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APPROACHES TO DETERMINE THE DRUG MEMBRANE INTERACTION

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ABSTRACT
When studying the effects of medications, it is common to overlook their direct interaction with the cell membrane. The natural membrane's intricacy makes systematic research difficult, but model membrane systems can provide a helpful substitute. Here, a few instances of how drug molecules can be investigated for their effects on the membrane structure and their potential effects on embedded membrane proteins are reviewed using model membrane architectures such as vesicles, solid supported membranes, and Langmuir.The creation of new drugs depends heavily on a deeper understanding of the molecular mechanisms behind drug-membrane interactions. Various biochemical and biophysical techniques have been established thus far to investigate 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. These methods' advantages and disadvantages were contrasted and thoroughly examined. Furthermore, a number of biomimetic model membrane types were described, such as liposomes, lipid monolayers, and supported lipid monolayers/bilayers. A brief introduction to the general mechanics behind the drug-membrane interaction process was also provided.

KEYWORDS : *Model membrane,Lipid bilayer ,Drug membrane interaction*

INTRODUCTION

Since most diseases are caused by malfunctions in these proteins, most medications are made to target membrane . For instance, medications are made to prevent protein binding or disrupt channel activity.Drug interactions with the membrane that surrounds proteins are frequently overlooked, despite the fact that drug–protein interactions have been well investigated. For membrane proteins to maintain their structural and functional integrity, an appropriate membrane must surround them. The natural membrane is a complicated structure made up of many distinct components, including proteins, carbohydrates, and lipids. Although membranes from related creatures share certain traits, the precise composition of membranes differs amongst them[(1)]. The membrane proteins themselves are generally quite brittle and unstable, and once they are removed from a membrane, they usually denature. Therefore, studying a membrane protein while it is entrenched in a lipid bilayer membrane is necessary to properly comprehend its functional characteristics. Despite the fact that the natural cell membrane is a very complex and diverse system made up of a wide range of various lipids, sterols, and carbohydrates, the structure and composition of the membrane are crucial to the functionality of the embedded membrane proteins. For instance, mechanosensitive membrane channels may open or close in response to modifications in the membrane's curvature[(2)].Despite the membrane's significance, research on pharmaceuticals frequently ignores how medications affect the membrane's composition and functionality. Similarly, little research has been done on how drug-induced modifications to the membrane's characteristics affect the way embedded membrane proteins operate. This is partly because systematic research are extremely difficult because of the membrane's great level of intricacy. Furthermore, studies involving whole cells or naturally occurring cell membrane patches are frequently expensive and time-consuming, and they are typically not appropriate for regular screening. Lastly, non-specific drug-membrane interactions, in which the drug attaches to the membrane, effectively lower the amount of free drug that is available, potentially decreasing the effectiveness of the treatment [(3-6)].It is evident from this that a thorough knowledge of medication interactions requires investigating the role of the membrane.In addition to providing an alternate platform to the real membrane, biomimetic model membrane systems allow the investigation of membrane–drug interactions under extremely controlled and regulated settings. Any membrane is made up of a lipid bilayer at its core. Various model systems have been created to imitate this bilayer's basic structural and functional characteristics. Vesicles or liposomes, Langmuir monolayers, solid supported bilayers, and tethered bilayer lipid membranes are well-known examplesmembrane systems. There are benefits and drawbacks to each of these systems when it comes to researching drug-membrane interactions.

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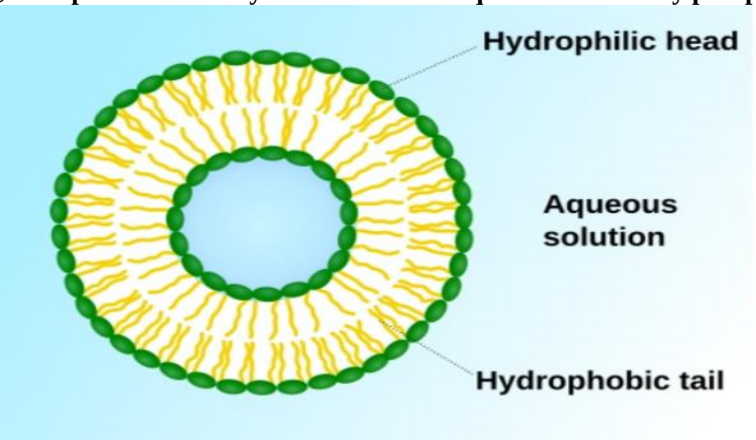
Vesicles

Liposomes, also known as vesicles, are spherical bilayers of phospholipid that are created either by sonicating a lipid dispersion or by extruding an aqueous lipid dispersion through a membrane with predetermined pore sizes. The fabrication of liposomes as unilamellar or multilamellar structures is comparatively simple. A vast range of distinct lipids and other membrane constituents can alter the bilayer's composition [7-9].Vesicles are readily available, but the variety of methods that can be employed restricts the research that can be done with them. Two distinct kinds of experiments can be carried out in theory. Dispersing techniques like light, small angle X-ray, or neutron scattering can be used to track changes in the vesicles' size and form caused by an external stimulus, such as the interaction with a drug. However, these trials provide little information about modifications to the membrane's functionality. Fluorescence investigations can be used to investigate the functional characteristics of the membrane, such as the movement of molecules across the bilayer via vesicles [10].A liposome is usually loaded with a fluorescent dye in such an experiment; for instance, pore formation in the bilayer would cause the dye to efflux and alter the fluorescence that is being monitored.Rifabutin, an antibacterial drug, was investigated in relation to different types of membranes using multilamellar vesicles . Phosphatidylglycerol headgroups are generally more abundant in bacterial membranes than in mammalian cell membranes, where phosphatidylcholine and phosphatidylethanolamine headgroups predominate. Therefore, in model systems, membranes from bacteria are commonly represented by lipids such as dipalmitoylphosphatidylglycerol (DPPG) whereas membranes from mammals are represented by dipalmitoylphosphatidylcholine (DPPC).The study examined liposomes made of cardiolipin (CL) and POPG (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol), which are both frequently found in bacterial cell membranes but not in those of mammals. Oritavancin-induced membrane permeabilization was quantified by measuring the amount of calcein leakage from liposomes. It was demonstrated that the lipid composition and, by extension, the surface charge, lipid packing, propensity to generate negative curvature, and fluidity of the bilayers determined the degree of permeabilization. The maximum rate and amount of calcein release was observed in liposomes containing CL, which was followed by liposomes containing POPC (1-Palmitoyl--oleoylphosphatidylcholine), POPG, and finally DPPG).

Figure1; A Liposome Partially Produced in an Aqueous Solution by phospholipid.



Langmuir Monolayer

The advantage of Langmuir monolayers over other model systems is that controlling the lipid layer's density and composition is comparatively much simpler. For instance, lipids with various head groups or varying cholesterol concentrations can be combined to form monolayers. Additionally, producing multi-component mixes is not too difficult. Thus, it is simple to conduct screening tests that examine how various lipids in the membrane affect how a drug molecule affects the structure of the membrane. Another helpful model system for describing drug-lipid membrane interactions at the molecular level is the Langmuir lipid monolayer, also known as lipid monolayer[11]. Amphiphilic lipids are dispersed across an air-water contact to produce Langmuir monolayers (Figure 3B). By measuring the surface pressure (π) changes of the Langmuir film as a function of the mean molecular area (A) of the lipids, or the surface pressure-area ($\pi - A$) isotherms, one can infer the interactions of drug molecules with the lipid monolayers.Monolayer systems have the following advantages over multilamellar or unilamellar bilayer dispersions: (1) they control the density of lipid lateral packing; (2) they allow unrestricted choice of parameters like lipid composition, subphase, pH, and temperature; and (3) the dispersion's precise geometry and lipid surface curvature are fixed [12-13]. AMPs that have undergone extensive testing for their capacity to pierce various phospholipids utilizing lipid monolayers include melittin, cardiotoxins, and defensin.More examples may be found in studies on membrane lipids and antibiotics interactions ,NSAID interactions, Anticancer, and other drug interactions.

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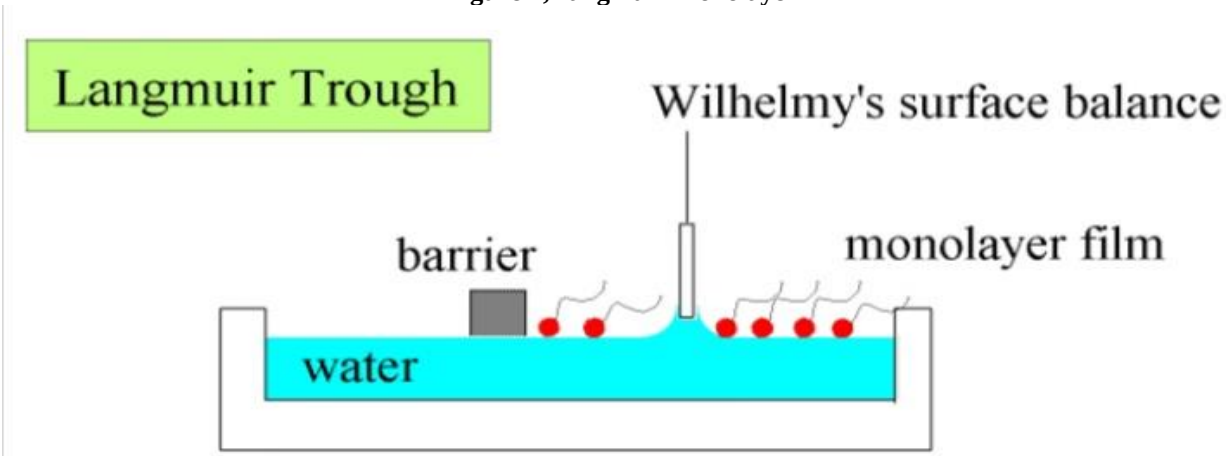
Figure 2;Langmuir Monolayer

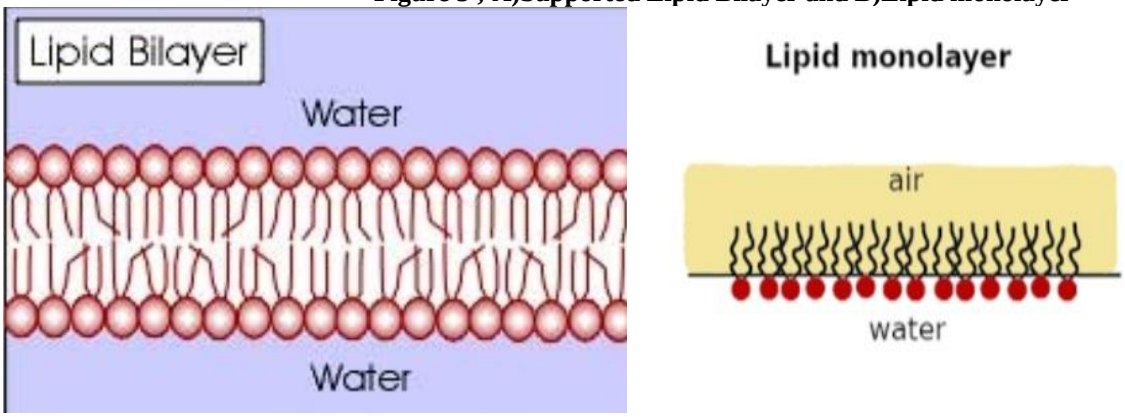


Supported Lipid Bilayer

One of the most model systems for researching surface biochemistry is likely solid supported lipid bilayers, or SLBs. SLBs have a comparatively simple geometry, have a high bilayer stability, and provide enough mobility for the lipid molecule .The creation of SLBs can occur on a variety of substrates, including metal, silicon dioxide, silica, mica, carbon nanotubes, and glass plates covered with metal or polymer , Vesicle fusion, transfer of Langmuir-Blodgett deposition followed by -Shaefer deposition, and a mixture of the first two procedures are the three traditional methods for manufacturing SLBs [14-15].Micellar lipid-surfactant combinations can also be adsorbed to create SLBs . When compared to lipid vesicles, SLBs provide the flexibility to conduct heterogeneous assays and can be used with a wide range of surface-sensitive analytical methods, including spectroscopic methods (31-34)and atomic force microscopy (AFM). Consequently, SLBs have been extensively employed in the in vitro study of drug-membrane interaction.

Using fluorescence spectroscopy, the affinity of the anesthetic medication tetracaine (TTC) for supported phospholipid bilayers produced on glass coverslips.Redondomorata et al. (2016) tracked how the hypolipidemic medication family known as statins affected the nanomechanical characteristics of SLBs using AFM imaging and nanomechanical mapping. Neutron reflectometry and sum frequency generation (SFG) have also been used to investigate interactions between large molecule medications, such as antimicrobial peptides (AMPs) and SLBs. Additionally, SLBs offer better throughput analysis and are simple to integrate into an on-chip platform. [16]

Figure 3 ; A)Supported Lipid Bilayer and B)Lipid monolayer



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Supported Lipid Monolayer

Furthermore helpful platforms for studying membranes are lipid monolayers that develop on solid substrates . Phospholipid analog monolayers can be covalently linked to the surface of immobilized artificial membranes (IAMs), also known as porous or nonporous silicon spheres. High-performance liquid chromatography (HPLC) frequently uses IAMs as stationary phases, and these phases have been effectively employed to investigate drug partitioning and binding interactions with membranes. IAMs are thought to be more stable and reproducible when compared to immobilized liposome chromatography (ILC) [17-18]. A thorough explanation of IAMs in the Section "Chromatographic techniques."

Table 1; Recent research on Drug-Membrane Interaction

Utilization and targets	Drugs and medication
High blood pressure treatment, Angiotensin II AT1 receptor	Losartan [19,20], andesartan [21]
Antiparasitic	Praziquantel [22]
Rheumatoid arthritis	Lapatinib [23]
Steroids	Danazol ,Hydocortisone [24-25]
Antiinflammatory drugs	Colchicine [26]
Pain medication	Paracetamol [27-29]
Immunosuppressant	Cyclosporine A and E [30]
Cardiac arrhythmias	Dronedarone [31]

CONCLUSION

A significant factor in determining a drug's overall efficacy is its impact on the composition and functionality of cell membranes. Model membrane systems can be used to systematically study these effects. The advantages of using solid supported membranes, Langmuir monolayers, or vesicles include reduced system complexity, access to a wide range of characterization techniques, and control over the constituent parts. Although studies utilizing whole cells will always be preferred, model membranes can serve as a valuable initial screening platform for examining drug-membrane interactions.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 approaches are strongly advised to obtain a thorough knowledge of drug-membrane interaction events.

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