internalize into the malignant cells specifically [24,27]. Generally, enhanced internalization of NPs can extensively occur through the receptor-mediated endocytosis. Taken all, to attain specific targeting of tumors, the over-expressed cancer marker molecules (CMMs) can be targeted by antibodies (Abs), peptides, proteins, aptamers (Aps) and even small molecules such as carbohydrates,