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Replacing microemulsion formulations experimental solubility studies with in-silico methods comprising molecular dynamics and docking experiments

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ABSTRACT

Usually, formulating hydrophobic drugs in microemulsions starts with screening the solubility of the active pharmaceutical ingredients in different oils and thereby selecting the best candidate according to its solubilising power. We hypothesise that in-silico methods such as molecular dynamics to simulate the oils domains together with docking of the investigated drug(s) on these simulated domains can offer extremely valuable tools saving researches long experimentation time in the laboratories and incalculable efforts exerted in developing sensitive and accurate methods of analysing drugs in oils.

1. Introduction

Microemulsions are excellent candidates for the delivery of hydrophobic drugs. They have been especially shown to overcome the hurdles that face the formulation of many weakly water-soluble drugs (Hathout and Woodman, 2012). One of the most important factors in developing microemulsion systems is the type of the solubilising oil used, and many microemulsion-based studies start with experimenting the solubility in different oil carriers (Patel and Vavia, 2007; Sharma and Kumar, 2012; Mehta et al., 2007; Zhao et al., 2005, 2006). This is usually performed prior to formulating a lipophilic drug such as testosterone in a microemulsion system to select the best oily carrier that can accommodate the drug (Hathout, 2010). The work in this study utilises molecular dynamics and docking studies in order to predict the best solubilising oil for a model drug *viz.* testosterone hormone as an alternative to adopting exhausting solubility studies that need complicated and sensitive methods and instruments of analysis. Recently, a similar study was performed where modeling of mixed micelles was adopted using computer simulations in order to record the possible interactions between mixed micelles and drugs (Xie et al., 2014). In another recent study, molecular simulations were utilised to gain deep insights about the inter- and the intramolecular interactions between a hydrophobic drug *viz.* Vinpocetine and different hydrophilic excipients such as: hydroxyl propyl methyl cellulose, polyvinyl alcohol and lactose to select the suitable candidates for nanoparticles preparation (Li et al., 2014). Comparing the potential

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of two surfactants; Cremophor®EL and Tween®80 to emulsify tocotrienol was also accomplished and the differences were interpreted according to their structural differences and spatial arrangement as revealed by molecular modeling and differences in binding energies obtained from docking results (Alayoubi et al., 2012).

The work in this study comprised using molecular dynamics simulation in the preparation of simulated oily domains of four different oils: oleic acid (OA), ethyl oleate (EO), isopropyl myristate (IPM) and mineral oil (MO) together with an additional simulated water domain. Consequently, docking of a lipophilic model drug; testosterone on these simulated drug carriers was performed and the results were compared with the solubility wet experiments.

2. Methods

2.1. Molecular dynamics simulations of the used oils and water

All-atom molecular dynamics simulations were carried-out using GROMACS (Pronk et al., 2013) v4.6.5 software package. The parameters of the oils were obtained using CgenFF (Vanommeslaeghe et al., 2010) available on line (https://cgenff.paramchem.org/). The oil system was initially prepared with 300 molecules for each of ethyl oleate, isopropyl myristate, mineral oil, and oleic acid. The mineral oil system was heterogenous and was prepared using 100 molecules of each of tetradecane, hexadecane, and octadecane. Prior to running molecular dynamics simulations, all systems were subjected to energy minimisation using the steepest descent method. The oily or aqueous system was then subjected to a molecular dynamics run, with a time step of 2 fs, full periodic boundary conditions, and a cut-off distance for van der Waal's and electrostatic interactions of 12 Å. PME was chosen to calculate long range electrostatic interactions. LINCS algorithm was used to constrain all bonds. The system was equilibrated at 25 °C using a v-rescale thermostat, and at a pressure of 1 bar using a Berendsen barostat for 6 ns.

2.2. Preparation of the investigated model drug for docking

The chemical structures of the studied drug; testosterone, was generated using ChemDraw® Ultra version 10 (Cambridgesoft, Waltham, MA). The corresponding Mol2 file needed for docking using the software adopted in this study was obtained using Chem3D® Ultra version 10 (Cambridgesoft, Waltham, MA) after energy minimisation using the MM2 force field of the same program.

2.3. Docking of the investigated drug on the simulated carriers

The docking analysis was carried out using AutoDock vina (Molecular graphics laboratory, The Scripps research group, La Jolla, CA). Docking was performed on a grid box consisting of 26 × 26 × 26 grid points corresponding to 9.75 Å cube (A box with a reasonable size to accommodate the docked drug) for all the carriers except for mineral oil where docking was only possible when the size of the grid box was increased to 35 × 35 × 35 grid points corresponding to 13.125 Å. Moreover, PyMol

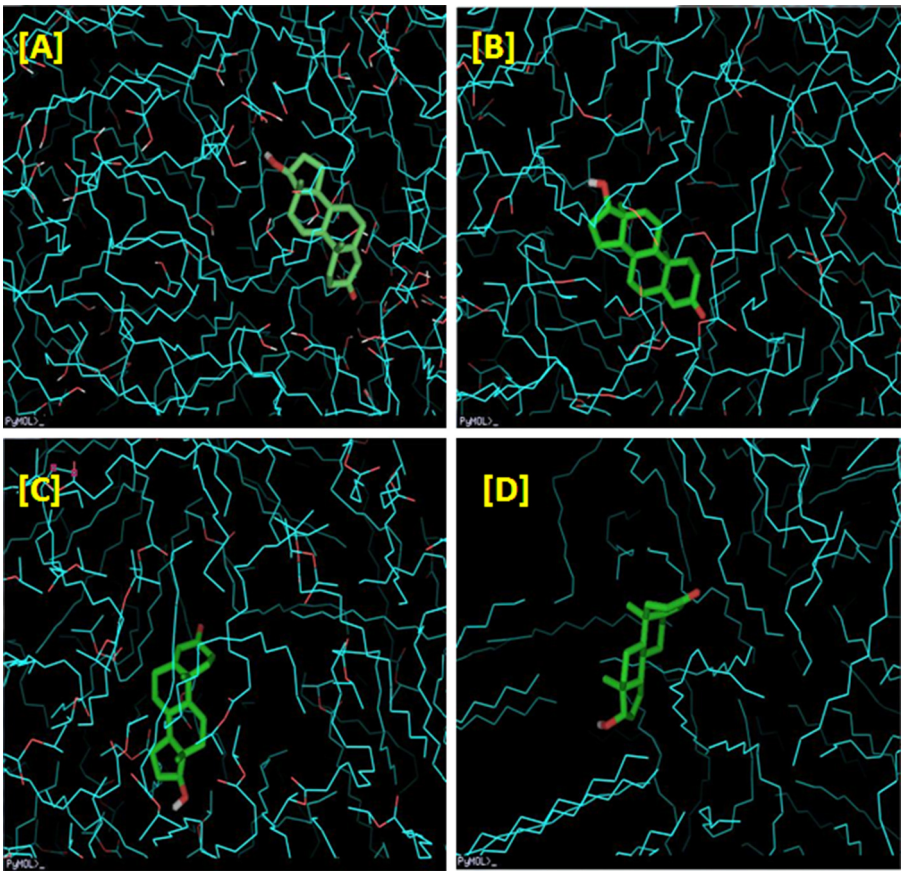

Fig. 1 – Successful docking of testosterone on the investigated oils: (A) oleic acid, (B) ethyl oleate and (C) isopropyl myristate (D) mineral oil. Images display spheres having a radius of 12 Å.