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Breaching the skin barrier — Insights from molecular simulation of model membranes☆

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ABSTRACT

Breaching the skin's barrier function by design is an important strategy for delivering drugs and vaccines to the body. However, while there are many proposed approaches for reversibly breaching the skin barrier, our understanding of the molecular processes involved is still rudimentary. Molecular simulation offers an unprecedented molecular-level resolution with an ability to reproduce molecular and bulk level properties. We review the basis of the molecular simulation methodology and give applications of relevance to the skin lipid barrier, focusing on permeation of molecules and chemical approaches for breaching the lipid barrier by design. The bulk kinetic model based on Fick's Law describing absorption of a drug through skin has been reconciled with statistical mechanical quantities such as the local excess chemical potential and local diffusion coefficient within the membrane structure. Applications of molecular simulation reviewed include investigations of the structure and dynamics of simple models of skin lipids, calculation of the permeability of molecules in simple model membranes, and mechanisms of action of the penetration enhancers, DMSO, ethanol and oleic acid. The studies reviewed illustrate the power and potential of molecular simulation to yield important physical insights, inform and rationalize experimental studies, and to predict structural changes, and kinetic and thermodynamic quantities.

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1. Introduction

Breaching the skin's barrier function by design is an important strategy for delivering drugs and vaccines to the body [1]. A key determinant of the skin barrier function is the lipids that fill the

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extracellular space of the skin's top-most layer, the stratum corneum. The lipids consist of a heterogeneous mixture of saturated long-chain ceramides, free fatty acids, and cholesterol in a roughly 1:1:1 molar ratio [2]. The extent of heterogeneity is illustrated by the ceramide fraction which is known to contain more than 300 different species [3,4]. As to the physical state of the skin lipid lamellae there is still no consensus; both a single gel phase [5] and the coexistence of a liquid crystalline and a crystalline phase [6–8] have been proposed. Furthermore, how the skin lipids are architecturally organized is still an outstanding problem and there are currently several competing models for the molecular architecture of these lipids [9–11].

While there are many proposed approaches for reversibly breaching the skin barrier, which include the use of chemical penetration enhancers [12], iontophoresis (use of a electrical potential) [13], electroporation (application of short, high-voltage pulses to induce temporary micropores in the skin tissue) [14], sonophoresis (use of low-level ultrasound) [15], and the use of microneedles [16], our understanding of the molecular processes involved these chemical and physical approaches is still rudimentary. Indeed this lack of understanding, which is a direct consequence of limitations associated with experimental methods, may be limiting technological progress. Molecular simulation offers a way forward, offering unprecedented molecular-level resolution with an ability to reproduce molecular and bulk level properties. It can yield important physical insights, inform and rationalize experimental studies, and has a significant predictive potential.

We review here the basis of the molecular simulation methodology and give applications of relevance to the skin lipid barrier, focusing on permeation of molecules and chemical approaches for breaching the lipid barrier by design. It is clear that the overwhelming heterogeneity in the chemical composition and the lack of consensus with regard to the organization of the skin lipids equally challenge both simulations and molecular-resolution experiments. Consequently, both approaches are mainly restricted to model membrane systems, and phospholipid-based model membranes still continue to serve as test-beds from which inferences are made for skin lipids. The situation is, however, rapidly evolving and both experiments and simulations are increasingly utilizing ceramide-based model membranes.

2. Molecular simulation methodology

The basis for molecular simulation is the now well-characterized molecular forces between atoms and molecules. These forces enable us to 'simulate' the collective behavior of a molecular system comprising, for example, a lipid membrane in water with embedded molecules of a particular penetration enhancer, as a function of time (trajectory). There are two main approaches, molecular dynamics (MD) and Monte Carlo (MC) simulation. MD simulations employ Newtonian mechanics to calculate the evolution of the molecular system (see Fig. 1), which is dictated by the interaction forces between the molecules. The force $\boldsymbol{F}$ acting on each particle due to the surrounding atoms is computed from the interaction potential, which is then used to determine the positions of the particles in a short time period (typically 1–2 fs, 10^{-15} s) by integrating Newton's second law of motion ($\boldsymbol{F}=m\boldsymbol{a}$). As the force on each particle depends on the positions of other particles a numerical integration algorithm is required. This time-stepping process is repeated to yield a molecular trajectory comprising a time period of the order of 100 ns. In contrast, in the MC approach, the configurations are generated by means of random atomic displacements, which are then accepted or rejected using a potential-energy criteria based on Boltzmann statistics, such as that of Metropolis et al. [17]. Both MD and MC simulations can be performed in all the standard thermodynamic ensembles, including conditions of constant temperature and pressure (NPT ensemble) that correspond to laboratory conditions. Starting from a given molecular configuration, assuming that the system is ergodic i.e. all possible configurational states are accessible, the NPT ensemble simulations therefore converge towards low free energy, thus mimicking real systems. Both techniques, MD and MC, yield structural information and estimates of thermodynamic quantities. MD, as it tracks the molecular trajectory, has the added advantage of yielding dynamical information such as diffusion coefficients and transition rates. With MC, as there is no time dimension and therefore formally no trajectory, the dynamical information is inaccessible. MD has certain technical advantages for large flexible molecules and tends to be the method of choice for lipid membrane simulations.

The molecular system size utilized in the simulations is of the order of 100,000 particles, which represents an extremely small volume element compared with a real laboratory system comprising Avagadro's number of particles. For such a small volume-element, surface effects would be significant and the simulations routinely employ periodic boundary conditions (the central simulation box is surrounded by its images) to remove unwanted surface effects in a bid to mimic a bulk environment.

The interaction between atoms (or groups of atoms) may be described at either the quantum mechanical level or using molecular mechanics. Quantum mechanics is necessary for interactions where the interest is in the electronic structure, in particular electron transfer and bond making and breaking. Such calculations are extremely expensive and currently limited to systems of a few hundred atoms for simulation times of less than a nanosecond. The molecular mechanics approximation is a higher level approach in which (generally) the integrity of the molecule is maintained i.e. there is no change in covalent bonding. The molecular structure is characterized by a "ball and spring" model, with the atoms being considered as spheres and linked together by springs. The potential energy of a molecular system and the associated intermolecular forces are calculated from a potential energy function (commonly referred to as the force field) that describes the interaction potential as a function of a set of parameters. The potential energy function comprises bonded and non-bonded interactions (see Fig. 2). The

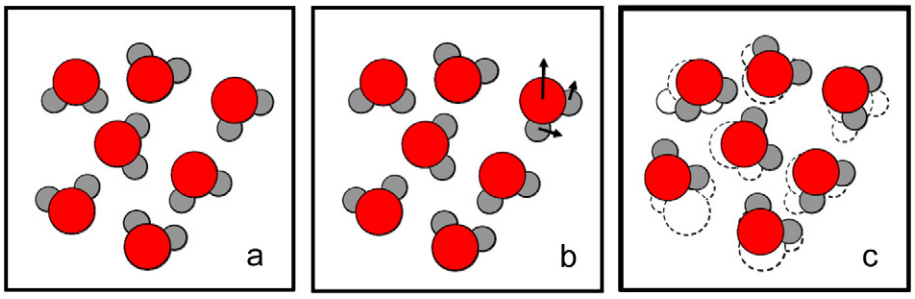

Fig. 1. Molecular dynamics simulation. (a) The initial positions of the molecules are specified (the staring configuration) and the atoms assigned velocities that are consistent with the required temperature. (b) The force on each atom due to the other atoms in its neighborhood is calculated. (c) From a knowledge of the forces, positions, and velocities, the set of positions of the atoms at some later time (typically 10^{-15} s) is calculated. The atoms are then displaced to their new positions. This process (the calculation of the forces and molecular displacements) is iterated millions of times to yield a trajectory of the dynamics of the molecules.