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NOVEL METHOD OF LIPID DRUG MEMBRANE INTERACTION

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ABSTRACT
A better knowledge of the molecular processes behind drug-membrane interactions is essential for the development of novel medications. To far, a number of biochemical and biophysical methods have been developed to study biological membranes at the molecular level. This review centers on the accomplishments and new uses of contemporary analytical methods, such as spectrometry, calorimetry, acoustic sensing, and chromatography, in the investigation of drug interactions with lipid membranes. The benefits and drawbacks of these approaches were compared and carefully considered. Moreover, several biomimetic model membrane types, including lipid monolayers, liposomes, and supported lipid monolayers/bilayers, were described. Additionally, a brief overview of the general mechanics underlying the drug-membrane interaction process was given.
KEYWORDS: *bioanalysis; drug-membrane interactions; drugs; lipid membrane*

INTRODUCTION

The primary components of the cell membrane, which are a wide range of distinct lipids, proteins, and polysaccharides, make up this extremely complex and diverse structure. Amphipathic phospholipids make up the majority of the continuous lipid bilayer that makes up the cell membrane matrix. The cell membrane, which serves as a cell's border, is crucial to a drug's absorption, distribution, metabolism, and excretion (1).A medication molecule must first enter the bloodstream (the absorption process) and subsequently be delivered to its action locations (the distribution process) after being administered. The blood-brain barrier (BBB), the walls of the small capillaries lining the stomach, and the barrier membranes in the gastrointestinal tract are only a few examples of the biomembranes that can be involved in the drug's action. A growing body of research has demonstrated that drug molecules can interact with the lipid membrane either directly or indirectly. This interaction can result in modifications to the pharmacological activity, bioavailability, and physicochemical characteristics of the drug molecules, as well as a wide range of pharmaceutical effects and chemical structures (2). Adverse consequences, including medication resistance and severe side effects, can result from unfavorable drug interactions with lipid membranes.Due to inadequate medication specificity (Gashaw et (3). Examples include anaesthetics (4), anticancer medications (5), and nonsteroidal anti-inflammatory medicines (NSAIDs) (6). Therefore, it is crucial for biomedical researchers as well as the pharmaceutical industry to comprehend the inherent interactions between drugs and biomembranes.

• Analytical methods to study Drug-Membrane Interactions

Drug-membrane interactions can be investigated using a variety of analytical techniques, such as spectrometry, calorimetry, chromatography, and acoustic sensing technologies (7).

Ion-Association Mechanism High-Performance Liquid Chromatography

For more precise determination of the partitioning of ionic and zwitterionic chemicals in different phases, the HPLC IAM stationary phase was created. IAM stationary phases, which are sold commercially by Regis Technologies, are essentially made up of phospholipid monolayers, primarily phosphatidylcholine, covalently bound to porous silica spheres fig 1.Consequently, the use of IAMs could lead to improved understanding of biological partition and biological activity. Furthermore, IAM-HPLC measurement is more appropriate for medium- or high-throughput screening in early drug discovery because it is straightforward, quick, and repeatable when compared to the traditional method of determining drug partitioning in liposome/water systems (8). Numerous parallels have been drawn between the lipophilicity measured by IAM and the capacity factor, log...and the conventional logP and logD liposome/water and n-octanol/water partitioning systems (9). The outcomes demonstrated that IAM-HPLC is a more precise and efficient method for determining drug-membrane partition.

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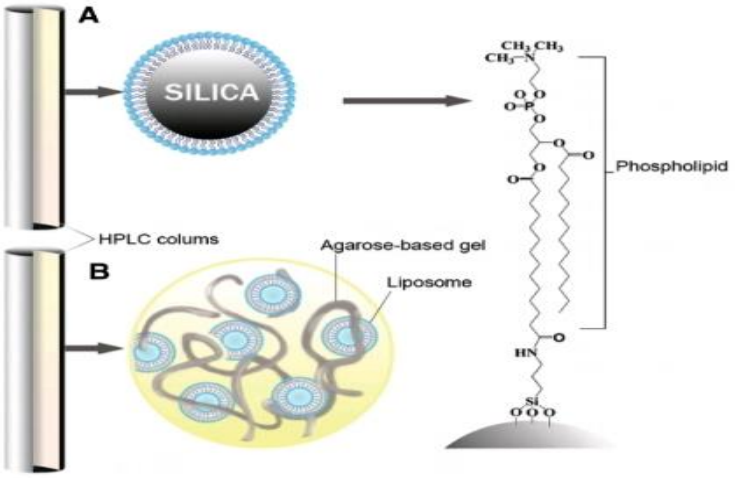


Fig 1: stationary phases of immobilized artificial membrane (IAM)

Immobilized Liposome Chromatography

In contrast to IAMs, variable membrane compositions may be used to change the biophysical characteristics of the lipid environment in ILC columns. The lipophilicity index calculated by ILC (logKs) and other techniques have different correlations. According to a comparative investigation, only for structurally related compounds were there substantial correlations discovered between logKs and the lipophilicity indices produced via IAM, n-octanol/water, and liposome/H2O systems (11).A comparative study revealed that significant correlations were only found between logKs and the lipophilicity indices obtained by IAM, n-octanol/water, and liposome/H2O systems for structurally related compounds. The lipophilicity index as determined by ILC (logKs) and other methods have different correlations. In contrast to IAMs, variable membrane compositions may be used to change the biophysical characteristics of the lipid environment in ILC columns.This suggested that the equilibrium between hydrophobic and In these systems, drug partitioning was controlled by electrostatic interactions. Three major issues with ILC include limited liposome stability, high sample demand, and challenges with column preparation.However, a recently published innovative approach demonstrated that liposomes on silica-based particle surfaces allowed for simpler column modification and a lower consumption of Liposome (12)

Electrokinetic Chromatography

Electrokinetic capillary chromatography, commonly known as electrokinetic chromatography (EKC), is a capillary electromigration method based on an amalgamation of HPLC and electrophoresis. EKC quantifies the analytes' electrophoretic mobility as well as their differential partitioning between a lipid dispersion (pseudo-stationary phase) and an encircling aqueous buffer solution (mobile phase) (13).

Capillary Electrochromatography

A kind of capillary liquid chromatography, capillary electrochromatography (CEC) is a newly discovered technique in which electroosmotic flow propels the mobile phase through a capillary. More stable lipid coatings are produced in CEC measurements because an IAM stationary phase is packed into a fused-silica capillary 14)). shown that there were linear correlations between CEC and HPLC results in a research including sixteen structurally distinct substances (15). Additionally, they noted that compared to IAM-HPLC, CEC required less analyte, eluent, and stationary phase even if its management was more sophisticated. A recent review examined the use of several capillary electromigration methods to investigate the interactions between lipid membranes and analytes (13).

Spectroscopic Techniques

This section will provide an overview of the spectroscopic methods that are frequently employed in the investigation of drug-membrane interactions. These methods include vibrational spectroscopy, mass spectroscopy (MS), electron paramagnetic resonance (EPR), fluorescence spectroscopy, X-ray diffraction (XRD), and small-angle neutron scattering (SANS). (33).

Fluorescence Spectroscopy

measures variations in fluorescence intensity to keep an eye on intermolecular interaction. When compared to alternative methods, fluorescence spectroscopy provides exceptional flexibility, great spatial resolution (down to the level of hundreds of nanometers), and

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sensitivity (down to the single-molecule level) (16). Fluorescent probes are frequently utilized since intrinsic fluorescence is uncommon in biological systems. presented an introduction to fluorescence probing of biological membranes (17).

NMR Spectroscopy

The magnetic characteristic of an atom's nucleus is known as NMR. According to the fundamental idea behind NMR spectroscopy is that some atoms' nuclei have a magnetic moment, which causes them to exhibit distinct energy levels and resonance frequencies when exposed to an external magnetic field (18),There are several of these nuclei in atoms found in lipid molecules, such as 1H, 13C, 31P, 17O, and 14N. According to lipids can also be chemically tagged with additional nuclei of interest, deuterium (2H), or fluorine (19F)(19).

EPR

Electron spin resonance spectroscopy, or EPR, is a technique that enables the direct identification of paramagnetic entities that have unpaired electrons (20).

Vibrational Spectroscopy

Vibrational spectroscopy examines an atom's nuclear vibration characteristics with little disturbance. It is mostly concerned with infrared absorption and Raman scattering. According to (21), it offers the most reliable way to distinguish between membrane behaviors, bilayer assemblies, and membrane structure and composition. Measuring the drug-induced vibrational shifts attributed to the particular chemical functional groups inside membrane systems allows for an analysis of drug-membrane interactions. The most used infrared spectroscopy technique for biophysical research is called Fourier transform infrared spectroscopy (FTIR). Analyte interactions with lipid membranes at the molecular level may be fully understood by using FTIR to monitor frequency fluctuation in the PO_2^- stretching, C=O stretching, and CH_2 stretching modes (22).

Diffraction of X-rays

When an entering X-ray beam has a wavelength that is comparable to the interatomic distances in the sample, some of the beam will be scattered, which is how XRD measurements work (23). X-ray diffraction (XRD) provides a direct and non-invasive method of determining the sample's structural characteristics, chemical makeup, and physical attributes by examining the angular distribution of the scattered intensity. Furthermore, X-ray diffraction (XRD) offers the benefit of estimating bilayer thickness of unsupported lipid membranes under near-native circumstances, down to Ångstrom length scales (24)

Neutron Scattering at small angles

Similar concepts underlie both SANS and SAXS, with the exception that in SANS, the neutron rather than the electron is the source of the scattering. Consequently, for a precise structural description of the biological membranes, SAXS and SANS may be applied as complementing approaches (25).

Calorimetric Techniques

The assessment of heat effects related to drug-membrane interaction forms the basis of calorimetric approaches (26). The quantity of material involved in the reaction and the pace of heat production are, in general, related to the amount of heat produced or consumed in a chemical reaction. Thus, calorimetric techniques may be used as thermodynamic and quantitative analytical tools. Pharmacology science has employed a number of sophisticated calorimetric methods (27). The most common methods for characterizing the drug interaction with membrane process are pressure perturbation calorimetry (PPC), isothermal titration calorimetry (ITC), and DSC. In Figure 2 typical instances of all three approaches are compiled.

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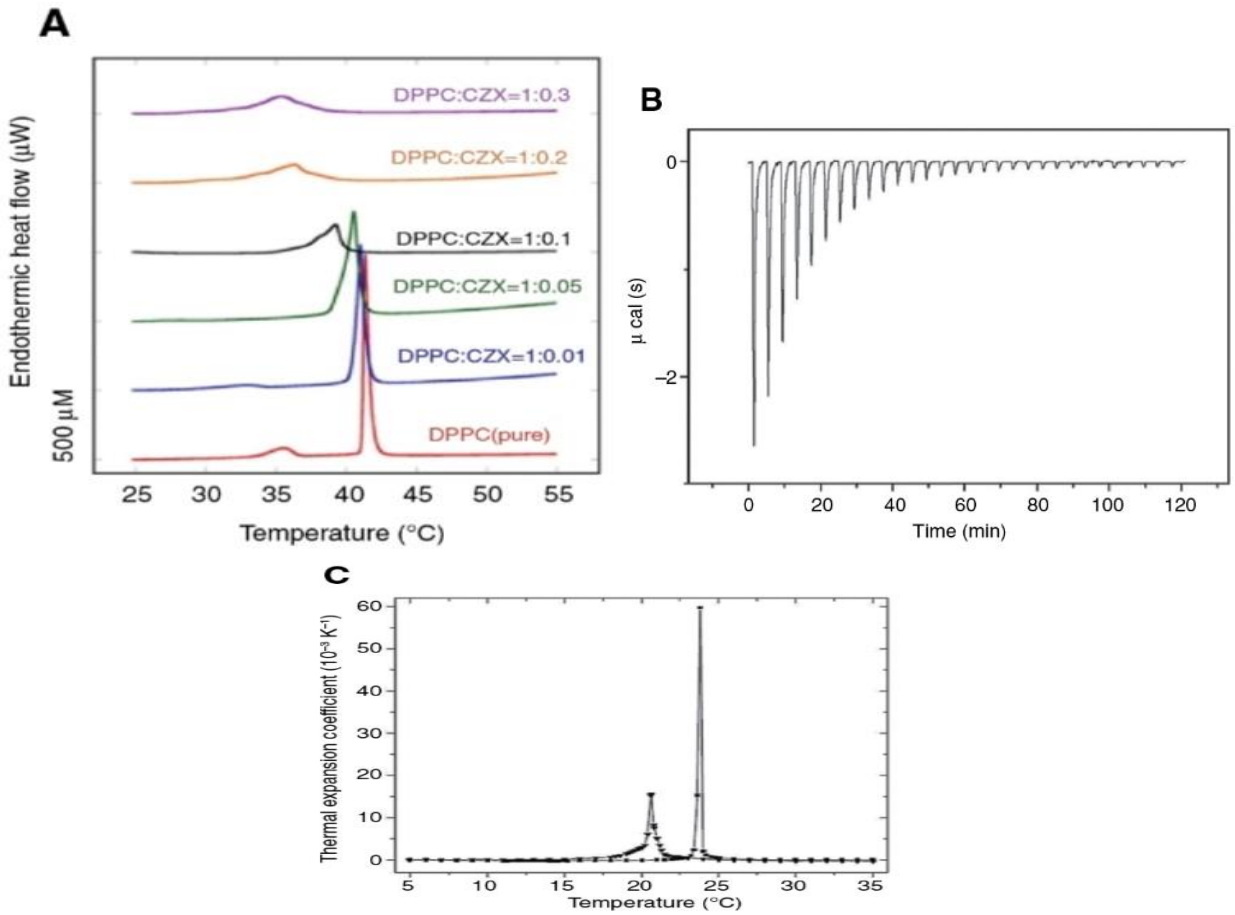


Fig 2 Calorimetry Technique

Differential Scanning Calorimetry

Heat capacity (Cp) of a material is measured using DSC, a non-perturbing method, as a function of temperature and time. It was created in 1962 by E. S. Watson and M. J. O'Neill, and Chapman utilized it for the first time in the 1960s to study the thermotropic behavior of biomembranes (28). The calorimetry of isothermal titration With the exception of operating at a constant temperature and including a titration module, the fundamental idea of ITC and DSC are identical (29). Every injection produces a record of the heat flow until the binding reaches saturation. The criteria for binding the generated isotherm may be used to determine thermodynamic values for the drug-lipid binding (30).

Pressure Perturbation Calorimetry

A relatively recent thermodynamic method called pressure perturbation calorimetry (PPC) analyzes the change in heat (ΔQ) that occurs when the pressure (ΔP) above a solution containing proteins or other biomolecules c4hanges (31).

Chromatographic Methods

Chromatography comprises a set of analytical methods that are employed to isolate, recognise, and measure distinct constituents within a blend.A stationary phase and a mobile phase interact and partition distinct substances differently, which is the foundation of chromatographic processes. To improve the identification of separated components, technologies such as electrochemical techniques and spectroscopy are frequently applied. There are several ways to classify chromatography, including gas chromatography, capillary liquid chromatography, supercritical fluid chromatography, liquid chromatography (LC), TLC, and others. based on the choice of stationary phase and mobile phase. Here, we'll focus on HPLC-based techniques, which are frequently used in studies of drug-membrane interactions.(32)

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CONCLUSION

comprising the drug's orientation, conformation, and localisation inside the membrane; the drug-inserted membrane's structural stability and phase behaviour; the drug's dynamics of interaction with the lipid membrane; and the effects of the drug-membrane interaction on the drug's ADME characteristics. Drug-membrane interactions can, in fact, be influenced by a number of variables, including the van der Waals force, hydrogen bonds, and hydrophobic and electrostatic interactions between certain lipid moieties, drug molecules, and membrane proteins. Therefore, additional analytical techniques are strongly advised to obtain a thorough knowledge of drug-membrane interaction events. Furthermore, the efficiency of on-site screening in the early stages of drug development will be significantly increased by the development of potent innovative combinations of methods, such as lab-on-a-chip hyphenation with MS methodologies.

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