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Drug biophysical profiling using lipid-based colloidal nanosystems and human serum albumin as biomimetic interfaces

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The development of new drugs is a highly complex and expensive process, so it is crucial that less promising compounds are rejected early in the discovery phase before progressing to more expensive phases. This scenario impels researchers to refine and speed up the drug discovery process and to seek tools to support decisions related to modifications of the drug chemical structure to improve drugs' properties and thus increase the probability of success in the process of drug discovery. [1], [2] In the drug discovery process it should be considered that in physiological environment there will be reciprocal interactions between drugs and biological interfaces, such as cell membranes or plasma proteins, and from those interactions different pharmacokinetic profiles can be achieved. [3] Thus, it is important to develop i*n vitro* high throughput methods to evaluate the pharmaceutical profile, consisting in measuring properties such as permeability, lipophilicity, plasma protein binding, and biophysical changes of the membranes, which in turn affect other properties, such as the bioavailability of a drug and its pharmacokinetic profile. [4] Herein, the characterization of a newly synthesized drug (MIT-3) will be based on the measurement of fundamental biophysical properties, which allow inferring about its ADMET profile (absorption, distribution, excretion and toxicity at the membrane level). For this purpose, lipid-based colloidal nanosystems of different compositions were prepared as membrane mimetic models and several biophysical techniques were applied: derivative spectroscopy; quenching of steady-state and time-resolved fluorescence; quenching of intrinsic fluorescence of human serum albumin; synchronous fluorescence; dynamic and electrophoretic light scattering, differential scanning calorimetry and small and wide angle x-ray diffraction. The application of these techniques allowed to predict that MIT-3 has an ubiquitous location at the membrane level, presenting good membrane permeability and a good distribution in the therapeutic target. However, it is also predicted bioaccumulation with distribution in non-therapeutic targets and under conditions of prolonged exposure the drug may cause membrane toxicity as concluded by the impairment of membrane biophysical properties. It is also possible to conclude that the biophysical

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techniques and the biomimetic models used, constitute a toolbox of strategies for the future evaluation of other drugs.

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