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Trends

Recent progress in solid-state NMR studies of drugs confined within drug delivery systems

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ABSTRACT

Recent progress in the application of solid-state NMR (SS NMR) spectroscopy in structural studies of active pharmaceutical ingredients (APIs) embedded in different drug carriers is detailed. This article is divided into sections. The first part reports short characterization of the nanoparticles and microparticles that can be used as drug delivery systems (DDSs). The second part shows the applicability of SS NMR to study non-steroidal anti-inflammatory drugs (NSAIDs). In this section, problems related to API–DDS interactions, morphology, local molecular dynamics, nature of inter- or intramolecular connections, and pore filling are reviewed for different drug carriers (e.g. mesoporous silica nanoparticles (MSNs), cyclodextrins, polymeric matrices and others). The third and fourth sections detail the recent applications of SS NMR for searching for antibiotics and anticancer drugs confined in zeolites, MSNs, amorphous calcium phosphate and other carriers.

Contents

1. Introduction

"Drug delivery" (DD) is a broad term which covers issues such as formulation, technology, and the system for transporting active pharmaceutical ingredients (APIs) in the body. The major goal of a DD strategy is to safely achieve the desired therapeutic results with minimal side effects. DD technologies modify the release profile, absorption, distribution and elimination of drugs to improve the efficacy and safety of drugs, as well as to aid convenience and compliance for the patient.

The crucial point of the technological approach is the appropriate choice of the drug carriers, known in the literature as "drug delivery systems" (DDSs), which fulfill the desired functions. Such functions can be, for example, that the drug is active only in the target area of the body and/or released over a period of time in a controlled manner from a formulation. Moreover, DDSs can protect APIs sensitive to environmental and physiological effects. Several medications, such as peptides, proteins, antibodies, vaccines and gene-based drugs, cannot be delivered using oral, topical and inhalation routes because they might be susceptible to enzymatic degradation.

The demand for DDSs is growing. It is predicted that, in the USA, the DDS market will reach $>$ \$135 billion by 2015 as a result of growth of $\approx$ 9% every year since 2010. The largest share is expected to be produced by oral drugs and parenteral or injectable DDSs.

In this review, we describe recent progress in the structural studies of drugs confined in different DDSs. Several spectroscopic

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methods can be applied for this purpose. As we will reveal, solid-state nuclear magnetic resonance (SS NMR) spectroscopy may be the most powerful.

2. DDSs

Due to the rapid growth of new medications introduced for specific therapies, "intelligent" DDSs are strongly desired. Thus, during the past decades, intensive studies to discover new particles that allow transportation of APIs to the preferred places in the body and control of API release have been carried out. Current requirements have elicited new trends and new exceptions in DDS development. One of the biggest challenges in pharmaceutical sciences is finding biocompatible and biodegradable carriers that do not harm patients.

Fig. 1 shows the collection of species which are currently considered to be DDSs [1]. These particles can be classified according to different features: geometry and surface effects; composition; surface chemistry; or targeting elements. However, the common feature of all the particles shown in Fig. 1 is size: the range is in nanometers and these agents are called "nanoparticles".

One interesting class of nanoparticles is based on the carbon skeleton (fullerenes, carbon nanotubes, nanodiamonds and nanofoams). Another group is constructed with a silicon framework. Lipid-based polymers, polymeric and metallic nanoparticles, dendrimers and metal structures (quantum dots, nanoshells) belong to the group of well-defined systems. However, not all of these newly introduced particles fulfill the demands expected for DDSs. In the case of polymeric structures, the most limiting disadvantage is the inability to deliver the drug to its final location. Conversely, the advantage of these materials is the ability for synthetic modifications which create innovative "constructions" of biocompatible and biodegradable species with extended applications [2,3]. Several studies have focused on the use of natural polymer materials as alternatives to synthetic nano-polymers with the intention to reduce the number of side effects.

One of the first drug carriers used in modern therapies was based on biological samples, including lipids in the form of nanotubes, nanospheres, nanoparticles or emulsions. Among them, liposome vesicles comprising phospholipid bilayers were used as effective DDSs to transport and release chemotherapy drugs such as cisplatin, doxorubicin and cytarabine [4]. Lipids have also been shown to be effective carriers of peptides [5] and viral nanostructures that play important parts in selective gene therapy [6].

Interestingly, relatively new materials are hollow metal nanoshells (mainly gold, silver, platinum or palladium). They are important not only as DDSs but also in diagnostic procedures. In some cases, however, the toxicity of these particles limits their use.

Recently, amorphous colloidal and mesoporous silica nanoparticles (MSNs) have found several spectacular applications as universal, efficient and safe drug carriers [7,8]. The attractiveness and usefulness of MSNs as DDSs is due to their unique geometrical features, high surface area, large pore size and large pore volume that can be adapted to the specific needs. Moreover, mesoporous materials can be synthesized and modified readily [9]. Several authors have shown that surface changes on MSNs can facilitate drug loading [10,11]. Table 1 shows the structural parameters of the most popular and most frequently used MSNs. Mobile crystalline matter/mobile composite matter (MCM)-41 and Santa Barbara amorphous (SBA-15) are commercially available species applied in different branches of industry and science. In recent years, they have also become popular objects in the study of API–DDS interactions employing SS NMR spectroscopy [12].

Table 1
Porous structures of mesoporous materials. (Reprinted with permission from Ref. [7]).

Mesoporous solid	Space group	Pore diameter [nm]	Structure
MCM-41	P6mm	2–5	Hexagonal 1D channel
MCM-48	Ia3d	2–5	Bicontinuous 3D
SBA-15	P6mm	5–10	Hexagonal 1D channel
SBA-16	Im3m	Min 1–6; max 4–9	Body centre arrangement of cages
SBA-1	Pm3n	2–4	Cubic 3D
SBA-3	P6mm	2–4	2D hexagonal
MSU	P6mm	2–5	2D hexagonal
HMS	P6mm	2–5	Hexagonal

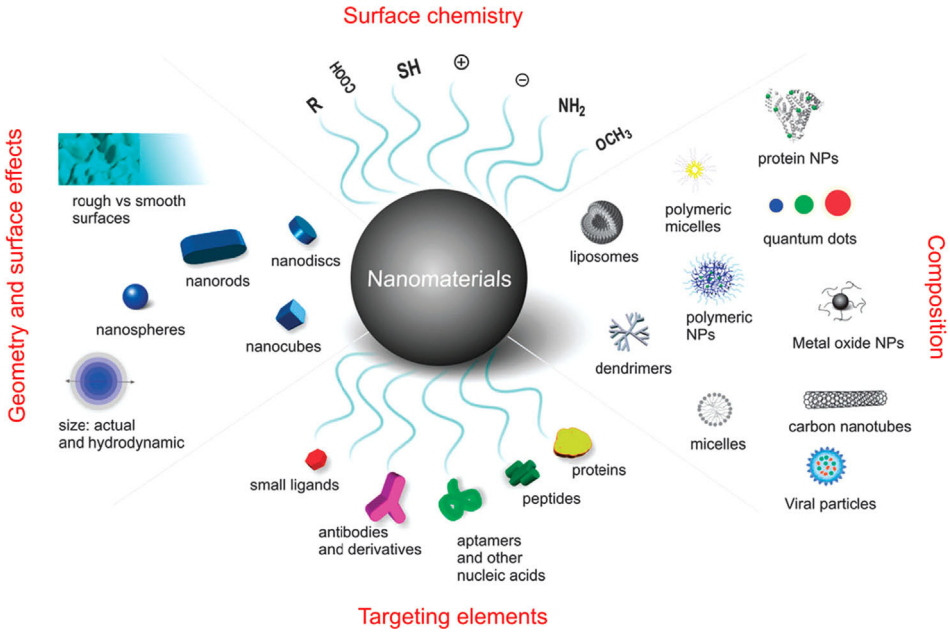

Fig. 1. Nanoparticles and the bio-physicochemical characteristics that affect their performance in vitro and in vivo. Reprinted with permission from Ref. [1].