REVIEWS

Using Molecular Simulations to Probe Pharmaceutical Materials

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ABSTRACT: Evolved through the past 60 years, molecular simulations have become one of the most important analytical tools in many theoretical and applied scientific disciplines. This paper provides a brief introduction to molecular simulations as a means of addressing important scientific questions of interest to pharmaceutical scientists. The focus is on fundamental questions such as: (1) Why do simulations work? (2) How to simulate? (3) How to make the results of simulations "real?" (4) Where can simulations be applied? To demonstrate the fundamental rationale of molecular simulations, three perspectives, thermodynamics, statistical mechanics, and general statistics, are compared. The concept of stochasticity is introduced, followed by a brief account of the two major methods used in simulations, molecular dynamics and Monte Carlo simulations. A brief discussion is then given on force fields to indicate their central importance. To facilitate the discussion about possible applications to pharmaceutical systems, the characteristics of molecular simulations are first compared with those of laboratory experiments. Case studies are then introduced to demonstrate the strengths of simulations. Some frequently encountered questions also are presented and discussed. ©2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:2000–2019, 2011

Keywords: molecular modeling; molecular dynamics; Monte Carlo; stochasticity; force field; thermodynamics/statistical mechanics; materials science

INTRODUCTION

Starting from the first publication of Monte Carlo (MC) simulations (the Metropolis algorithm) in 1949,[1] molecular simulations have evolved through the past 60 years and have become one of the most important analytical tools in many theoretical and applied scientific disciplines. Founded upon the theoretical principles of statistical mechanics, simulation approaches have thrived, as advanced by the increasing power of modern computers, to tackle difficult problems in various areas such as physics, physical chemistry, material sciences, and structural biology. In a survey conducted in 2000,[2] the Metropolis algorithm[1] was named among the 10 algorithms that have had the greatest influence on the development and practice of science and engineering in the 20th century. In the context of theoretical studies, molecular simulations serve as first-line tests for new theories and hypotheses, whereas in the context of experimental studies, they function as so-called "computer experiments." A variety of phase transitions and phenomena have been successfully reproduced in simulations, including the ones that are of direct interest to the pharmaceutical sciences such as melting,[3] crystallization,[4] condensation,[5] liquid–liquid phase separation,[6] liquid crystal formation,[7] and cyclodextrin inclusion.[8] Through these efforts, a great many microscopic details that were once difficult to access have been revealed. Currently, molecular simulation approaches are an indispensable tool in many scientific fields.

In this context, this paper attempts to provide a brief introduction to molecular simulations. The focus is more on fundamentals than on applications. We will try to discuss the following fundamental questions: (1) Why do simulations work?; (2) How are simulations performed?; (3) How are the results of simulations made physically "real?"; (4) Where can simulations be applied? The first question is approached by a brief review of the theoretical foundation upon which simulations are constructed, followed by an account of the two major simulation approaches, molecular dynamic (MD) and MC simulations. The third question is addressed by invoking some quantum mechanical concepts. Finally, some examples, both from the literature and from our own studies, are discussed

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to demonstrate the applicability and power of this technique.

It should be stressed that this presentation is an introduction and a perspective rather than a comprehensive review. Given the significance of molecular simulations in many scientific fronts and the vast amount of literature, it is impossible to do justice to all aspects of this topic in a paper of this size. The author elected to focus on addressing the abovementioned fundamental questions, whereas leaving detailed methodology to be obtained from more general references. Furthermore, with statistical mechanics as their foundation, molecular simulations have traditionally been presented in a statistical–mechanical paradigm. With the rigor and convenience in all regards, this tradition usually demands a familiarity of statistical–mechanical concepts and languages. To bypass this demand, the author seeks an alternative approach in this work. Taking advantage of the basic statistical concepts familiar to most scientific disciplines, we try to demonstrate why simulations work. This approach, though being more reader friendly, will necessarily compromise mathematical rigor to some extent. For the sake of minimizing the burden on the reader, the author believes that this is an appropriate compromise. We hope this can be compensated for the reader interested in pursuing this topic further through the references provided in the text.

WHY DO MOLECULAR SIMULATIONS WORK?

Why Do Systems Seek to Attain Equilibrium?

Physical states of pharmaceutical systems have long been recognized to influence the physicochemical properties and clinical performance of drug products. Hence, understanding and control of such physical states are critical steps to ensuring the quality of pharmaceutical products. To place this in a broader perspective, although certain material properties are of particular interest to pharmaceutical scientists, such as the solubility and compressibility of a drug substance, they are only a portion of the picture. Material systems exhibit an almost incredible diversity in our observations. Materials, for example, can be in different phases such as gases, liquids, crystals, glasses, and liquid crystals (mesophases). Each object may have a color, an odor, a density, an electric conductivity, a hardness, a compressibility, a brittleness, a shear modulus, a viscosity, a solubility, a saturated vapor pressure, and so on.[9] Thus, it is of great interest to study material properties comprehensively and to find the common laws underlying this diversity.

Phenomenogically, when given sufficient time, all systems can reach certain steady states under prescribed thermodynamic conditions (e.g., temperature, pressure, and composition), wherein their macroscopic (thermodynamic) properties, such as the ones listed above, are no longer variable with time. This final destiny, under a given set of thermodynamic conditions, is termed the equilibrium state. The journey for systems to move from out-of-equilibrium states to the equilibrium state is the equilibration process. A simple example would be to drop some sucrose crystals in a cup of water. The sucrose–water system sets off from a two-phase state (out-of-equilibrium), undergoes dissolution of sucrose crystals (equilibration), and finally reaches a solution state (equilibrium) wherein system properties no longer change over time. As in this example, most material systems encountered in the pharmaceutical field are either in equilibrium or in the equilibration process. To name just a few, processes reaching an equilibrium that are well known among pharmaceutical scientists include drug solubility and solution properties, crystalline states, cocrystallization (hydrates, solvates, and cocrystals), hygroscopicity, mesophases, and liquid crystals. Metastable polymorphs, amorphous solids, emulsions, and liposomes, on the contrary, are in the equilibration process, meaning that they are metastable states and will eventually evolve to equilibrium states. From this incomplete list, it is evident that equilibrium states and equilibration processes are of great concerns in the pharmaceutical sciences, and a fundamental understanding of them is of ultimate importance to pharmaceutical scientists. Given this information, a fundamental question arises naturally: Why do all systems equilibrate? In the case of the sucrose–water system, for instance, why do the crystals have to dissolve once dropped into water? This question in the context of molecular simulations will be considered from three perspectives given below. These perspectives provide the basis for the successful application of molecular simulations.

Thermodynamic Perspective

The Second Law of Thermodynamics deals with this question. It points out that the direction of a process or reaction is determined by the entropy of an isolated system, which always increases in a spontaneous process. Consequently, every system equilibrates to a steady state, wherein the system entropy maximizes under a given set of thermodynamic conditions, and thereafter the system properties stay invariable over time. This law, the Second Law of Thermodynamics, is the foundation of physical pharmacy, so it is not new to pharmaceutical scientists. For the purpose of differentiating it from the other perspectives, we will only make a few comments without getting into the details.

Historically, the Second Law of Thermodynamics has achieved tremendous success in many scientific

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