MOLECULAR DYNAMICS STUDIES ON THE INFLUENCE OF AMPHIPHILIC MOLECULES AND BIO-COMPATIBLE IONIC LIQUID ON THE STRUCTURAL STABILITY OF LIPID BILAYERS

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by

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Submitted

in fulfillment of the requirement of the degree of doctor of philosophy

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Dedicated to

My Family

Certificate

This is to certify that the thesis titled "**MOLECULAR DYNAMICS STUDIES ON THE INFLUENCE OF AMPHIPHILIC MOLECULES AND BIO-COMPATIBLE IONIC LIQUID ON THE STRUCTURAL STABILITY OF LIPID BILAYERS**" is being submitted by **Ms. Pratibha Kumari** to the Department of Chemistry, Indian Institute of Technology Delhi, for the award of the degree of **Doctor of Philosophy**. This thesis is a record of bonafide research work carried out by her under my supervision. In my opinion, the thesis has reached the standards fulfilling the requirements of the regulations relating to the degree.

The results contained in this thesis have not been submitted to any other University or Institute for the award of any degree or diploma.

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Abstract

In this thesis, we study the impact of amphiphilic molecules and a bio-compatible ionic liquid (IL) on the structural stability of different lipid bilayers by employing all-atom molecular dynamics (MD) simulations. Motivation behind this work originates from the fact that binding and permeation of amphiphiles and ions across the cell membranes depend not only on the chemical nature of the solute, but also on the composition and thermodynamic phases of the membrane bilayers. The outer leaflet of the plasma membrane of most eukaryotes is made up of phosphatidylcholine (PC), sphingomyelin (SM), cholesterol along with other species. The modulation of the functions and physico-chemical characteristics of lipid membranes by amphiphilic molecules is crucial for many bio-technological and bio-medical applications, including transdermal drug delivery, anesthesia, and cryopreservation. In the literature, most of the simulation and experimental studies pertaining to the interaction of biologically relevant amphiphilic molecules have been carried out on the simplest biological membrane model based on PC lipids. Though, SM and PC lipids share similar head group structures, the presence of high average saturation rates and strong inter- as well as intra-molecular H-bonding network make SM-based bilayers different than that of PC-based bilayers. In this thesis, we first investigate the concentration dependent effects of acetone, dimethyl sulfoxide (DMSO) and ethanol on the structure and stability of homogeneous N-palmitoyl-sphingomyelin (PSM) lipid bilayer. The molecular basis of the interaction of these amphiphiles is investigated through computing various bilayer structural properties, such as order parameter, density profiles, lateral area per lipid, and bilayer thickness. Also, the variations in the possible H-bonding interactions are explored to gain insight on the molecular basis of the interaction of these solutes with the PSM lipid bilayer. In the next step, we extended our study to explore how the presence of other lipid species and cholesterol varies the effects of ethanol and DMSO on the binary bilayer system consisting of PSM and 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipids and ternary bilayer system consisting of cholesterol together with PSM and POPC, which is more realistic model towards natural biological membrane. Furthermore, we investigate the energetics of the permeation of each single solute from the bulk water phase to the center of the homogeneous PSM,

binary and ternary bilayer systems in the respective chapters. The last part of this thesis is directed to understand the impact of choline based bio-compatible IL on the structural stability of lipid bilayers. Recent experimental investigations reported that choline cation coupled with amino acid based anions constitutes a more biodegradable and bio-compatible solvent.[1, 2] Herein, we investigate, for the first time, the effect of bio-compatible IL choline glycinate ([Ch][Gly]) on the structure and stability of homogeneous POPC and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine (POPE) lipid bilayers by employing atomistic MD simulations.

सार

इस थीसिस में, हम एटमिस्टिक आणविक गतिशीलता सिमुलेशन को नियुक्त करके विभिन्न लिपिड बाइलेयर की संरचनात्मक स्थिरता पर एम्फीफिलिक अणुओं और एक जैव-संगत आयनिक द्रव के प्रभाव का अध्ययन करते हैं। इस कार्य के पीछे प्रेरणा इस तथ्य से उत्पन्न होती है कि कोशिका झिल्ली में एम्फीफाइल्स और आयनों के बंधन और पारगमन न केवल विलेय की रासायनिक प्रकृति पर निर्भर करते हैं, बल्कि झिल्ली की संरचना और थर्मोडायनामिक स्थिति पर भी निर्भर करते हैं। अधिकांश यूकेरियोट्स के प्लाज्मा झिल्ली का बाहरी लेयर फॉस्फेटिडिलकोलाइन (पीसी), स्फिंगोमेलिन (एसएम), कोलेस्ट्रॉल के साथ-साथ अन्य प्रजातियों से बना होता है। एम्फ़िफ़िलिक अणुओं द्वारा लिपिड झिल्ली के कार्यों और भौतिक-रासायनिक विशेषताओं का मॉड्यूलेशन ट्रांसडर्मल ड्रग डिलीवरी, एनेस्थीसिया और क्रायोप्रेज़र्वेशन सहित कई जैव-तकनीकी और जैव-चिकित्सा अनुप्रयोगों के लिए महत्वपूर्ण है। साहित्य में, जैविक रूप से प्रासंगिक एम्फीफिलिक अणुओं की इंटरएक्शन से संबंधित अधिकांश सिमुलेशन और प्रयोगात्मक अध्ययन पीसी लिपिड पर आधारित सबसे सरल जैविक झिल्ली मॉडल पर किए गए हैं। हालांकि, एसएम और पीसी लिपिड समान हेड ग्रुप संरचनाओं को साझा करते हैं, उच्च औसत संतृप्ति दर और मजबूत अंतर की उपस्थिति के साथ-साथ इंट्रा-आणविक एच-बॉन्डिंग नेटवर्क एसएम-आधारित बाईलेयर को पीसी-आधारित बाइलेयरस की तुलना में अलग बनाते हैं। इस थीसिस में, हम सबसे पहले सजातीय एन-पामिटोइल-स्फिंगोमेलिन (पीएसएम) लिपिड बाइलेयर की संरचना और स्थिरता पर एसीटोन, डिमेथाइल सल्फॉक्साइड (डीएमएसओ) और एथेनॉल के सघनता पर निर्भर प्रभाव की जांच करते हैं। इन एम्फीफाइल्स के प्रभाव के आणविक आधार की जांच विभिन्न बाईलेयर संरचनात्मक गुणों, जैसे ऑर्डर पैरामीटर, घनत्व प्रोफ़ाइल, प्रति लिपिड के पार्श्व क्षेत्र, और बाईलेयर मोटाई की गणना के माध्यम से की जाती है। इसके अलावा, पीएसएम लिपिड बाइलेयर के साथ संभव एच-बॉन्ड इंटरएक्शन में बदलाव द्वारा इन विलेय की इन्ट्रेक्शन के आणविक आधार पर जानकारी हासिल करने के का पता लगाया है। अगले चरण में, हमने यह पता लगाने के लिए अपने अध्ययन का विस्तार किया कि कैसे अन्य लिपिड प्रजातियों और कोलेस्ट्रॉल की उपस्थिति पीएसएम और 1-पामिटॉयल-2-ओलेय्ल-स्न-ग्लिसरो-3- से मिलकर बाइनरी बाइलियर सिस्टम तथा पीएसएम और फॉस्फोकोलीन के साथ मिलकर कोलेस्ट्रॉल से मिलकर बना टर्नरी लिपिड बाइलियर सिस्टम, जो प्राकृतिक जैविक झिल्ली की ओर अधिक यथार्थवादी मॉडल है पर एथेनॉल और डीएमएसओ के प्रभाव को बदलती है। इसके अलावा, हम संबंधित अध्यायों में सजातीय पीएसएम, बाइनरी और टर्नरी बाईलेयर सिस्टम के लिए प्रत्येक एकल एम्फीफिलिक अणु के बल्क से बाईलेयर के केंद्र में पहुँचने के क्रम की ऊर्जावानता की जांच करते हैं। इस थीसिस का अंतिम भाग लिपिड बाइलेयरस की संरचनात्मक स्थिरता पर कोलीन आधारित जैव-संगत आयनिक तरल के प्रभाव को समझने के लिए निर्देशित है। हाल की प्रायोगिक जांच में बताया गया है कि अमीनो एसिड आधारित आयनों के साथ युग्मित कोलीन का एक अधिक बायोडिग्रेडेबल और जैव-संगत विलायक है। यहाँ, हम, पहली बार, सजातीय फॉस्फोकोलीन (पीओपीसी) और 1-पामिटॉयल-2-ओलेयोल-एसएन-ग्लिसरो-3-फॉस्फोएथेनोलेमाइन (पीओपीई) लिपिड बाइलेयरस की संरचना और स्थिरता पर जैव-संगत आयनिक द्रव कोलीन ग्लाइसिनेट [Ch] [Gly] के प्रभाव परमाणु एमडी सिमुलेशन द्वारा जांच करते हैं।

Permissions

Permissions have been taken from the respective journals to reprint the publications related to the work presented in this thesis.

List of Publications Related to Work Presented in this Thesis

1. **Pratibha Kumari**, Supreet Kaur, Shobha Sharma, and Hemant K. Kashyap, Impact of Amphiphilic Molecules on the Structure and Stability of Homogeneous Sphingomyelin Bilayer: Insights from Atomistic Simulations, *J. Chem. Phys.*, **148**, 165102 (2018).

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Contents

Certificate i

Acknowledgements iii

Abstract v

Permissions vii

Table of Contents ix

List of Figures xiii

List of Tables xxiii

1 Introduction 1

1.1 General Introduction 2

1.1.1 Cell to Lipid Bilayers 2

1.1.2 Types of Membrane Lipids 3

1.1.3 Biological Relevance of Membrane Lipids and Role of Cholesterol 6

1.1.4 Interaction of Lipid Bilayers with Small Drug-like Molecules . . 7

1.1.5 Interaction of Lipid Bilayers with Ionic Liquids 14

1.2 Computational Details 17

1.2.1 Potential Energy Surface and Force Field 17

1.2.2 Ensembles and Time Averages 20

1.2.3 Integration of Equation of Motion 21

1.2.4 Temperature and Pressure Control 23

1.2.5 Periodic Boundary Conditions and Minimum Image Convention 25

1.2.6 Calculation of Long-range Electrostatic Interactions 25

1.2.7 Free Energy Calculations 27
1.2.8 Area per Lipid (APL) 29
1.2.9 Density Profiles and Bilayer Thickness 29
1.2.10 Deuterium Order Parameter of Lipid Tails 30
1.2.11 P-N Vector Angle and Tilt Angle 30
1.2.12 Two Dimensional Radial Distribution Functions 31
1.2.13 Hydrogen Bonds 31
1.3 Motivation and Organization of the Thesis 32

2 Influence of Ethanol, DMSO and Acetone on the Structural Stability of Homogeneous PSM Bilayer 35
2.1 Introduction 35
2.2 Simulation Details 37
2.3 Results and Discussion 39
2.3.1 Area per Lipid and Bilayer Thickness 39
2.3.2 Partial Electron Density Profiles 41
2.3.3 Lipid Tail Order Parameter 47
2.3.4 Hydrogen Bonds 48
2.3.5 Potential of Mean Force 54
2.4 Conclusion 55

3 Counter-effects of Ethanol and Cholesterol on the Structural Stability of Heterogeneous PSM+POPC Bilayer 57
3.1 Introduction 57
3.2 Simulation Details 60
3.3 Results and Discussion 63
3.3.1 Lateral Bilayer Area and Bilayer Thickness 63
3.3.2 Bilayer Structure and Partitioning of Water and Ethanol Molecules 65
3.3.3 Distribution of Ethanol Along Bilayer Normal 72
3.3.4 Orientational Ordering of Lipid Tails 73
3.3.5 Cholesterol Tilt Angle 74
3.3.6 Lateral Structure of the Bilayers 75
3.3.7 Hydrogen Bonding 76

3.3.7.1 Hydrogen Bonding in Binary Bilayer (PSM+POPC) Systems . . . 76
3.3.7.2 Hydrogen Bonding in Ternary Bilayer (PSM+POPC+CHOL) Systems . . . 79
3.3.8 Free Energy Profile of Ethanol Insertion . . . 81
3.4 Conclusions . . . 83

4 DMSO Induced Dehydration Effects on PSM+POPC and PSM+POPC+CHOL Heterogeneous Bilayers 85
4.1 Introduction . . . 85
4.2 Simulation Details . . . 86
4.3 Results and Discussion . . . 88
4.3.1 Orientational Ordering of Lipid Tails . . . 88
4.3.2 Electron Density Profiles of Lipids, Water and DMSO across the Lipid Bilayer . . . 90
4.3.3 Atomistic Number Density Distribution along the Bilayers . . . 91
4.3.4 Distribution of P-N Vector Angle of PSM and POPC Lipids and Tilt Angle of Cholesterol . . . 96
4.3.5 H-bond Analysis . . . 98
4.3.6 Free Energy of Transfer of DMSO . . . 102
4.4 Conclusions . . . 104

5 Impact of Bio-compatible Choline Glycinate [Ch][Gly] Ionic Liquid on the Structure of Lipid Bilayers 107
5.1 Introduction . . . 107
5.2 Simulation Details . . . 109
5.3 Results and Discussion . . . 112
5.3.1 Bilayer Structure and Partitioning of Water, $[Ch]^+$ and $[Gly]^-$ . . . 112
5.3.2 Distribution of $[Ch]^+$ and $[Gly]^-$ Atoms Along Bilayer Normal . . . 116
5.3.3 Orientational Ordering of Lipid Tails and P-N Vector in Lipid Head Group . . . 118
5.3.4 Lateral Membrane Structure . . . 120
5.3.5 Hydrogen Bonding . . . 121

5.3.5.1 Hydrogen Bonding in POPC-[Ch][Gly] Systems 121
5.3.5.2 Hydrogen Bonding in POPE-[Ch][Gly] Systems 124
5.4 Conclusions 126

6 Conclusions and Future Research Perspectives **129**

Bibliography **133**

Biodata **161**

List of Figures

1.1 Typical structure of a (a) lipid molecule and (b) lipid bilayer. Here, lipid tails are rendered in cyan color whereas nitrogen and phosphorus atoms of head groups are shown as blue and yellow color, respectively. In subfigure (b), water molecules are rendered in red color. 3

1.2 Flow chart of different types of major lipids found in the biological membranes. Here, R, R', and R" represent fatty acid chains that can vary in the saturation levels and number of carbon atoms. 5

2.1 Chemical structures of (a) ethanol, (b) acetone, (c) DMSO, and (d) PSM lipid. 37

2.2 (a) Area per lipid (APL) as a function of solute concentration for different solutes. (b) Solute concentration dependence of bilayer thickness (D_{PP}) for different systems. 40

2.3 Solute concentration dependence of the partial electron density profiles for (a) PSM lipid, (b) solute, and (c) water at 323 K. 41

2.4 Initial and an equilibrium simulation snapshots of the bilayer system containing 5 ((a) & (b)), 10 ((c) & (d)), 20 ((e) & (f)) and 30 ((g) & (h)) mol% of ethanol. In the snapshots, the ethanol molecules are shown in red and water molecules are shaded with transparent white. The nitrogen and phosphorous atoms of the phosphocholine group are shown as blue and brown-green spheres, respectively. The lipid tails are rendered in light green color. 43

2.5 Initial and an equilibrium simulation snapshots of the bilayer system containing 5 ((a) & (b)), 10 ((c) & (d)), 20 ((e) & (f)) and 30 ((g) & (h)) mol% of acetone. In the snapshots, the acetone molecules are shown as ice-blue sphere. The other representations are same as in Fig. 2.4. 45

2.6 Initial and an equilibrium simulation snapshots of the bilayer system containing 5 ((a) & (b)), 10 ((c) & (d)), 20 ((e) & (f)) and 30 ((g) & (h)) mol% of DMSO. In the snapshots, the DMSO molecules are shown as orange spheres. The other representations are same as in Fig. 2.4. . 46

2.7 Lipid tail order parameter (SCD) as a function of carbon number in the acyl chain of PSM with varying concentration of solutes. Here the error bars represent one standard deviation. 47

2.8 Variation of number of PSM-solute hydrogen bonds per PSM lipid molecule in the last 100 ns of the simulation run for (a) ethanol, (b) acetone, and (c) DMSO containing systems. 48

2.9 Variation of number of PSM-PSM hydrogen bonds per PSM lipid molecule in the last 100 ns of the simulation run for (a) ethanol, (b) acetone, and (c) DMSO containing systems. In each subfigure, variation of PSM-PSM hydrogen bond with time for pure PSM bilayer is also shown for comparison. 48

2.10 Variation of number of PSM-water hydrogen bonds per PSM lipid molecule in the last 100 ns of the simulation run for (a) ethanol, (b) acetone, and (c) DMSO containing systems. In each subfigure, variation of PSM-PSM hydrogen bond with time for pure PSM bilayer is also shown for comparison. 49

2.11 Variation of number of solute-water hydrogen bonds per (solute+water) molecule in the last 100 ns of the simulation run for (a) ethanol, (b) acetone, and (c) DMSO containing systems. In each subfigure, variation of PSM-PSM hydrogen bond with time for pure PSM bilayer is also shown for comparison. 49

2.12 Potential of mean force (PMF) for the transfer of ethanol, acetone and DMSO across the bilayer. The error bars in the PMFs represent one standard deviation. 54

3.1 The chemical structures of (a) PSM, (b) POPC, (c) CHOL, and (d) ethanol. 61

3.2 APL and Bilayer thickness as a function of ethanol concentration for binary and ternary lipid bilayer systems. 64

3.3 Electron density profiles of lipid, water and ethanol molecules along bilayer normal (z-axis) for (a) binary and (b) ternary bilayer systems containing 0, 5, and 20 mol% of ethanol. 66

3.4 Equilibrium snapshots depicting partitioning of water and ethanol molecules along in the binary bilayer systems consisting of (a) 0, (b) 5, and (c) 20 mol% of ethanol. Here, the oxygen atoms of water molecules are rendered in cyan color. Ethanol molecules are shown in red color with licorice representation as implemented in VMD. The phosphorus and nitrogen atoms of phosphocholine group of PSM and POPC lipids are shown as yellow and blue spheres, respectively. The other parts of PSM and POPC lipids are omitted here for visual clarity. 67

3.5 Equilibrium snapshots of the ternary bilayer systems consisting of (a) 0, (b) 5, and (c) 20 mol% of ethanol. All the representations used here are same as in Fig. 3.4. 67

3.6 The atomic number density profiles of the phosphorus atoms of the phosphocholine headgroups of PSM/POPC lipids and the oxygen atom of water along the bilayer normal (z-axis) for the binary ((a) & (b)) and ternary ((c) & (d)) bilayer systems consisting of 5 ((a) & (c)) and 20 ((b) & (d)) mol% of ethanol. In each subfigure, for comparison, the number density profiles of corresponding atoms in pure binary bilayer system are also plotted as dashed line. Also, note that the number densities of the oxygen atoms of water molecules has been divided by 20 in order to enhance the visualization of the placement of water molecules near the lipid headgroup regime. 68

3.7 Equilibrium snapshots displaying the partitioning of ethanol molecules in binary ((a) & (b)) and ternary ((c) & (d)) bilayer systems consisting of 5 ((a) & (c)) and 20 (((b) & (d))) mol% of ethanol. Here, PSM and POPC lipid tails are shown in light green and orange colors, respectively. The phosphocholine headgroup atoms, phosphorous and nitrogen are rendered as yellow and blue spheres, respectively. Water molecules are presented with light cyan color in the quick surface mode. Ethanol and cholesterol molecules are shown in red and magenta colors, respectively. 70

3.8 Equilibrium snapshots showing the lateral distribution (top view) of PSM and POPC lipid molecules in the binary bilayer systems consisting of (a) 0, (b) 5, and (c) 20 mol% of ethanol. Subfigures 3.8(d)-3.8(f) show the lateral distribution of PSM, POPC and CHOL in the ternary bilayer systems consisting of (d) 0, (e) 5, and (f) 20 mol% of ethanol. In the snapshots, the PSM and POPC molecules are rendered in green and orange colors, respectively. The cholesterol molecules are shaded in magenta color. The phosphorus and nitrogen atoms of phosphocholine headgroup of lipid molecules are shown as yellow and blue spheres. The hydroxyl oxygen atoms of cholesterol molecules are shown as red spheres. 71

3.9 Atomic number density profiles (ANDPs) of different polar groups present in individual lipids and oxygen atom of ethanol for (a) binary and (b) ternary bilayer systems consisting of 5 mol% of ethanol. For ternary bilayer system, ANDP of the oxygen atom of the hydroxyl group of cholesterol is also provided. 72

3.10 Change in the orientational ordering of the carbon atoms of the palmitoyl tail of PSM and POPC lipid molecules for (a) binary and (b) ternary bilayer systems containing 5 and 20 mol% of ethanol. For comparison, the order parameter profiles of the carbon atoms of the palmitoyl tail of respective PSM and POPC lipids in the absence of ethanol are also plotted. 73

3.11 The variation of probability distribution function P(θ) (in $a.u$) of the angle θ between the cholesterol C3-C17 vector and the bilayer normal in ternary system for different concentration of ethanol. 74

3.12 Two-dimensional RDFs of P-P and N-N atomic pairs of PSM and POPC lipids in (a) binary and (b) ternary bilayer systems. 75

3.13 Distribution of number of (a) lipid-ethanol (PSM-ethanol and POPC-ethanol) and (b) interlipid (PSM-PSM and PSM-POPC) H-bonds for binary bilayer systems. For lipid-ethanol pairs, the number of lipid-ethanol H-bonds is normalized by corresponding number of lipid molecules. 77

3.14 Distribution of number of (a) lipid-ethanol (PSM-ethanol, POPC-ethanol, and CHOL-ethanol), (b) interlipid (PSM-PSM and PSM-POPC), and (c) lipid-CHOL (PSM-CHOL and POPC-CHOL) H-bonds for ternary bilayer systems. For lipid-ethanol pairs, the number of lipid-ethanol H-bonds is normalized with respect to number of respective lipid molecules. 80

3.15 PMF profiles for the insertion of an ethanol molecule from aqueous phase to the center of the homogeneous PSM, binary (PSM+POPC) and ternary (PSM+POPC+CHOL) bilayers in the corresponding systems. The PMF profile for the transfer of ethanol molecule across pure homogeneous PSM bilayer was taken from chapter 2. 81

4.1 Orientational order parameter (SCD) of palmitoyl tails of PSM and POPC lipids in (a) binary and (b) ternary bilayer systems. The order parameter profiles of hydrocarbon lipid tails of respective pure binary and ternary bilayers are also shown for comparison. Here, the error bars represent one standard deviation. 89

4.2 Partial electron density profiles (EDPs) of PSM and POPC lipids, water and DMSO for (a) binary and (b) ternary bilayer systems consisting of 5 and 20 mol% of DMSO. The EDPs of lipid and water molecules for pure binary and ternary bilayer systems are also plotted for comparison. The color coding for each mole fraction is same as used in Fig. 4.1. . . 90

4.3 The atomic number density profiles (ANDPs) of the polar group atoms of lipids and oxygen atoms of water and DMSO as a function of position along the bilayer normal for binary ((a) & (b)) and ternary ((c) & (d)) bilayer systems containing 5 ((a) & (c) and 20 ((b) & (d)) mol% of DMSO. ANDPs for atoms corresponds to pure binary and ternary bilayers are also plotted in the respective graphs for comparison. Here, dashed (- -) and solid (—) lines represent density profiles of atoms corresponding to pure and DMSO consisting bilayer systems, respectively. For ternary bilayer systems, the ANDPs of the hydroxyl oxygen atom of cholesterol (CHOL) is also provided. 93

4.4 Final equilibration snapshots of the binary bilayer ((a) & (b)) and ternary ((c) & (d)) bilayer systems comprising of 5 ((a) & (c)) and 20 ((b) & (d)) mol% of DMSO. In the snapshots, the carbon atoms of hydrocarbon tails of PSM and POPC lipids are rendered as green and cyan, respectively, with licorice representation. The nitrogen, phosphorus, oxygen and carbon atoms of the phosphocholine head group and interfacial regions are shown in blue, tan, red, and cyan respectively. The hydrogen atoms (H-atoms) for the interfacial hydroxyl and amide group of PSM and hydroxyl group of cholesterol are shown in white color whereas other H-atoms are removed for visual clarity. DMSO molecules are shown in mustered yellow whereas water molecules are rendered with light cyan color. Cholesterol molecules are shown in pink color. 94

4.5 The variation in the P-N angle distribution function P(θ)(in arbitrary units) of PSM and POPC lipid molecules for (a) binary and (b) ternary bilayer systems containing 0, 5 and 20 mol% of DMSO. The standard deviation (σ) values for the distributions are also depicted. 97

4.6 The variation in the tilt angle distribution function P(θ)(in arbitrary units) of cholesterol molecules for ternary bilayer systems consisting 0, 5 and 20 mol% of DMSO. Here, tilt angle represents the angle θ between the cholesterol C3-C17 vector and the bilayer normal. The standard deviation (σ) values for the distributions are also depicted. 97

4.7 Free energies (or PMF) for the transfer of DMSO molecule from bulk water to bilayer center for homogeneous PSM, binary (PSM+POPC) and ternary (PSM+POPC+CHOL) bilayer systems. Here, the error bars in the PMFs are computed using 5 data sets of equal length, saved during 1-1.2 μs. 102

5.1 Chemical structures of (a) POPC, (b) POPE, (c) cholinium ($[Ch]^+$) cation, and (d) glycinate ($[Gly]^-$) anion. 110

5.2 (a) Area per lipid (APL) and (b) bilayer thickness (D_{PP}) as a function of [Ch][Gly] IL concentrations for POPC and POPE lipid bilayer. The bilayer thickness is defined as the distance between the peaks in the phosphate electron density profile along bilayer normal. 111

5.3 Number density profiles of lipid molecules along bilayer normal (z-axis) for (a) POPC-[Ch][Gly]and (b) POPE-[Ch][Gly] systems containing 0, 2.5, 5, 10, and 20 mol% of cholinium glycinate biocompatible liquid. . . 112

5.4 Number density profiles of water, $[Ch]^+$ cations, and $[Gly]^-$ anions along z-direction for (a) POPC and (b) POPE bilayer consisting 2.5, 5, 10, and 20 mol% of [Ch][Gly] bio-ionic liquid. Number density profiles of water for respective pure bilayer is also shown for comparison. 113

5.5 Equilibrium shapshots showing the distribution (seen from top) of $[Ch]^+$ and $[Gly]^-$ within lipid-water interfacial region in POPC-[Ch][Gly] system containing (a) 2.5 (b) 5 (c) 10 and (d) 20 mol% of [Ch][Gly] IL. In the snapshots, the $[Ch]^+$ cations and $[Gly]^-$ anions are shown in red and green colors, respectively. The lipid molecules are shaded in white along with molecular representation of phosphate groups. Water molecules are not shown for clarity. 114

5.6 Equilibrium shapshots showing the distribution (seen from top) of $[Ch]^+$ and $[Gly]^-$ within lipid-water interfacial region in POPE-[Ch][Gly] system consisting (a) 2.5 (b) 5 (c) 10 and (d) 20 mol% of [Ch][Gly] IL. In the snapshots, the $[Ch]^+$ cations and $[Gly]^-$ anions are shown in red and green colors, respectively. The lipid molecules are shaded in white along with molecular representation of phosphate groups. Water molecules are not shown for clarity. 115

5.7 Atomic number density profiles of nitrogen (N), phosphorous (P), ester groups of lipid tails along with oxygen and nitrogen atoms of $[Ch]^+$ cations and $[Gly]^-$ anions for POPC bilayer (a,b) and POPE bilayer (c,d) containing lowest (2.5%) and highest (20%) concentration of [Ch][Gly] IL. Atomic number density profiles of respective neat lipid bilayer are also plotted for comparison. 117

5.8 Orientational order parameter (SCD) of palmitoyl tail of lipid molecules for (a) POPC-[Ch][Gly] and (b) POPE-[Ch][Gly] systems. The order parameter profiles of hydrocarbon lipid tail of respective neat bilayer are also shown for comparison. 118

5.9 The variation of probability distribution function $P(\theta)$(in arbitrary units) of the angle θ between the lipid headgroup P-N vector and the bilayer normal in (a) POPC and (b) POPE lipid bilayers for different concentration of [Ch][Gly] IL. For comparison, the P-N angle distributions of pure POPC and POPC lipid bilayer are also shown in the respective Figures. 119

5.10 Two-dimensional RDFs for (a) N-N and (b) P-P atoms of lipids in POPC-[Ch][Gly] systems. RDFs for (c) N-N and (d) P-P atoms of lipids in POPE-[Ch][Gly] systems. 120

5.11 [Ch][Gly] concentration dependence of number of (a) POPC-$[Ch]^+$, (b) POPC-$[Gly]^-$, (c) POPC-water, (d) water-$[Ch]^+$, and (e) water-$[Gly]^-$ H-bonds for POPC-[Ch][Gly] systems. 122

5.12 Frequently observed configurations ((a) and (b)) showing association of POPC lipid molecule with $[Ch]^+$ and $[Gly]^-$ ions for system containing 20 mol% [Ch][Gly] IL. In the figures, nitrogen and oxygen atoms of IL ions are shown in blue and red colors, respectively. Representations shown here clearly indicate that $[Gly]^-$ ions stay close to the choline group of POPC lipid due to electrostatic interaction whereas $[Ch]^+$ cations can penetrate in the interfacial region and stay close to the phosphoryl or ester group oxygens of the lipids. The distances shown by dashed lines are in Å unit. 123

5.13 [Ch][Gly] concentration dependence of number of (a) POPE-$[Ch]^+$, (b) POPE-$[Gly]^-$, (c) POPE-water, (d) water-$[Ch]^+$, and (e) water-$[Gly]^-$ H-bonds for POPE-[Ch][Gly] systems. 125
5.14 Representative configurations ((a) and (b)) showing association of POPE lipid molecule with $[Ch]^+$ and $[Gly]^-$ ions for system containing 20 mol% [Ch][Gly] IL. Representations in (a) and (b) indicate that $[Gly]^-$ ions prefer to stay close to the ammonium group of POPE lipid because of H-bonding or electrostatic interaction (shown as dashed lines). $[Ch]^+$ ions are observed to be close to the phosphoryl or ester group oxygens of lipids. The distances shown by dashed lines are in Å unit. 126

List of Tables

2.1 Summary of the simulated bilayer solute systems 38

2.2 Solute mol%, average APL and bilayer thickness*, D_{PP}, in different solute bilayer systems. To calculate standard error, we divided trajectory into 5 equal sized (20 ns each) blocks and calculated the average and standard deviation. 40

2.3 Number of H-bonds per PSM lipid molecule computed for various H-bond acceptor and H-bond donor groups of PSM lipid and solute in the PSM bilayer systems containing 5 and 30 mol% of ethanol, acetone and DMSO. 50

2.4 Number of PSM-PSM H-bonds per PSM lipid molecule for PSM bilayer systems containing lowest and highest concentration of ethanol, acetone and DMSO. 51

2.5 Number of PSM-water H-bonds per PSM lipid molecule for PSM bilayer systems containing lowest and highest concentration of ethanol, acetone and DMSO. 51

2.6 Number of H-bonds per solute+water molecule computed for solute and water H-bonds interactions in the PSM bilayer systems containing lowest and highest concentration of ethanol, acetone and DMSO. 51

3.1 Summary of the simulated binary and ternary bilayer systems. 62

3.2 Ethanol mol%, Average APL, and bilayer thickness (D_{PP}) in binary and ternary bilayer systems 64

3.3 The average number of H-bonds per respective lipid molecule computed for H-bonding interactions between different polar groups of individual lipid and hydroxyl group of ethanol for binary and ternary bilayer systems consisting of 5 and 20 mol% of ethanol. 77

3.4 The average number of H-bonds per PSM molecule computed for interlipid PSM-PSM and PSM-POPC pairs for binary and ternary bilayer systems consisting of 0, 5 and 20 mol% of ethanol. For ternary bilayer systems, the H-bond number for PSM-CHOL and POPC-CHOL pairs are also provided. . 78

4.1 Summary of the simulated binary and ternary bilayer systems. 87

4.2 Average APL and bilayer thickness*, D_{PP} for binary (PSM+POPC) and ternary (PSM+POPC+CHOL) bilayer systems consisting 0, 5 and 20 mol% of DMSO. 89

4.3 Average number of H-bonds per corresponding lipid molecule formed by water with different polar groups of individual lipids (present in binary and ternary bilayer systems) in the presence of different concentrations of DMSO. 99

4.4 Average number of DMSO-PSM and DMSO-CHOL H-bonds per corresponding lipid molecule for binary and ternary bilayers consisting 5 and 20 mol% of DMSO. 99

4.5 Average numbers of DMSO-water and water-water H-bonds for binary and ternary bilayer systems consisting 0, 5 and 20 mol% of DMSO. . . 100

4.6 Average number of inter-lipid PSM-PSM and PSM-POPC H-bonds per PSM molecule for binary and ternary bilayer systems consisting different concentration of DMSO. For ternary bilayer systems PSM-CHOL and POPC-CHOL H-bonds also provided. 101

5.1 Summary of the simulated bilayer-[Ch][Gly] systems. 109

5.2 [Ch][Gly] mol% dependence of average APL and bilayer thickness, D_{PP}, in POPC and POPE bilayer systems. D_{PP} is defined as the distance between the peaks in the phosphate electron density profile along bilayer normal. . . 111

5.3 Ensemble average of number of H-bond per lipid molecule computed for POPC-$[Ch]^+$, POPC-$[Gly]^-$, POPC-water pairs and per solvent molecules for water-$[Ch]^+$, and water-$[Gly]^-$ pairs in POPC-[Ch][Gly] systems. 123

5.4 Ensemble average of number of H-bond per lipid molecule computed for POPE-$[Ch]^+$, POPE-$[Gly]^-$, POPE-water pairs and per solvent molecules for water-$[Ch]^+$and water-$[Gly]^-$ pairs in POPE-[Ch][Gly] systems. 125