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Review

Drug targeting using solid lipid nanoparticles

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ABSTRACT

The present review aims to show the features of solid lipid nanoparticles (SLNs) which are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery and research. Because of some unique features of SLNs such as their unique size dependent properties it offers possibility to develop new therapeutics. A common denominator of all these SLN-based platforms is to deliver drugs into specific tissues or cells in a pathological setting with minimal adverse effects on bystander cells. SLNs are capable to incorporate drugs into nanocarriers which lead to a new prototype in drug delivery which maybe used for drug targeting. Hence solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence attracted wide attention of researchers. This review presents a broad treatment of targeted solid lipid nanoparticles discussing their types such as antibody SLN, magnetic SLN, pH sensitive SLN and cationic SLN.

Contents

1. Introduction

Solid lipid nanoparticles (SLNs) which were introduced in 1991 are used as alternative carrier systems to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles (Uner and Yener, 2007; Zhang et al., 2010; Hu et al., 2004; Wasutrasawat et al., 2013; Zhang et al., 2006; Parhi and Suresh, 2010). SLNs indicate lipids, which are used in the manufacturing of nanoparticles, are solid at room temperature and also at body temperature. Various methods have been developed for the preparation of SLNs *via* applying biocompatible lipids or lipid molecules with a history of safe use in medicine. The essential excipients of SLNs are solid lipid as matrix material, emulsifier and water. The term lipid is used here in a broader sense and includes triglycerides (*e.g.* tri-stearin), partial glycerides (*e.g.* Imwitor), fatty acids (*e.g.* stearic acid), steroids (*e.g.* cholesterol) and waxes (*e.g.* cetyl palmitate) (Mehnert and Mader, 2001). SLNs combine advantages of the traditional systems but avoid some of their major

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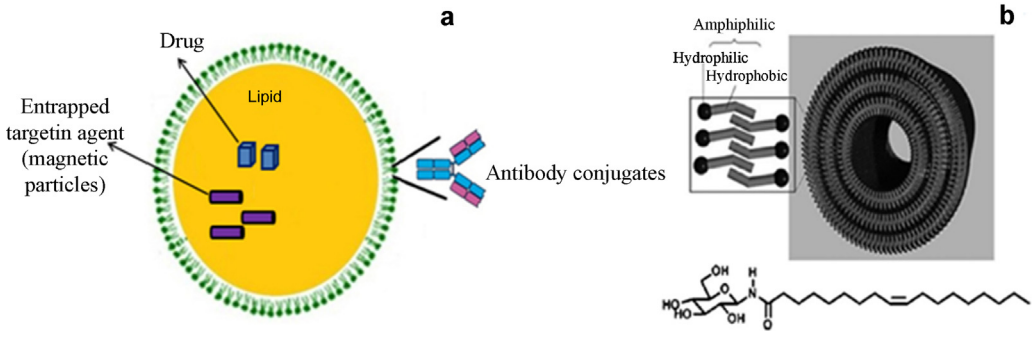

Fig. 1. The schematic figure of SLN targeting systems (a) and solid lipid nanotubes used as a pH sensitive drug delivery system (b) (Han et al., 2012).

disadvantages. SLNs have major potential application rules in drug delivery and research (Uner and Yener, 2007; Mehnert and Mader, 2001). Lipid nanoparticles offer possibility for developing new therapeutics because of their unique size and dependent properties. There have been considerable efforts in developing various nanoparticles as effective drug delivery vehicles over the past few decades. Due to their small sizes and large surface areas they are suitable to be covered with functionalized ligands (Kluza et al., 2011; Sudimack and Lee, 2000) moieties (Neuberger et al., 2005; Hirosue et al., 2010; Pissuwan et al., 2011), antibody (Mokhtarieh et al., 2012; Wang et al., 2013; Saha et al., 2007) and other functional groups (Kashanian et al., 2011; Xiang et al., 2013). Nanoparticles can be targeted to specific locations or cells within the body with this approach (Kamble et al., 2012). SLNs have another ability in incorporating drugs into nanocarriers which lead to offer a new prototype in drug delivery that could be applied for drug targeting (Kamble et al., 2012). Until now several reviewers focused on targeted drug delivery due to the importance of the nanomedicine filed (Koo et al., 2005; Sutton et al., 2007; Yezhelyev et al., 2006; Cho et al., 2008; Wang and Thanou, 2010; Xu et al., 2013).

Among the nanoparticulate carriers, SLNs hold great promise for reaching the goal of controlled and site specific drug delivery and hence attracted wide attention of researchers (Kamble et al., 2012). All these platforms must be compatible to the physiological environment and prevent undesirable interactions with the immune system. When developing new strategies in drug and gene delivery, avoiding immune stimulation or suppression is an important consideration, whereas in adjuvants for vaccine therapies, immune activation is desired (Peer, 2012). One of the features of SLNs is enabling the encapsulation, embedding or association with a wide range of molecules (*i.e.*, small molecules drugs, antigens, proteins and nucleotides) and also enhancing the delivery of therapeutic payloads into specific tissues and cells. SLNs also improve *in vitro* and *in vivo* stability and reduce adverse effects (Peer, 2012). There are several challenges with these carriers which are included rapid clearance, serum instability (dependent on the specific formulation) and nonspecific uptake by the mononuclear phagocytic system, which its function is to remove foreign materials from the circulation. Poly ethylene glycol was introduced for coating lipid-based carriers to provide a hydrophilic layer resulting in increased circulation time to overcome mentioned limitations (Uner and Yener, 2007; Papahadjopoulos et al., 1991), since surface-engineer drug delivery systems gaining attention for molecular targeting. This strategy exploits the differences between cancer cells and healthy cells, in particular surface antigen differences. Ideally, the antigen which would allowed molecular targeting is expressed exclusively on cancer cells, is an integral part of an essential cellular function of the cancer cells, and does not easily mutate as the cancer cells prolife rate (Wong et al., 2007). The selectivity to cell surface markers, targeting moieties were attached to the SLN surface *via* a PEG spacer arm, which reduced steric hindrances for further enhance (Uner and Yener, 2007; Papahadjopoulos et al., 1991; Blume et al., 1993). SLNs are mainly applied in targeted drug delivery approach (Blasi et al., 2007; Martins et al., 2013; Mandal et al., 2013). Therefore, in this article we focused on some categories for *in situ* drug delivery with this carrier such as antibody mediated, cationic lipid, pH sensitive lipid mediated attachments.

2. Antibody mediated targeted drug delivery using lipidic carriers

Precise targeted drug delivery to specific sites or organs in the body is so important. To achieve this goal the host immune response to tumor-specific antigens in chemotherapy and other disorders could be a very specific and low toxic option in medicine applications. Thus, antibodies that target tumor specific and tumor-associated antigens can be applied in targeted drug delivery (Brannon-Peppas and Blanchette, 2012; Alley et al., 2010; Casi and Neri, 2012). Generally in this filed, biopharmaceutical and biotechnological drugs are distinguished and used for targeted drug delivery. Biopharmaceuticals (biopharmaceutical drugs) are defined as recombinant proteins and monoclonal antibodies or nucleic acid-based products that Food and Drug Administration classifies them as medical devices (Muller and Keck, 2004).

Monoclonal antibody is another class of commonly used targeting moiety in drug delivery (Fig. 1a) (Torchilin, 2007; Beduneau et al., 2007; Demos et al., 1998). Either the whole antibody or the variable Fab fragment of the monoclonal antibody can be chemically conjugated to the surface of lipid nanocarriers to bring about increased cellular uptake at the targeted disease sites. By the way the coupling a drug molecule to one monoclonal antibody, due to limitation of receptors actions, is difficult to reach the therapeutic level inside the cells. Also the introduction of a spacer, that means attaching a polymer chain to the antibody, and subsequent coupling of many drug molecules to this spacer leads to molecular sizes, which are being recognized by the mononuclear phagocytic system (Muller and Keck, 2004). One solution for this issue is incorporation of drug molecule into the core or displayed on the surface of lipidic carrier and directs the carrier *via* a targeting antibody to the desired site of action for various diagnostic and therapeutic applications (Messerschmidt et al., 2009).

Lim and coworkers have conjugated anti human fibrinogen and intercellular adhesion molecule antibodies onto acoustically reflective liposomes composed of phospholipids and cholesterol. This group investigated that incorporation of drugs into these antibody conjugated carriers may be a potential future application to actively target drugs to the atherosclerotic plaques (Lim et al., 2012).

Peer described general concepts of the immune system and the interaction of subsets of leukocytes with lipid-based nanoparticles. He detailed the different immune toxicities reported and proposes ways to manipulate leukocytes' functions using lipid-based nanoparticles (Peer, 2012).