

Light Scattering as Spectroscopic Tool for the Study of Disperse Systems Useful in Pharmaceutical Sciences

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ABSTRACT: The use of colloidal systems in pharmaceutical formulations, for addressing the issue of selective and controlled drug delivery or for improving drug availability, requires an accurate previous characterization of their chemical and physical properties. Light scattering is a useful and non-invasive method to study the structure and conformation of colloids in a wide space-scale, encompassing nanometric- to micrometric-sized particles, as well as their size distribution, surface electrostatic potential and aggregation phenomena occurring under proper conditions. In this review the physical bases of the light scattering approach are described and many examples are reported to discuss the examination of various multiphase systems useful in pharmaceutical fields. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 97:1703–1730, 2008

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INTRODUCTION

In all their accepted meanings, disperse systems include both solids dispersed in a continuous phase and gaseous/liquid systems. In the first class a huge number of systems can be listed, from macromolecules and aggregated structures in solutions to gels, and in the second one aerosols or foams. The description of the physico-chemical properties of such disperse systems (with molecular weight higher than 10000 Da) is the subject of the colloidal science and light scattering techniques are an extremely useful and powerful

method for characterizing them. Besides being suitable for investigating space (1–1000 nm) and time (10^{-6} –0.1 s) scales which are typical of colloids, the light scattering approach is non-invasive and allows for the study of the structural and conformational properties of particles directly in their liquid (or gaseous) environment. Indeed, evaporation of the solution (carried out in optical or electron microscopy) or depositing on proper surfaces (Surface Plasmon Resonance) is not required for light scattering investigation. In this context, cryo-TEM, which rapidly freezes the solutions, gives results which could be compared more properly with light scattering, although the freezing process (e.g., freezing rate) of water in bio-systems must be considered with caution.

In recent years, colloidal science has focused the attention on self-assembled nanometer-sized particles made of organic or inorganic materials.

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The highly interdisciplinary field of nanoparticles encompasses chemistry, material science, biotechnology, and pharmaceutical sciences. In the pharmaceutical industry, for instance, self-organized molecular assemblies (liposomes and vesicles) of amphiphiles (possessing both hydrophilic and hydrophobic segments) in water have attracted a lot of attention as biomembrane models or carriers in drug delivery systems (DDSs) and many investigations have been performed *in vivo* or *in vitro*^{1,2} from a pharmacological and pharmaceutical point of view. For tissue targeting, water-soluble non-immunogenic biocompatible polymers, which can be either degraded or eliminated by the body, are chemically linked to the carrier.

Effective DDSs must be able to entrap the drug, to retain it without any leakage and to release it when the proper condition or environment is reached. In this context, many attempts have been made by designing liposomes and vesicles sensitive to a change in the surrounding conditions, such as pH,^{3–10} temperature,^{11–13} UV light^{14–16} and to the presence of specific molecules.^{17,18} Especially, the pH-sensitive liposomes and vesicles have been noteworthy as DDSs because the pH value around any damaged tissue is different from that around other normal tissues.^{19–23}

Static and Dynamic Light scattering techniques are very useful in the analysis of particle size and morphology, as well as of the stability of colloidal systems, which are fundamental in both process and quality control of pharmaceutical products and formulations. The particle size distribution is an important feature of many products whose target depends on their size; moreover, the stability against flocculation, which is ensured by the electric double layer around the particle (DLVO potential^{24–26}), is related to the environment properties (pH, ionic strength) and must be taken into account for designing new systems. Electrophoretic light scattering, for instance, allows for the investigation of the colloidal stability through the measurement of the particle mobility, and hence of the surface charge density.

Also micellization^{27–29} and thermoreversible sol to gel transition of amphiphilic copolymers in aqueous solution^{30–32} find potential applications in drug delivery system.^{33–38} The hydrophobic core of micelle can easily entrap hydrophobic drugs by hydrophobic interaction, while the outer hydrophilic shell provides a protection for the drugs. When polymer concentration is approaching the critical gelation value, the system

entangles and passes to a hydrogel state depending on the temperature. In the last years, hydrogels have been extremely useful in biomedical and pharmaceutical applications mainly due to their high water content and rubbery nature which is similar to natural tissue, and to their biocompatibility. For topical applications, for example, gel and hydrogel have replaced pomades and ointments in pharmaceutical formulations. Moreover, large molecules like proteins and DNA could be loaded into the hydrogel structure to be released as the hydrogel responds to a physiological trigger.

On this basis, solutions of some amphiphilic block copolymers can be employed as vehicles of bioactive molecules and matrixes for the sustained-release of drugs after subcutaneous injection. In the last decades, a significant effort towards new drug delivery systems has been done, for instance, to improve ocular administration of drugs.^{39–41} Treatment with these systems increases bioavailability, reduces the frequency of administration, promotes targeting of drugs to specific sites.

Also in the case of sol-gel transition, static and dynamic light scattering furnish useful information for microrheological studies on biological complex fluids. The results on the viscoelastic properties of such systems can give valuable information to improve the characterization and the applications of gels.

Targeting of drugs to specific sites is one of the main challenges and goals in designing and realizing new materials for pharmaceutical applications. Indeed, the efficiency of DDSs depends crucially on the amount of the administered drug which reaches infected tissues or tumor sites and stays there. Therefore, the factors that influence persistence, biodistribution, availability, and metabolism are of critical importance in developing effective macromolecular based drugs. With this goal some self-organizing nanoparticles have been modified by grafting bio-recognizable carbohydrates or saccharides;^{17,18,42–47} these nanoparticles are able to bind specific proteins which are, for instance, over-expressed in different diseases (tumoral cell membranes, virulence, etc) and to transport and release the drug to the specific site of action.

For the study of the binding between drug and carrier, the fluorescence correlation spectroscopy (FCS) technique is particularly useful and effective; this method exploits the fluorescence intensity fluctuations (instead of the fluctuations of the scattered intensity) to measure the dynamic

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