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Review article

Advances in the design of solid lipid nanoparticles and nanostructured lipid carriers for targeting brain diseases

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ABSTRACT

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) comprise a category of versatile drug delivery systems that have been used in the biomedical field for > 25 years. SLNs and NLCs have been used for the treatment of various diseases including cardiovascular and cerebrovascular, and are considered a standard treatment for the latter, due to their inherent ability to cross the blood brain barrier (BBB). In this review, a presentation of the most important brain diseases (brain cancer, ischemic stroke, Alzheimer's disease, Parkinson's disease and multiple sclerosis) is approached, followed by the basic fabrication techniques of SLNs and NLCs. A detailed description of the reported studies of the last seven years, of active and passive targeting SLNs and NLCs for the treatment of glioblastoma multiforme and of other brain cancers, as well as for the treatment of neurodegenerative diseases is also carried out. Finally, a brief description of the advantages, the disadvantages, and the future perspectives in the use of these nanocarriers is reported, aiming at giving an insight of the limitations that have to be overcome in order to result in a delivery system with high therapeutic efficacy and without the limitations of the existing nano-systems.

1. Introduction

Over the years, numerous nanostructures of various sizes and shapes have been reported in the literature for the treatment of different diseases. These nanostructures are comprised by various materials either synthetic or natural, and their properties vary depending on the materials used and the functionalization they undergo. It has been > 50 years since the first appearance of spherical nano/microstructures [1], and during these years these structures have been evolved and found use in many industrial and biomedical applications. In the biomedical field, the evolution of various nanostructures, organic and inorganic, has been rapid due to the imminent need to replace conventional strategies of treating untreatable diseases. In fact, the unmet clinical needs of many diseases were the leading cause for the development of nanostructures with tailored properties, aiming at fabricating a superior drug delivery system, which will specifically target diseased tissues without affecting its healthy niece. Nano-medicinal carriers have been used for the treatment of various diseases including cancer [2,3], atherosclerosis [4–6], intervertebral disc degeneration [7,8], cardiovascular diseases [9,10], and cerebrovascular diseases [11,12].

Due to the complexity of each pathology, each nanostructure has to be properly studied and designed in order to achieve the maximum therapeutic effect with the lowest possible side effects. Most of these nanostructures can be modified in a way that makes them responsive to various internal or external stimuli, a property which is useful for the controlled release of encapsulated therapeutic substances. A significant number of these nanostructures, such as inorganic nanoparticles or other polymeric/lipid nanoparticles, have also been used as diagnostic tools. The combination of therapy and diagnosis led to the fabrication of "theranostic" nanoparticles, but unfortunately, to date, most of these theranostic devices make use only of synthetic polymers and not of lipid-based nanostructures such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs).

Among the diseases that these nanostructures target, we find conditions that affect the central nervous system (CNS), the most important of which are brain cancer, ischemic stroke (IS), Parkinson's disease (PD), Alzheimer's disease (AD) and multiple sclerosis (MS). The cause of appearance is different for each disease, and it is affected by genetic and/or environmental factors. This diversity is one of the reasons that the design of drug delivery systems has to be very specific in order to successfully target the diseased area without affecting the surrounding tissues, and to result in its regression or even its complete cure. Even

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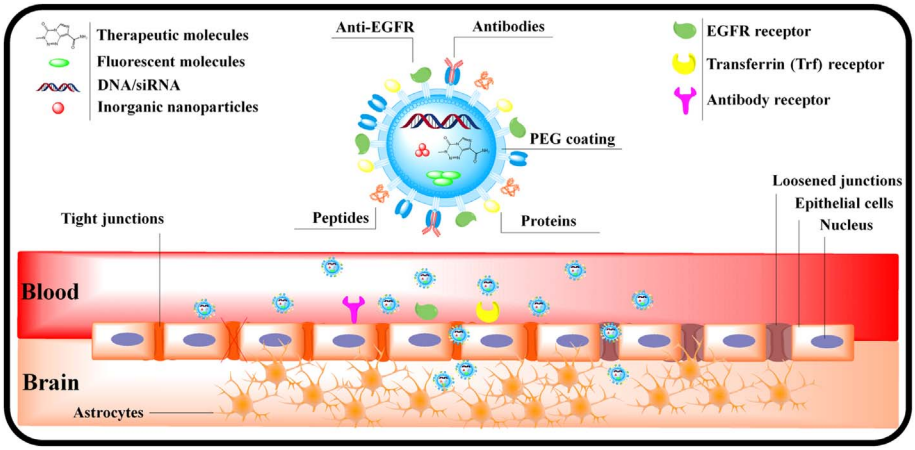

Fig. 1. Schematic representation of a multifunctional solid lipid nanoparticle and the targeted delivery of therapeutics. Upper part: Potential therapeutics (chemotherapeutic and/or antioxidant substances, fluorescent dyes, genes and inorganic nanoparticles) that can be encapsulated inside the lipid matrix and potential targeting moieties on the outer surface (proteins, peptides, and antibodies), are depicted. Bottom part: The representation of the BBB and the penetration of SLNs that are traveling through blood are depicted. The tight junctions of the BBB make the penetration of nanoparticles in the CNS almost impossible (left bottom part). Functionalization of the SLNs with targeting moieties enhances the BBB penetration. In certain diseases, like ischemic stroke, the tight junctions of the BBB are loosened (right bottom part) allowing an easier penetration of the nanoparticles.

though all the CNS diseases have a different cause, they all share a common characteristic in terms of targeted delivery, and this characteristic is the blood-brain barrier (BBB). BBB is one of the main reasons why the delivery of therapeutic molecules inside the brain is so complex. The tight junctions of the endothelial cells make almost impossible each attempt of delivering drugs into the brain if they are not functionalized with specific targeting segments or if they are not encapsulated inside other nanostructures. In order to overcome this limitation, current therapeutics like drugs, antioxidants, enzymes, genes, DNA/RNA and/or inorganic nanoparticles are properly cloaked inside polymeric or lipid nanostructures that have the ability to penetrate the BBB (Fig. 1). In the literature, most of the nanoparticulate delivery systems that have been used for treating brain diseases are comprised by synthetic polymers like polyethylene glycol (PEG) or poly (lactide-*co*-glycolide) (PLGA) [11–14]. These polymeric nanostructures present versatility in their size, shape, physicochemical properties, and surface functionalization, that allows them to penetrate the BBB and to deliver their encapsulated cargo in a controlled and sustained way. Nevertheless, most of these nanoparticulate systems present toxicity issues due to the acidic by-products that are formed during their degradation, rendering them inappropriate for extended use in the brain. An alternative approach with respect to these polymeric nanoparticles is represented by either inorganic nanoparticles (that indeed also present an inherent toxicity) and lipid-based structures. Liposomes, solid lipid nanoparticles, and nanostructured lipid carriers are the most important representatives of the lipid-based nanosystems, and they have been used for the treatment of brain diseases in the last 30 years. These lipid nanostructures are more biocompatible if compared to the polymeric or inorganic nanoparticles, and they have an inherent ability, due to their small size and to their lipid nature, to penetrate the BBB even without any functionalization. One more advantage of these nanostructures compared to the synthetic polymers is the possibility of their production at large scale, and this is one of the reasons why these nanostructures are becoming more and more attractive as a DDS. Unfortunately, to date, very few of these systems have been in clinical trials or commercially available, and one of the possible reasons is their major drawback which lies to their low loading capacity.

The reported literature on polymeric and lipid-based nanoparticulate systems for the treatment of CNS diseases is extensive, and in this review, we are going to briefly describe the advances in the synthesis, characterization, and *in vitro/in vivo* studies for SLNs and NLCs that were carried out during the last seven years. Briefly herein, we are describing the most important brain diseases and some of their main characteristics, followed by a description of the type of lipid-based nanostructures and their fabrication techniques. Finally, an extensive report to the literature on active and passive targeted SLNs and NLCs for CNS, followed by the conclusions and the future perspectives for this type of delivery systems, is carried out.

2. Solid lipid nanoparticles and nanostructured lipid carriers: synthesis, characterization, and comparison with other DDSs

2.1. Type of lipid carriers

Lipid-based carriers can be divided into various categories depending on their physicochemical properties and the method that is used for their fabrication. The main lipid-based carriers include 1) niosomes, which are lamellar self-assembled structures that comprise of non-ionic surfactants and cholesterol [15,16], 2) transferosomes, which are similar to niosomes and to liposomes and they consist of a lipid bilayer created by a lipid matrix that is stabilized by a variety of surfactants [17], 3) liposomes, which are spherical vesicles created by a lipid bilayer of phospholipids [18,19], 4) solid lipid nanoparticles which consist of a solid lipid core at room and body temperature [20], and 5) the nanostructured lipid carriers, the core of which comprises a liquid lipid phase inside the solid lipid phase [21].

Although all of the above-mentioned nanostructures have been used as drug delivery systems for treating brain diseases [20–26], this review will focus only on two types of lipid-based nanocarriers, the SLNs and the NLCs.

2.1.1. Solid lipid nanoparticles

Solid lipid nanoparticles are one of the newest members of the lipid-based nanocarriers family and they made their first appearance almost twenty-five years ago [27–29]. The need of overcoming the limitations of other nanostructured systems (niosomes, transfersomes, micelles, liposomes, emulsions, polymeric nanoparticles) like toxicity, stability and low loading capacities led to their fast development, and since then many studies demonstrating their usefulness in numerous diseases have been published [20,30,31].

SLNs are fabricated using a variety of lipids that share common characteristics including low melting point and solidness at ambient and body temperature, and a variety of surfactants and/or co-surfactants. Some of the main lipids that have been used to date are, monostearin, stearyl alcohol, stearic acid, glycerol monostearate, Precirol® ATO5, Compritol® 888 ATO, cetyl palmitate, while some of the main surfactants that act also as stabilizers are, poloxamer 188, Tween® 80 and dimethyl dioctadecyl ammonium bromide (DDAB). The proper selection of lipids and surfactants as well as the composition of SLNs, approximately 0.1–30% w/w for the solid core and 0.5–5% w/v for the surfactants, affects their physicochemical properties such as size, polydispersity, surface charge, short and long-term stability, drug loading and release profile.

One of the main reasons for the fast development of SLNs was their ability to effectively deliver in numerous diseased tissues both lipophilic and hydrophilic drugs, as well as other therapeutic molecules including oligonucleotides, peptides, genes and even smaller