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Review

Nano lipid-drug conjugate: An integrated review

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ABSTRACT

Lipid-drug conjugates (LDC), which may also be addressed as lipoidal prodrug, have the therapeutic actives chemically bound to a lipid moiety like fatty acids or phospholipids. Fabricated in nano-size, lipid-drug conjugate forms another breed of lipid nanoparticles. LDCs are prepared in order to increase the drug loading and hence prevent leakage of a highly polar drug from a lipophilic matrix. In turn, it assists to achieve active targeting of therapeutics with reduced side effect by altering the pharmacokinetic profile of the drug. These self-assembled systems take the benefit of metabolic pathways of lipid biochemistry, allowing suitable organ targeting depending upon its size. These lipids because of its similarities with physiological lipids, enhances the solubility of the therapeutic agents and thereby improve the bioavailability. This present review is meant to encompass different aspects related to lipid drug conjugates which include types of lipids and drugs that can be used to develop this type of formulation. Here, we throw light on methods of preparation of lipid drug conjugate, processing them into nanoparticle, its characterization and different applications of lipid drug conjugate. We aim to present a holistic view on lipid drug conjugate as a suitable drug delivery approach.

Contents

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1. Introduction

Nanotechnology is a fast-growing field globally playing a valuable role in drug delivery. The National Nanotechnology Initiative has put forward the definition of nanotechnology to be the study of particles with size range roughly from 1 to 100 nm and its use in novel applications. The principle aim of nanotechnology in medicine is to diagnose and treat the diseases early and effectively (Koo et al., 2005; Mishra et al., 2010).

Nanoparticles are colloidal carriers having diameters in the nanometer size range. Some of the key attributes of nanoparticles are improved target specificity, reduced toxicity towards non-targeted tissues, improved bioavailability, and increased residence time in the body with superior biodistribution and pharmacokinetics (Koo et al., 2005; Müller, 1991; Mudshinge et al., 2011).

The development of lipid based drug carriers is a major area of interest in research over the years. They have distinctive size–dependent properties and provide the prospect to be generated as new therapeutics. These drug carriers offer the advantages of higher degree of biocompatibility, versatility, safety and efficacy (Patidar et al., 2010; Attama et al., 2012).

The lipid nanoparticles were brought into action a long time back; some of the common lipid nanoparticles being solid lipid nanoparticles (SLNs), nanostrucured lipid carriers (NLCs) and lipid-drug conjugate (LDCs) (Battaglia and Gallarate, 2012; Joshi and Müller, 2009). The first instance of producing lipid particles in the micrometer size range was reported by the end of 1950s and in the early 1960s (Joshi and Müller, 2009). In the 1960s, the first fat emulsion for parenteral route was developed (Waitzberg et al., 2006; Wanten and Calder, 2007; Dudrick et al., 1972). The main reason for the use of these emulsions was to reduce the possible side effects of drug but the physical instability of the incorporated drug prevented its application to broader field (Müller et al., 2000). Liposomes were first described by Bangham et al. in 1960s and were applied as drug delivery systems in the 1970s (Wissing et al., 2004). But the marketed formulations of liposomes are limited because of its high cost (Müller et al., 2000). Solid lipid nanoparticles (SLN) were first produced and reported by Müller and his team (Müller and Lucks, 1993) from Germany in parallel with Gasco and her group (Gasco, 1993) from USA in 1993. The application of SLN for oral delivery was reported for the first time in 1986 and termed as nanopellets (Speiser, 1986). In the late 1990s nanostructured lipid carrier (NLC) was developed as second generation of lipid nanoparticles (Severino et al., 2012) where as lipid-drug conjugates (LDC) were first reported in the late 1990s (Saracibar et al., 2012).

Lipid nanoparticles (LNPs) are extensively used in drug delivery systems because of the fact that lipid matrices are safe, biocompatible, and versatile rendering it to be suitable for different routes of administration marking the pre-requisites for any ideal drug delivery vehicle. Within a short duration of around 20 years, a wide variety of different LNPs have been successfully developed. However, some of the lipid nanoparticles like SLNs and NLCs possess the drawback of low drug loading capacity for the hydrophilic drugs. In order to overcome this limitation, LDCs were eventually developed. The typical preparation method for LDCs involves first preparation of an insoluble drug- lipid conjugate bulk either by salt formation or by covalent linking. This is followed by processing of the obtained LDC with an aqueous surfactant solution to produce a nanoparticulate formulation using High pressure homogenization (HPH) or other methods for nanoparticle formulation (Battaglia and Gallarate, 2012; Joshi and Müller, 2009).

Several reports on LDCs have been published, but as of date no comprehensive treatment on the entire technological aspects of LDC has been presented. Therefore, this review aims at presenting a holistic overview of the technology of LDC, their preparation and characterization, applications in drug delivery as well as current regulatory status.

2. Lipid nanoparticles

The lipid nanoparticles are becoming one of the most acceptable drug delivery systems for both lipophilic as well as hydrophilic drugs because of ease of production, easy scalability and, most advantageously, the lipid excipients are a physiological component with generally recognized as safe (GRAS) status and can be administered through a variety of routes (Severino et al., 2012; Neupane et al., 2013).

Solid lipid nanoparticles (SLNs) are carriers which are colloidal in nature consisting of lipid matrix which is solid at both body and room temperature (Koo et al., 2005) as shown in Fig. 1. These were developed as a substitute to emulsions, liposomes and polymeric nanoparticles. SLN are prepared by dispersing solid lipid or blend of solid lipids in an aqueous medium stabilized by a surfactant, with the mean particle size distribution ranging between 50 and 1000 nm. In SLN the lipid concentration can vary from 0.1% to 30% and surfactant concentration from 0.5% to 5%. Because of their physiological and biodegradable properties, SLN are investigated for administration through different routes, including oral, dermal, ocular, pulmonary, rectal and parenteral route for pharmaceutical and cosmeceutical applications (Joshi and Müller, 2009; Soni et al., 2015; Lade et al., 2015; Pardeike et al., 2009; Pastoriza et al., 2014).

In contrast to the emulsions and liposomes which contain liquid lipid, solid lipid matrix in SLN offers several advantages. Emulsions and liposomes frequently illustrate lack of protection of the encapsulated drugs and drug release occurs as a burst or uncontrolled. While in SLN absence of burst effect, small size (which extends the circulation time), and the large scale production feasibility makes them promising drug carrier (Severino et al., 2012; Lu et al., 2014).

However, some of the possible disadvantages of SLN are insufficient drug loading capacity, relatively higher water content in the dispersion and polymorphic transition of the lipid during storage (Wissing et al., 2004). The loading capacity of SLN for hydrophilic drugs is usually below 0.5%, which is satisfactory for