الجمهورية الجزائرية الديمقراطية الشعبية

Democratic and Popular Republic of Algeria

Ministry of Higher Education and Scientific Research

Université Ferhat ABBAS Sétif 1

FERHAT ABBAS UNIVERSITY - SETIF1

FACULTY OF TECHNOLOGY

THESIS

Presented to the Department of Process Engineering

To obtain the diploma of

DOCTORAT

Field : Science and Technology

Sector : Process Engineering Option : Pharmaceutical Engineering

Par

BENNAADJA Souhib

THEME

Development of Novel Natural Product-Based Formulations: Enhancing Ferulic Acid Delivery via NADES in DMPC Bilayer Systems

Supported on O5/11/2025 before the Jury:

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Dedication

I dedicate this work to my family, especially to my beloved parents, whose unconditional love, unwavering support, and wise guidance have been my greatest strength.

To my brothers and sisters, thank you for your constant presence and the laughter that helped me through the most difficult times.

To my wife, whose patience, understanding, and love have been a pillar throughout this journey this achievement is as much yours as it is mine.

And to my dear children, Assil and Amira you are my inspiration and the light that brightens every step of my path.

S. Bennaadja

Acknowledgements

All praise and gratitude are due to God, by whose grace good deeds are accomplished.

These five years of doctoral study have been an intense and transformative journey, filled with continuous learning, meaningful encounters, and invaluable discoveries. I extend my deepest and most sincere gratitude to **Dr. El Khamsa Soltani**, whose remarkable scientific expertise and scholarly mentorship were essential to the successful completion of this research. Her insightful guidance, academic rigor, and intellectual generosity laid a strong foundation for the advancement of my work. At every stage, her thoughtful supervision and critical feedback refined my thinking and strengthened the quality of this study. Her unwavering support, patience, and encouragement were profoundly inspiring.

Dr. Soltani's mentorship has significantly enriched my academic and personal growth. It has been an honor and privilege to conduct this research under her esteemed guidance.

I would like to express my gratitude to all the professors who have supported me throughout this academic journey. I am especially thankful to **Professor Charef Noureddine**, Director of the Laboratory of Applied Biochemistry at Ferhat Abbas University of Sétif, and to **Professor Djamel Ghernouat**, for their scientific and emotional support, which has been both constant and immeasurable.

I am also sincerely grateful to my co-supervisor, **Professor Benguerba Yacine**, for his guidance, thoughtful advice, and continued dedication throughout the course of my research.

My thanks also go to the Chairman and members of the examination committee, who graciously accepted to review and discuss my thesis. This work would not have reached its current form without their valuable feedback and kind guidance.

I take this opportunity to thank all the staff of the teaching laboratory for their warm welcome and for assisting me with the use of various tools and equipment.

Acknowledgements

Above all, I wish to acknowledge those who have had the most profound influence on my life my generous parents, whose love and sacrifices have shaped my path. I also extend my heartfelt thanks to **my mother, my father, my brothers, my wife, my children, and my colleagues**, whose unwavering support and encouragement carried me through the most challenging moments.

Summary

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Abbreviations

FA	**Ferulic Acid**
DDS	**Drug Delivery System**
DMPC	**Dimyristoylphosphatidylcholine**
DES	**Deep Eutectic Solvents**
NADES	**Natural Deep Eutectic Solvents**
COSMO-RS	**COnductor-like Screening MOdel for Real Solvents**
COSMOmic	**COnductor-like Screening Model for Micelles and Membranes**
EPR	**Enhanced Permeability and Retention**
W_{SLE}	**Weight Solubility Limit Extension**
HBA	**Hydrogen Bond Acceptor**
HBD	**Hydrogen Bond Donor**
$Log_{10}(x\_SLE)$	**Logarithm of Mole Fraction Solubility in Liquid Equilibrium**
DFT	**Density Functional Theory**
UAS	**Ultrasound-Assisted Synthesis**
MAS	**Microwave-Assisted Synthesis**

General Introduction

With the increasing focus on green chemistry and sustainable solutions, Deep Eutectic Solvents (DES) and Natural Deep Eutectic Solvents (NaDES) have been gaining attention [1]. They're seen as promising, eco-friendly alternatives to traditional solvents, mainly because they can dissolve various bioactive compounds [2]. These solvents are especially useful in the pharmaceutical world, improving the solubility and stability of hydrophobic molecules like ferulic acid [3]. NaDESs, which are made from naturally occurring molecules like choline chloride and organic acids, have proven to be particularly effective at improving the solubility of compounds that struggle to dissolve in water [4]. This feature is crucial, especially for pharmaceutical applications where poor solubility often limits how well a drug can be absorbed by the body [1]. In addition to increasing solubility, NaDESs can also improve the stability of these compounds, making them valuable for drug delivery systems. One of the biggest challenges in drug formulation is increasing bioavailability or how much of the drug actually reaches the bloodstream and can be used by the body. This is where NaDESs can play a key role [5].

Moreover, combining NaDESs with dimyristoylphosphatidylcholine (DMPC) bilayer liposomes offers a powerful approach to improving drug delivery. Liposomes, which are small spherical structures made of lipids, are widely used to encapsulate drugs, protecting them from degradation and controlling their release [6]. By integrating NaDESs into these liposomes, it becomes possible to address the solubility issues that often arise with hydrophobic bioactive compounds. This combination allows for better encapsulation and stabilization within lipid-based environments, where traditional solvents or delivery methods fall short. Essentially, it provides a more controlled, sustained release of active compounds, which can be crucial for maintaining therapeutic efficacy over time [7]. This research focuses on the encapsulation and controlled release of two natural bioactive compounds: ferulic acid which are well-known for their antioxidant, anti-inflammatory, and anticancer properties [8-15]. Despite their strong pharmacological potential, both of these flavonoids face significant challenges in terms of water solubility and bioavailability, meaning they don't dissolve easily in water and have a hard time being effectively absorbed into the body.

To address these issues, the study focuses on using Natural Deep Eutectic Solvents (NaDES) as the solvent system. NaDESs have shown great promise in enhancing the solubility and stability of bioactive compounds like ferulic acid. By using NaDES, the research delves deeper into the molecular interactions that occur within DMPC bilayer lipid structures that are often used to

encapsulate drugs for better delivery [5,7]. The study takes advantage of advanced computational techniques, specifically COSMO-RS **(Conductor-like Screening Model for Real Solvents)** and COSMOmic **(Conductor-like Screening Models for micelles and membranes)** simulations, to get a more detailed understanding of how these compounds behave at the molecular level [16,17]. These simulations help predict how well ferulic acid will dissolve in the NaDES and how stable they will be over time. In addition, the simulations shed light on the diffusion profiles of these compounds essentially, how they move and spread within the DMPC bilayers. This information is crucial for optimizing the controlled release of the compounds, ensuring that they are delivered more effectively and efficiently in therapeutic applications [7]. The ultimate goal of this research is to gain a deeper understanding of how NaDES can enhance the therapeutic potential of hydrophobic bioactive compounds, like ferulic acid. These compounds often face significant challenges with solubility, which limits their effectiveness as pharmaceutical agents. By using NaDES, the study aims to improve their solubility and stabilize them within liposomal structures, specifically DMPC bilayer liposomes, which are widely used for drug delivery.

Another key aspect of the research is the controlled release mechanism. By encapsulating these bioactives in NaDES-liposome combinations, the research aims to create a system where the release of the active compounds can be more finely tuned. This is important because it ensures that the compounds are delivered at the right time and in the right amounts, maximizing their therapeutic efficacy while minimizing potential side effects. The findings from this study are expected to contribute significantly to the development of more effective, stable, and sustainable pharmaceutical formulations. The research offers insights into how NaDES can overcome the common limitations of hydrophobic compounds. This could pave the way for better, more reliable drug delivery systems that improve both the stability and bioavailability of these potent natural compounds [2,3,4].

This thesis investigates the solubility, stability, and controlled release of two natural bioactive compounds, ferulic acid, using Dimyristoylphosphatidylcholine (DMPC) liposomes and Deep Eutectic Solvents (DES), including Natural DES (NaDES). The present study employed computational techniques, including COSMO-RS and COSMOmic, to predict the behavior of the compounds under investigation in different solvent and liposome environments.

The thesis is divided into several chapters:

In Chapter 1, an exhaustive introduction to Deep Eutectic Solvents (DES), is provided, encompassing their synthesis and distinctive properties, such as their ability to enhance solubility

and their environmentally friendly profile, making them highly suitable for pharmaceutical applications. The chapter also explores the formulation of DMPC liposomes for drug delivery, emphasizing their role in improving therapeutic efficacy. Furthermore, it provides a comprehensive overview of ferulic acid, highlighting their significant therapeutic potential while addressing the challenges related to their solubility**.**

In the second chapter, we delve into the application of computational chemistry tools, specifically COSMO-RS (Conductor-like Screening Model for Real Solvents) and COSMOmic, to investigate the solubility behavior and molecular interactions of the studied compounds. COSMO-RS is a powerful thermodynamic model that integrates quantum chemical calculations with statistical thermodynamics to predict solubility, activity coefficients, and other physicochemical properties of molecules in various solvents, including deep eutectic solvents (DES). COSMOmic, an extension of COSMO-RS, is designed to simulate the behavior of solutes within anisotropic systems such as micelles, membranes, or liposomes. In this chapter, we employ these tools to gain insights into the solvation mechanisms and to assess the potential of different solvent systems for enhancing the solubility, stability, and delivery efficiency of the target compound.

Chapter Three presents the integration of advanced computational chemistry tools with an in-depth analysis of the experimental outcomes obtained in this study. This chapter is specifically concerned with the application of COSMO-RS (Conductor-like Screening Model for Real Solvents) and COSMOmic to evaluate the solubility, molecular interactions, and solvent compatibility of the selected hydrophobic compounds. These predictive models offer valuable insights into the thermodynamic behavior of molecules in both isotropic solvents, such as Natural Deep Eutectic Solvents (NaDES), and anisotropic environments, including lipid bilayers like DMPC liposomes.

The chapter explores the behavior of ferulic acid, covering NaDES synthesis, its impact on solubility enhancement, effective encapsulation within DMPC liposomes, and the achievement of sustained drug release.

The results indicate that DES and NaDES serve as green, efficient solvent systems capable of significantly enhancing the solubility, stability, and release profiles of poorly water-soluble bioactive compounds. Overall, the study underscores the potential of these solvent systems in pharmaceutical formulation and encourages further research into their application in broader drug delivery contexts.

Chapter 1: Advanced Solvents for Pharmaceutical Applications

1. Deep Eutectic Solvents

1.1. Introduction

Deep eutectic solvents (DESs) are a relatively new type of solvent that has been getting a lot of attention in the areas of green chemistry and materials science. They are made by mixing two or more components, usually a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), which interact through hydrogen bonding to create a eutectic mixture. What's interesting is that this mixture often has a much lower melting point than the individual components, so you often end up with a liquid at room temperature [18].

One of the reasons DESs are so appealing is because they're versatile, low in toxicity, and biodegradable. This makes them a great alternative to traditional organic solvents, and in some cases, even to ionic liquids. Their properties, such as viscosity, polarity, and conductivity, can be readily tuned, enhancing their applicability across diverse fields, including pharmaceuticals, electrochemistry, catalysis, and materials synthesis. They've also been used for extracting metals, processing biomass, and serving as a medium for various chemical reactions, thanks to their ability to dissolve a wide range of substances like metal salts, organic compounds, and polymers [19].

Another significant advantage of deep eutectic solvents (DESs) is their relatively simple and cost-effective synthesis compared to ionic liquids [20]. In many cases, DESs can be prepared by simply mixing readily available and inexpensive components, like choline chloride and urea [21]. Their potential to improve sustainability, combined with their cost-effectiveness and efficiency, has driven a lot of research, as scientists are keen to explore their full range of uses across different fields and industries [18,4].

1.2. Synthesis of Deep Eutectic Solvents

Making DES (Deep Eutectic Solvents) usually involves mixing two or more ingredients typically a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) in specific ratios. The goal is to hit a eutectic point, which basically means the mixture's melting point is way lower than that of its individual parts. This depression in melting point is one of the defining characteristics of DESs. The general steps of DES preparation are illustrated in **Figure 1**[18].

For example, common hydrogen bond donors include things like citric acid or lactic acid, while hydrogen bond acceptors are often quaternary ammonium salts, like choline chloride. By tweaking the ratio between the donor and acceptor, researchers can adjust the physical properties of DES,

such as how thick it is, how polar it is, or how well it dissolves other substances. This flexibility is a big perk because it lets people design solvents that are just right for specific uses like dissolving drugs, for instance.

One of the best things about DES is how easy and eco-friendly they are to make. Unlike ionic liquids, which can require pretty complicated and expensive processes, DES can be made simply by mixing and heating affordable, biodegradable materials. This simplicity makes them an appealing option, especially for industries like pharmaceuticals, where there's a growing focus on sustainability and cost savings.

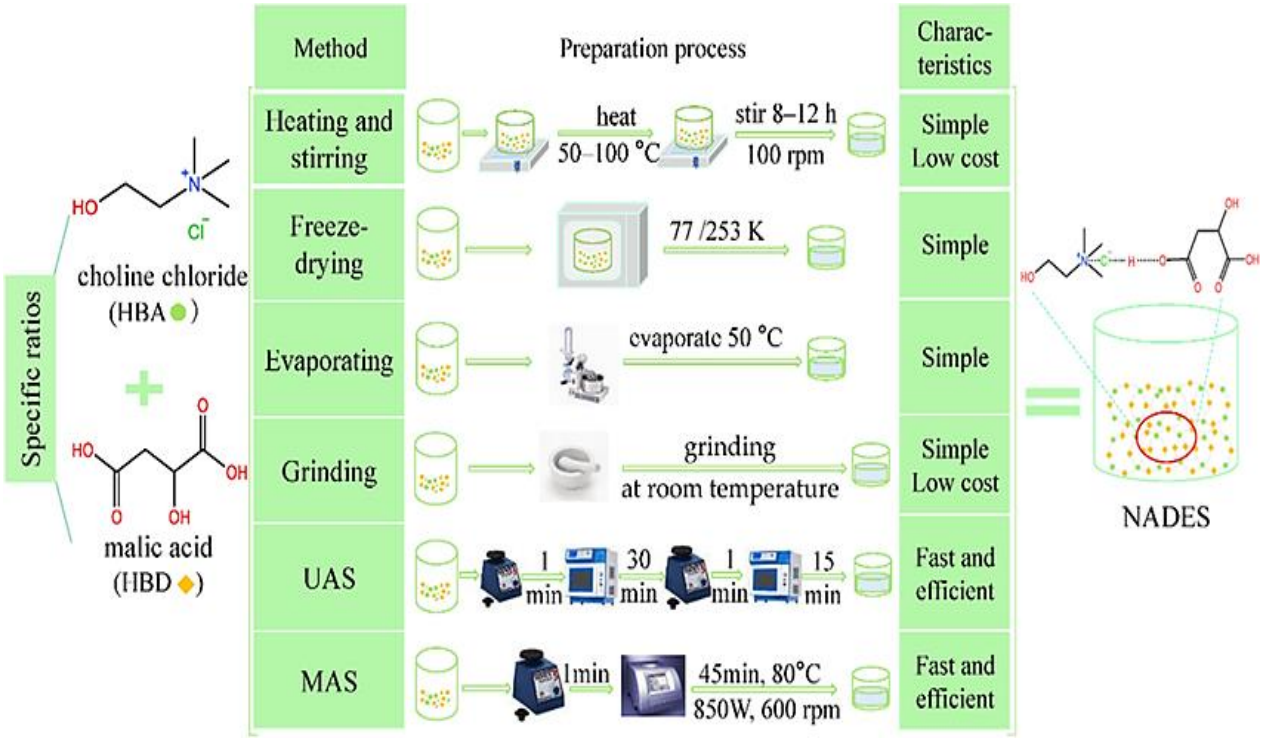


Figure 1: Different preparation methods can be used for synthesizing Natural Deep Eutectic Solvents (NaDES) such as choline chloride (HBA) and malic acid (HBD). These include heating and stirring, freeze-drying, evaporating, grinding, ultrasonication (UAS), and microwave-assisted synthesis (MAS), each differing in temperature, time, and efficiency.

1.3. Common DES Formulations

Table 1 presents the formulation of various Deep Eutectic Solvents (DESs), categorized according to the types of hydrogen bond donors (HBDs) and hydrogen bond acceptors (HBAs) employed in their composition. These classifications highlight the structural diversity and functional flexibility of DES systems, as referenced in sources [4,18,22].

Table 1 Different DES formulations and their properties

Components	Melting Point	Viscosity	Conductivity	Stability	Typical Applications
Quaternary ammonium salt + metal salt	Low	Moderate	High	High (due to metal ions)	Metal processing, electrodeposition
Quaternary ammonium salt + HBD (e.g., urea)	Low	High	Low to moderate	Moderate	Extraction of natural products, catalysis
Metal chloride + HBD	Very Low	Very High	Low	Low to moderate	Catalysis, metal extraction
Transition metal salt + HBD	Low	High	Low to moderate	Moderate to High	Biomedical applications, nanomaterials synthesis
Natural compounds (sugars, amino acids, etc.)	Very Low	Very High	Low	High (biocompatible)	Pharmaceutical, cosmetic, and food industries

The primary types include:

- **Quaternary Ammonium Salt with Metal Salt**: In this type, a quaternary ammonium salt like choline chloride is combined with a metal salt such as zinc chloride, creating a DES with enhanced conductivity.
- **Quaternary Ammonium Salt with a Hydrogen Bond Donor (HBD)**: This is one of the most common DES types, where a quaternary ammonium salt, such as choline chloride, is mixed with a hydrogen bond donor like urea or glycerol. These DESs have high hydrogen bonding capacity and are often used in extraction processes.
- **Metal Chloride with a Hydrogen Bond Donor**: This type involves a metal chloride, like aluminum chloride, combined with a hydrogen bond donor, which gives the DES unique properties suitable for catalysis and extraction.
- **Transition Metal Salt with a Hydrogen Bond Donor**: Transition metal salts such as cobalt or iron salts can be combined with a hydrogen bond donor, creating DESs used in applications requiring metal stabilization or catalytic activity.

- **Natural Deep Eutectic Solvents (NaDES)**: are formulated using naturally occurring substances such as sugars, amino acids, and organic acids, which are critical components in many biological processes. These materials are widely available in nature, making NaDES relatively easy to produce. What's interesting is how closely they mimic natural systems as many of these components are already found in the metabolic pathways of living organisms.

1.4. Applications of DES and NaDES:

Natural Deep Eutectic Solvents (NaDES) are widely used to enhance drug solubility, stability, and bioavailability. Their applications span pharmaceuticals, cosmetics, and natural product extraction due to their biocompatibility and eco-friendly nature. **Figure 2** illustrates the diverse applications of NaDES across these fields.

Chemical extraction:

Deep Eutectic Solvents (DES) and Natural Deep Eutectic Solvents (NaDES) are eco-friendly options for extracting valuable bioactive compounds from plants, like polyphenols and flavonoids. These compounds are known for their health benefits, such as antioxidant and anti-inflammatory effects. DES and NaDES are great at dissolving a wide range of substances, which makes them especially useful for pulling these beneficial compounds out of medicinal plants and herbs. This distinctive property makes deep eutectic solvents (DESs) an attractive option for researchers seeking safer and more environmentally friendly alternatives to conventional solvents. Unlike many traditional solvents, which tend to be toxic and harmful to the environment, DESs offer a greener approach without compromising effectiveness [21].

Electroplating and Metal Recovery:

Deep Eutectic Solvents (DES) are used in electroplating and for recovering metals like gold, silver, and copper from electronic waste. They provide a greener, eco-friendly alternative to the traditional solvents often used in metallurgy [22].

Catalysis:

Deep Eutectic Solvents (DES) are used in a range of catalytic reactions, like hydrogenation, oxidation, and capturing carbon dioxide. They're great at stabilizing metal nanoparticles, which makes them effective for these types of catalytic processes [18].

Cosmetic Formulations:

Like DES, NaDES are used in eco-friendly cosmetic formulations. They boost the solubility of bioactive compounds like antioxidants and anti-aging ingredients, allowing for the creation of natural and sustainable personal care products [23].

Pharmaceuticals and Drug Delivery:

NaDES have been found to improve the solubility and stability of drugs that don't dissolve easily, making them useful for drug formulations. They also demonstrate significant potential for application in sustained-release drug delivery systems, offering controlled and prolonged release of therapeutic [23,24].

Biotechnology and Enzyme Stabilization:

NaDES are being explored for enzyme stabilization and biocatalysis. Their natural components help maintain enzyme activity, which makes them great solvents in biotechnological processes where enzymes are key for synthesis or degradation [25].

Agriculture:

NaDES are being studied for use in agriculture, especially in the development of eco-friendly pesticides and fertilizers. Their biodegradability and non-toxic nature make them perfect for reducing the environmental impact of traditional agricultural chemicals [26].

Figure 2: Application of deep eutectic solvents

2. Liposomes

2.1. Introduction

Liposomes are spherical vesicles composed of one or more phospholipid bilayers, which can encapsulate both hydrophilic and hydrophobic molecules. Discovered in the 1960s, they have become a key tool in drug delivery and therapeutic applications. Their structural properties, biocompatibility, and ability to carry diverse types of molecules make liposomes valuable across pharmaceutical, cosmetic, and diagnostic fields [7,27].

2.2. Liposome structure and composition

Liposomes are spherical vesicles composed of one or more concentric lipid bilayers surrounding an aqueous core. Their structure is primarily built from phospholipids amphiphilic molecules with hydrophilic (water-attracting) head groups and hydrophobic (water-repelling) tail region allowing them to self-assemble in aqueous environments. This unique architecture provides a versatile platform capable of incorporating hydrophilic compounds within the internal aqueous phase and hydrophobic drugs within the lipid bilayer. To further improve membrane rigidity and reduce permeability, cholesterol is commonly integrated into the lipid matrix [7,28]. **Figure 3** illustrates the structural composition of liposomes, highlighting their bilayer organization and key molecular components.

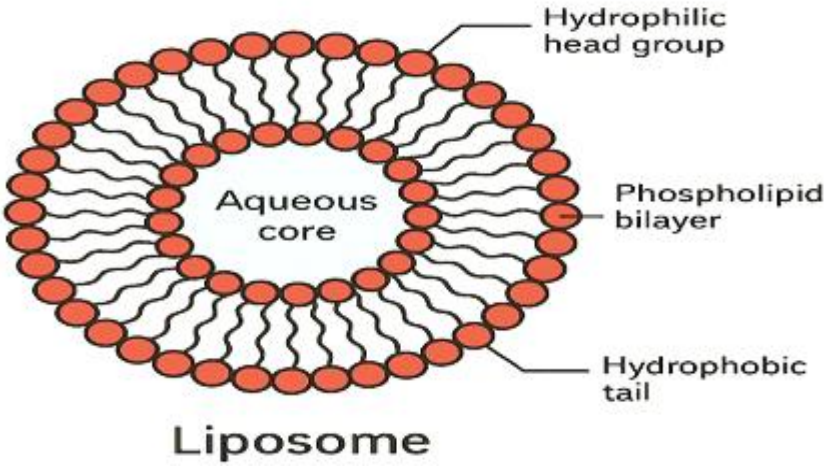


Figure 3:Liposomes structure

2.3. Classification of Liposomes

Liposomes are classified into different types based on their size and number of lipid bilayers [29]. The main types include (figure 4):

- **Small Unilamellar Vesicles (SUVs):** These are single-layered liposomes with a size

range of 20-100 nm.

- **Large Unilamellar Vesicles (LUVs):** Larger than SUVs, these vesicles have a size range of 100-1000 nm and also contain a single lipid bilayer.
- **Giant Unilamellar Vesicles (GUVs)** are synthetic lipid vesicles with a single bilayer and a diameter typically greater than 1 μm, often ranging from 1–100 μm. Due to their size and similarity to biological cells, GUVs are widely used in biophysical studies, membrane research, and drug delivery
- **Modeling Multilamellar Vesicles (MLVs):** These liposomes contain multiple concentric bilayers, resembling an onion-like structure, and are typically larger (up to several micrometers).

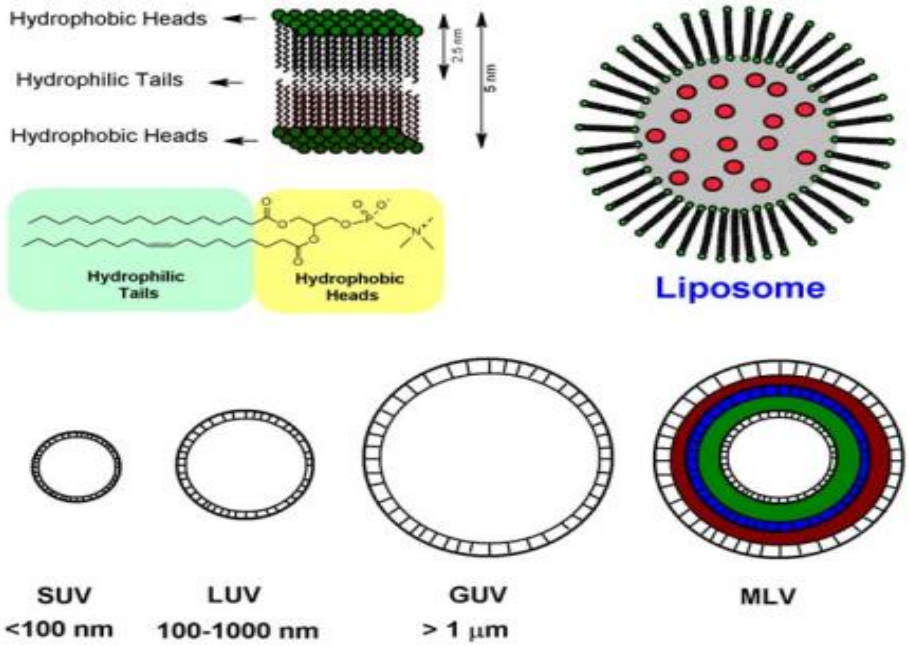


Figure 4: Schematic of Liposome Structure and each Type Methods of Liposome Preparation [30]

2.4. Liposomes Preparation

Each method used to prepare liposomes has its own unique characteristics that affect things like the size, how well they encapsulate materials, and their overall stability.

Thin-Film Hydration Method:

This is the most common and traditional way to make liposomes. It involves evaporating an organic solvent to create a lipid film, which is then hydrated with an aqueous solution. The liposomes that form from this method are usually multilamellar vesicles (MLVs), meaning they have multiple layers. If you want smaller, more uniform liposomes called unilamellar vesicles (ULVs) you'll need extra steps like sonication or extrusion. These additional processes help reduce the size and make

the liposomes more uniform, but they can sometimes lead to the loss of the encapsulated material or affect stability because of the mechanical forces applied **(see figure 05)** [31,32,33].

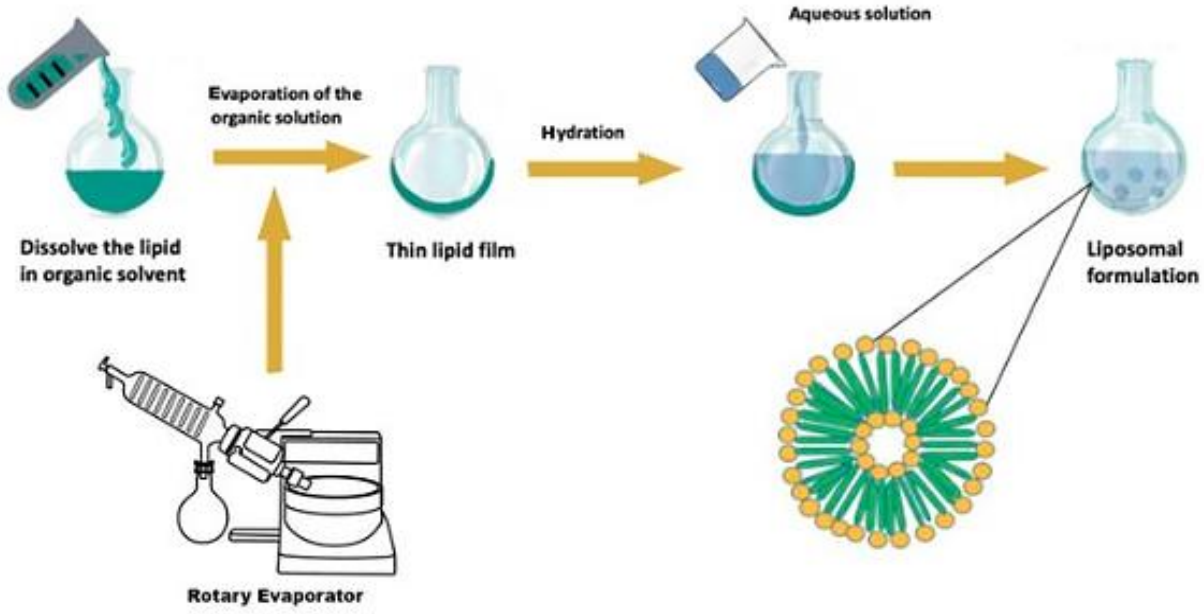


Figure 5 : Liposomal formulation by Thin-Film Hydration Method [33]

Reverse-Phase Evaporation:

This method is great when you need to encapsulate large amounts of water-soluble substances. It involves dissolving lipids in an organic solvent and mixing with an aqueous solution to form a water-in-oil emulsion. As the solvent evaporates, the lipids reorganize into liposomes. This technique tends to produce large unilamellar vesicles (LUVs) with high efficiency in encapsulating water-soluble drugs or molecules, which is ideal for delivering larger payloads. However, since this process uses organic solvents **(figure 6),** it's important to handle them carefully and ensure they're properly removed to avoid any toxicity issues [34,29].

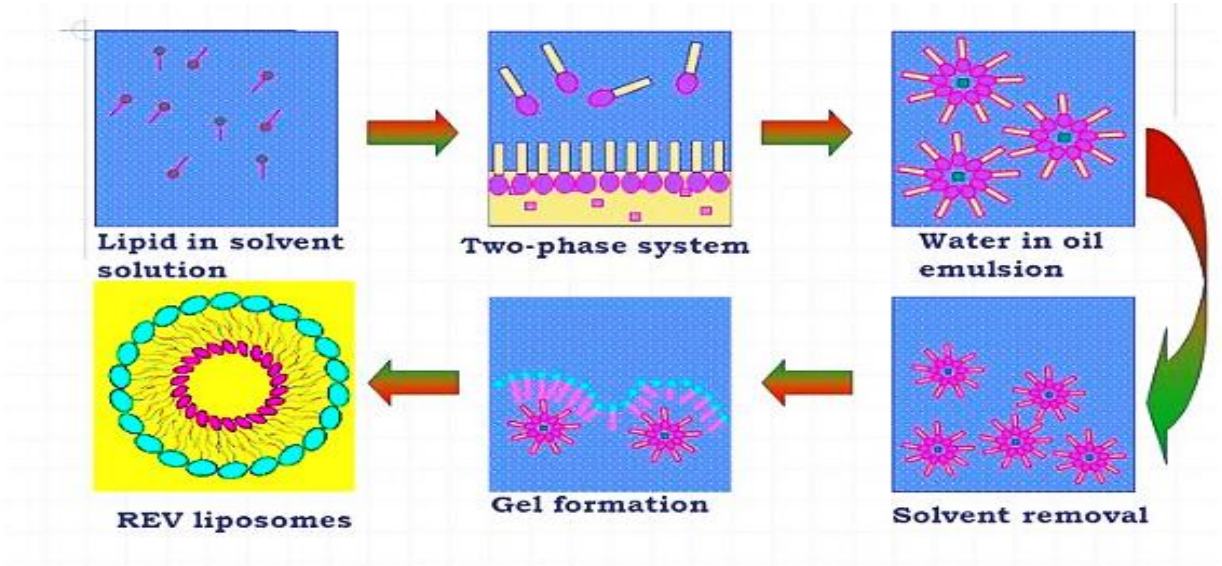


Figure 6: Liposomal formulation by Reverse-Phase Evaporation [35]

Injection Methods

These methods involve dissolving lipids in ethanol (or another organic solvent) and injecting them into an aqueous solution, which causes liposomes to form spontaneously. This approach is simple, quick, and doesn't require high-energy processes like sonication. One example is the ethanol dilution method, which allows for the controlled production of small liposomes with high uniformity (see figure 7). However, precise regulation of solvent concentration and injection rate is essential, as these parameters significantly influence the liposomes' size, encapsulation efficiency, and overall stability. [36,37].

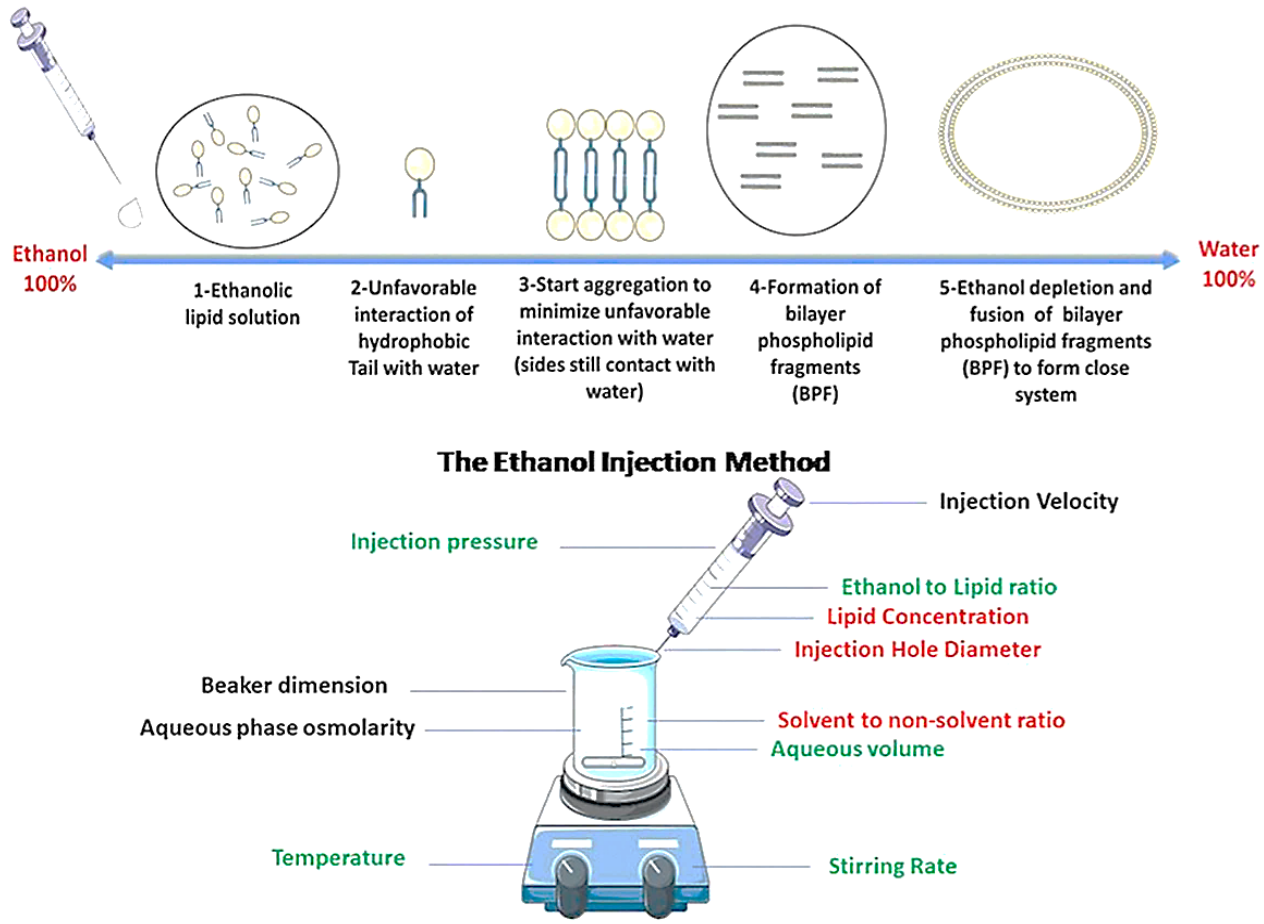


Figure 7: Liposomal formulation by Injection Methods [38]

2.5. Commonly used liposomes and their characteristics

Liposomes are versatile drug delivery systems, composed of lipid bilayers that can encapsulate both hydrophilic and hydrophobic substances. The type of lipids used to form liposomes greatly influences their properties, including their size, stability, fluidity, and drug encapsulation efficiency [7]. Below are some commonly used phospholipids in liposome formulation, along with their characteristics, as summarized in Table 2.

Table 2 Commonly used liposomes and their characteristics

Lipid	Full Name	Chemical Structure	Transition Temperature (Tm)	Characteristics
DMPC [39]	Dimyristoylphosphatidylcholine	C36H72NO8P	~23°C	Forms fluid liposomes at room temperature. Suitable for temperature-sensitive drug delivery systems.
DPPC [40]	Dipalmitoylphosphatidylcholine	C40H80NO8P	~41°C	Rigid bilayers at body temperature. Frequently used in lung surfactants and targeted drug delivery.
DSPC [41]	Distearoylphosphatidylcholine	C44H88NO8P	~55°C	Produces stable liposomes with a rigid structure. Suitable for long-circulating and temperature-stable systems.
DOPC [42]	Dioleoylphosphatidylcholine	C44H84NO8P	-20°C	Highly fluid at physiological temperatures. Used in flexible liposome formulations and fusion delivery systems.
Egg-PC [43]	Egg Phosphatidylcholine (derived from egg yolk)	Derived from egg yolk	~ -2°C to -10°C	Fluid and flexible liposomes at body temperature. Often used in natural and biocompatible formulations.
Cholesterol [44]	Cholesterol	C27H46O	N/A	Modulates membrane fluidity and stability. Does not have a defined Tm; instead, stabilizes membranes and adjusts lipid Tm.

2.6. Dimyristoylphosphatidylcholine (DMPC) for Drug Delivery Applications:

Among the various components used in liposome formulation, phospholipids play a crucial role in

determining their properties, such as size, stability, and drug release characteristics. One of the most widely used phospholipids is Dimyristoylphosphatidylcholine (DMPC), which has distinct characteristics that make it particularly useful in drug delivery applications, as shown in Figure 8 [45,46].

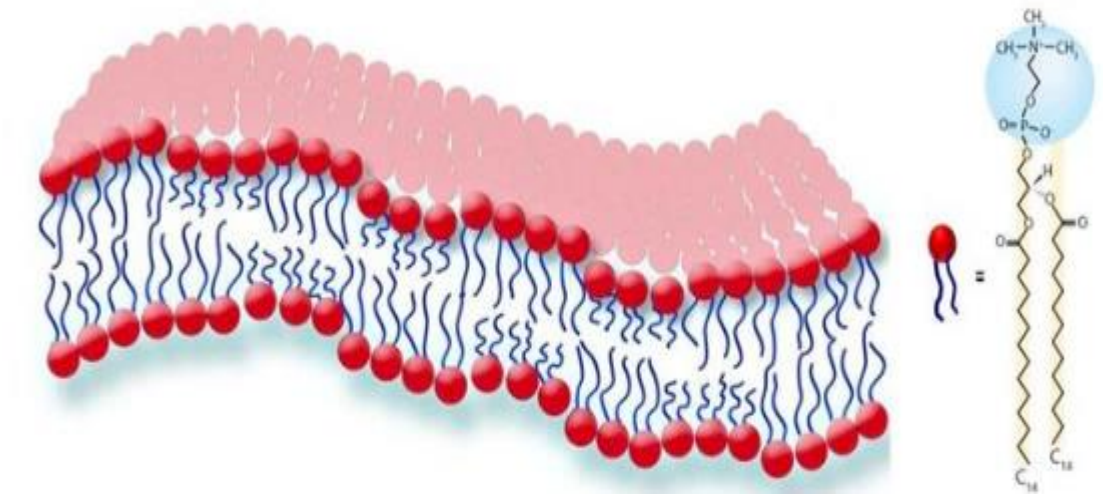


Figure 8 : Dimyristoylphosphatidylcholine (DMPC)

Lower Transition Temperature (Tm)

DMPC has a transition temperature (Tm) of around 23°C [64], meaning it shifts from a gel-like solid to a fluid, liquid-crystalline state just below body temperature. This makes DMPC-based liposomes flexible and fluid at physiological temperatures, which is particularly useful for drug delivery. The fluidity of these liposomes at body temperature allows for faster release of encapsulated drugs, making them ideal for therapies that need quick action, such as in cancer treatment or vaccine delivery [47,48].

Enhanced Encapsulation of Drugs

DMPC's bilayer is possesses a relatively fluid structure, enabling it to encapsulate both hydrophilic drugs within its aqueous core and hydrophobic drugs within the lipid bilayer. This dual encapsulation capability makes DMPC particularly versatile for drug delivery applications. This allows for the efficient encapsulation of various types of drugs, including small molecules, peptides, and proteins. The versatility of DMPC-based liposomes enables them to deliver a wide range of drugs, improve drug solubility, and protect sensitive drugs from degradation, making them highly effective for different therapeutic applications [49,37].

Controlled and Thermosensitive Drug Release

DMPC liposomes are commonly used in thermosensitive drug delivery systems due to their transition temperature being close to physiological conditions. When exposed to slightly elevated temperatures, such as during hyperthermia treatments, the liposome becomes more fluid, enabling controlled drug release [50]. This temperature-sensitive feature is particularly useful in cancer therapy, where localized heat can trigger the release of drugs directly at tumor sites, reducing systemic side effects and improving treatment precision [51-54].

Biocompatibility

DMPC is a naturally occurring phospholipid, meaning it is highly biocompatible and well-tolerated by the human body. It is often used in pharmaceutical formulations for intravenous, oral, or topical delivery because it mimics components of cell membranes. DMPC liposomes reduce the risk of toxicity or immune reactions, allowing for safer and more efficient drug delivery in clinical applications [55,56,57].

Improved Drug Stability

DMPC liposomes can protect encapsulated drugs from environmental factors, such as enzymatic degradation or premature release in the bloodstream, by encapsulating them within the liposome bilayer or aqueous core. This ensures that drugs, especially sensitive molecules like peptides or nucleic acids, remain stable until they reach the target site, improving the overall effectiveness of the therapy [58,59].

Flexibility in Liposome Formulation

DMPC can be mixed with other lipids like **cholesterol** or other lipids to modify the liposome's characteristics, such as increasing membrane rigidity, reducing drug leakage, or enhancing circulation time. This flexibility allows for tailored drug delivery systems that can be optimized for specific therapeutic goals, such as targeting cancer cells or reducing systemic toxicity [60].

Passive Targeting through the EPR Effect

DMPC-based liposomes can take advantage of the Enhanced Permeability and Retention (EPR) effect in tumors or inflamed tissues. Due to the leaky vasculature in these tissues, DMPC liposomes can accumulate more efficiently in these areas. This passive targeting enhances the concentration of the drug at the disease site, increasing therapeutic efficacy while minimizing exposure to healthy tissues [61,62].

Combination with Active Targeting Agents

DMPC liposomes can be functionalized with targeting ligands such as antibodies, peptides, or

aptamers that bind specifically to receptors on the surface of diseased cells (e.g., cancer cells). DMPC serves as the bilayer component while the targeting moieties guide the liposomes to their specific site of action. This allows for **active targeting** of the liposomes, improving the precision of drug delivery and reducing side effects [63,64]

Preparation of DMPC liposomes

DMPC liposomes are typically prepared using the thin-film hydration method followed by extrusion. First, DMPC is dissolved in an organic solvent like chloroform or a chloroform–methanol mixture, then evaporated under reduced pressure to form a thin lipid film. This film is hydrated with an aqueous buffer (like Phosphate Buffered Saline (PBS) or Tris-HCl Buffer) above DMPC's phase transition temperature (~24 °C), resulting in multilamellar vesicles (MLVs). To obtain more uniform and stable **Large Unilamellar Vesicles (LUVs)**, which are most commonly used in drug delivery, the suspension is repeatedly extruded through polycarbonate membranes with defined pore sizes. This process yields LUVs with consistent size and encapsulation properties, suitable for biomedical applications (figure 09).

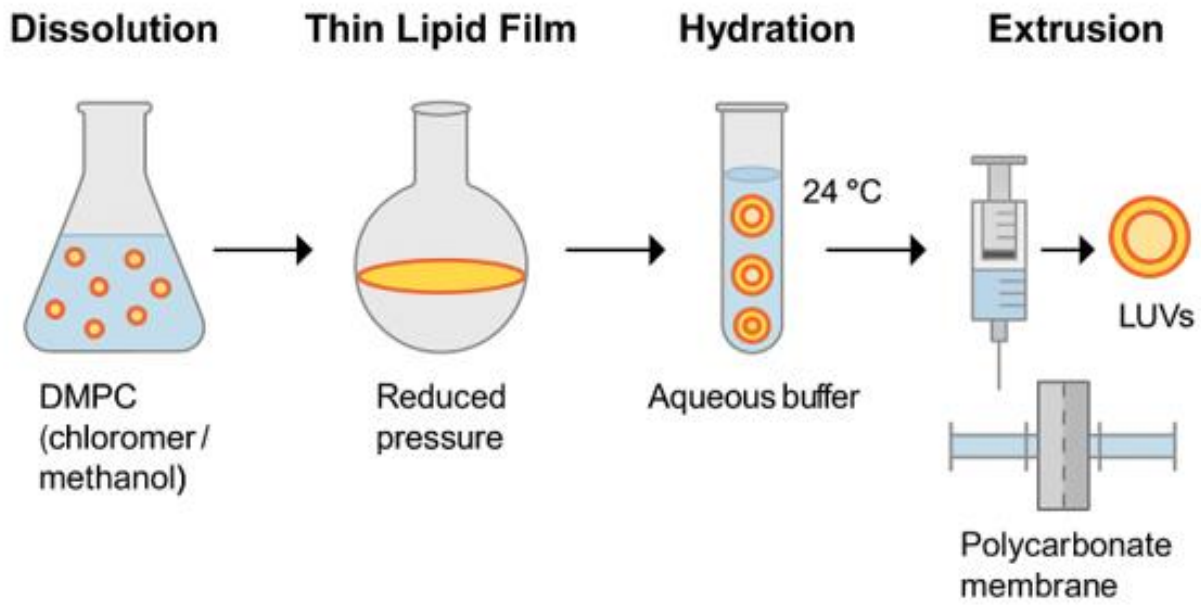


Figure 9: Preparation of DMPC liposomes through thin-film hydration and extrusion

3. Ferulic Acid: Structural Characteristics and Pharmaceutical Applications

Ferulic acid (FA), scientifically known as **4-hydroxy-3-methoxycinnamic acid**, is a prominent member of the hydroxycinnamic acid family, which are derivatives of phenylpropanoids. It occurs **naturally** in the cell walls of many plants, particularly in cereal grains such as wheat, oats, rice, and corn, where it is covalently bound to lignin and polysaccharides. As a plant-based phenolic compound, ferulic acid plays a protective role in the plant's defense against environmental stressors like ultraviolet radiation, pathogens, and oxidative damage. Beyond its role in plant biology, ferulic acid has garnered significant attention in the pharmaceutical and biomedical fields due to its wide spectrum of biological activities as shown in Figure 10 [65].

Structurally, ferulic acid comprise a substituted phenyl ring attached to a three-carbon side chain, giving it the characteristic **C6-C3** configuration of cinnamic acid derivatives. The phenyl ring bears a **hydroxyl group (-OH)** at the para position and a **methoxy group (-OCH_3)** at the meta position relative to the propenoic acid chain. This side chain includes a **conjugated double bond (–CH=CH–COOH)**, contributing to the molecule's resonance stability and enhancing its free radical scavenging properties. The combination of the hydroxyl and methoxy substituents significantly influences the molecule's **lipophilicity, reactivity, and antioxidant potential**. The conjugated system formed between the aromatic ring and the unsaturated side chain provides ferulic acid with the ability to **donate electrons or hydrogen atoms**, effectively neutralizing reactive oxygen species (ROS) and other free radicals. This property underpins many of its therapeutic applications (figure 8).[66]

Among its most recognized pharmacological roles, **ferulic acid is a powerful antioxidant**. It has been shown to effectively inhibit oxidative stress by preventing lipid peroxidation and protecting biomolecules such as DNA, proteins, and lipids from oxidative damage. This function is particularly relevant in the prevention and management of chronic diseases that are aggravated by oxidative stress, including cardiovascular conditions, diabetes, and neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Moreover, ferulic acid can synergize with other natural antioxidants, enhancing the overall antioxidant capacity of formulations, which is why it is often incorporated into functional foods, nutraceuticals, and skin care products [67].

In addition to its antioxidant properties, **ferulic acid exhibits significant anti-inflammatory activity**. It achieves this by modulating key signaling pathways involved in inflammation. Specifically, ferulic acid inhibits the activity of pro-inflammatory enzymes such as **cyclooxygenase (COX-2)** and **lipoxygenase (LOX)**, thereby reducing the production of inflammatory mediators like prostaglandins and leukotrienes. Furthermore, ferulic acid has been shown to suppress the expression of pro-inflammatory cytokines, including **tumor necrosis factor-alpha (TNF-α)**, **interleukin-1 beta (IL-1β)**, and **interleukin-6 (IL-6)**. These effects contribute to its therapeutic potential in treating inflammatory conditions such as arthritis, inflammatory bowel disease, and other chronic inflammatory syndromes [66].

Another promising area of research is the **anticancer potential of ferulic acid**. Various *in vitro* and *in vivo* studies have demonstrated its ability to inhibit the proliferation of cancer cells and induce apoptosis, particularly in colon, breast, liver, and lung cancer models. The mechanisms through which ferulic acid exerts these effects involve the modulation of several cell signaling pathways, including the **mitogen-activated protein kinase (MAPK)** and **phosphatidylinositol-3-kinase (PI3K)/Akt** pathways. Additionally, ferulic acid can block the activation of **nuclear factor-kappa B (NF-κB)**, This transcription factor is central in promoting cell survival and inflammation in tumor microenvironments. Its ability to selectively target cancer cells while sparing healthy cells makes it an attractive candidate for anticancer therapies and as a chemopreventive agent [68].

Ferulic acid also demonstrates **notable neuroprotective effects**, which are largely attributed to its antioxidant and anti-inflammatory activities. It has been shown to mitigate neuronal damage caused by oxidative stress and to prevent the aggregation of **amyloid-beta peptides**, a pathological hallmark of Alzheimer's disease. Animal studies have indicated that ferulic acid can enhance memory and cognitive performance, possibly by modulating neuroinflammatory responses and protecting against excitotoxicity. These findings suggest that ferulic acid may possess therapeutic value in the treatment of neurodegenerative diseases, age-related cognitive decline, and in facilitating recovery following stroke. [69].

The **antimicrobial properties** of ferulic acid further broaden its pharmaceutical potential. It has been demonstrated to exert inhibitory effects against a variety of pathogenic microorganisms, including both **Gram-positive and Gram-negative bacteria**, as well as **fungi and certain viruses**. The antimicrobial activity of ferulic acid is thought to arise from its ability to disrupt microbial cell walls, alter membrane permeability, and inhibit biofilm formation. These actions make ferulic acid

a candidate for use in topical antiseptics, oral hygiene products, and as a natural food preservative [67].

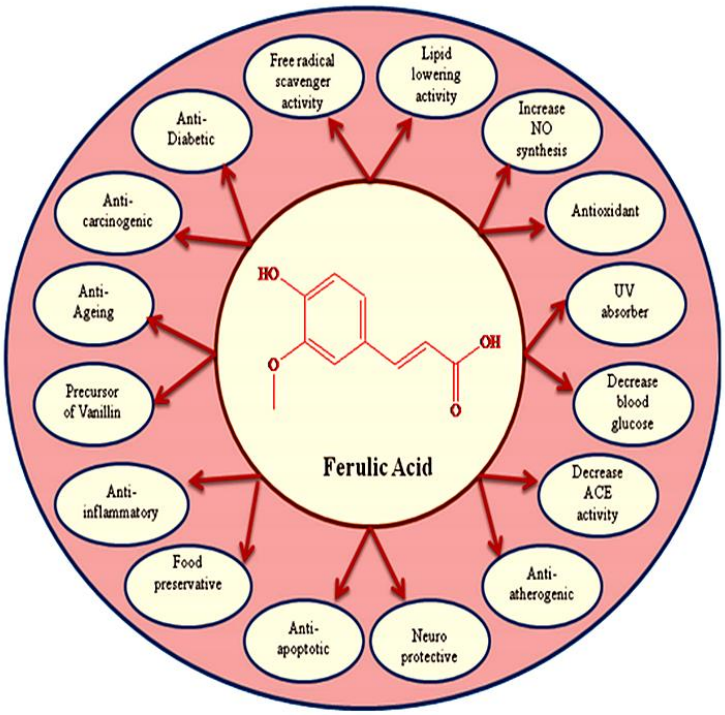


Figure 10: Potential applications of ferulic acid from natural sources

Chapter 2: COSMO-RS in drug formulation

1. Introduction:

COSMO-RS (Conductor-like Screening Model for Real Solvents) and its extension, COSMOmic (Conductor-like Screening Models for micelles and membranes), are advanced computational tools widely used in pharmaceutical formulation, particularly in the development of drug delivery systems. These methods are invaluable for accurately predicting a range of crucial physicochemical properties of drugs, such as solubility, partitioning, and interaction tendencies within various solvents and biological environments like lipid bilayers. This predictive power is essential in optimizing the performance of drug delivery systems, ensuring that the drugs are effectively absorbed and delivered to their target sites, as illustrated in **Figure 11**. The core of COSMO-RS is built on quantum chemical calculations, which analyze the electronic structure of molecules, combined with principles from statistical thermodynamics. This combination allows the method to predict molecular interactions in complex environments. For example, in the case of Deep Eutectic Solvents (DES), which are environmentally friendly solvents, COSMO-RS helps in understanding how a drug would dissolve or behave, aiding in the formulation of novel drug-solvent systems [70,71]. COSMOmic, an extension of COSMO-RS, is a powerful tool for modeling drug interactions within biological environments, like lipid membranes or micelles, making it especially useful for designing liposomal drug delivery systems. By simulating how drug molecules behave within these membranes such as DMPC and incorporating the effects of deep eutectic solvents (DES), COSMOmic helps predict how well drugs and DES will integrate, partition, and diffuse across lipid bilayers. This insight allows researchers to optimize drug delivery systems, ensuring efficient drug release and improved control over absorption and distribution, ultimately enhancing therapeutic effectiveness [16].

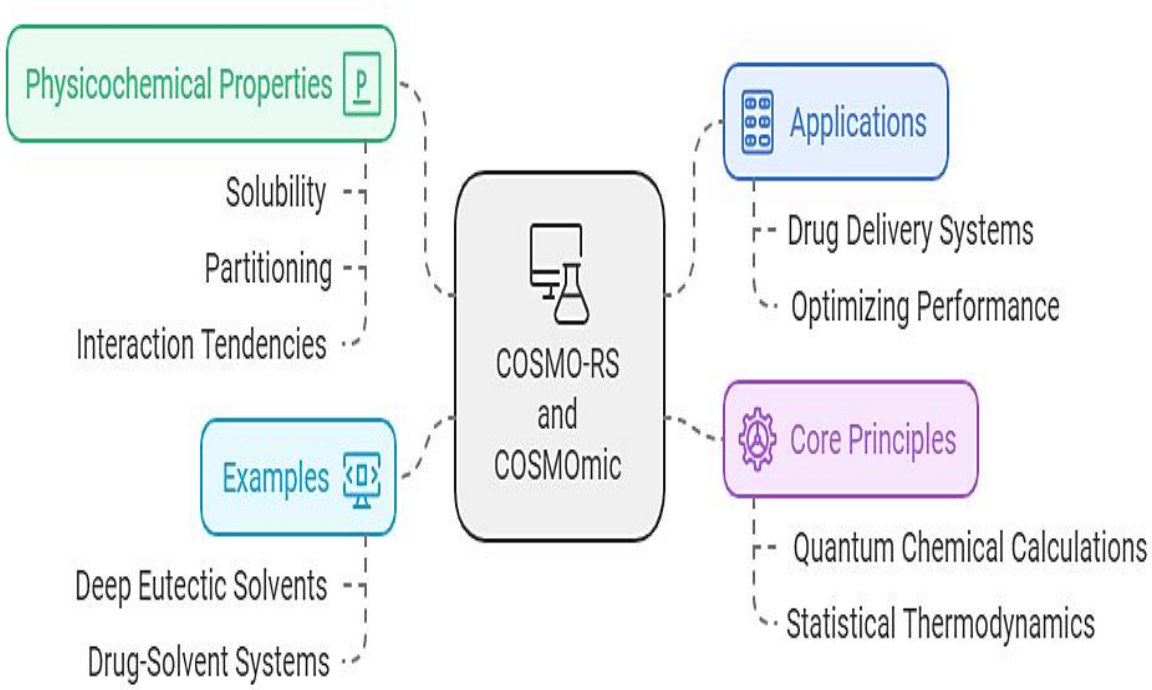


Figure 11:Application of COSMO-RS

2. COSMO-RS: Fundamentals and Mechanisms

2.1. Principles of COSMO-RS:

COSMO-RS is rooted in quantum chemical calculations, utilizing the COSMO (COnductor-like Screening MOdel) approach, a dielectric continuum solvation model. It begins with a quantum mechanical (QM) calculation of a molecule immersed in an idealized solvent, where the molecular surface is discretized into small segments [72]. The induced charges on these surface segments are computed by accounting for the polarization of the surrounding medium, treated as a perfect conductor, thus capturing the molecule's response to the solvent environment. This yields a "sigma profile," representing surface charge density, which encodes crucial information on how the molecule will interact with other molecules through electrostatic forces and hydrogen bonding. In the next phase, statistical thermodynamics is applied, where COSMO-RS analyzes the sigma profiles of all components to calculate pairwise molecular interactions, including electrostatic, van der Waals, and hydrogen bonding forces. Using these interactions, the model computes essential thermodynamic properties such as activity coefficients, solubility, and phase equilibria based on the Boltzmann distribution. COSMO-RS, as a "first-principles" method, requires no experimental data, making it a versatile tool for predicting the properties of complex mixtures in fields like chemical engineering, pharmaceuticals, and environmental science [73]. Additionally, COSMO-RS can predict partition coefficients, such as octanol-water partition coefficients (log P), which are critical

for understanding drug distribution between aqueous and lipid phases, a key factor in drug absorption and transport, as shown in **Figure 12**. This makes COSMO-RS an indispensable tool in pharmaceutical research, enabling the efficient screening of solvent systems and optimizing drug formulations [74].

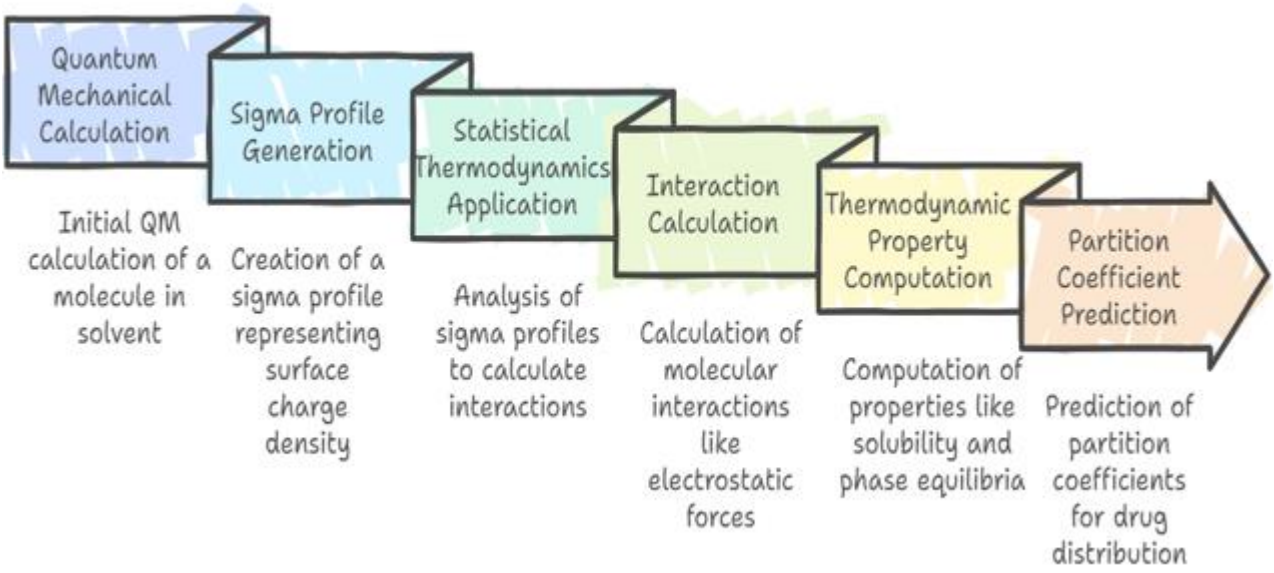


Figure 12: COSMO-RS process steps

2.2. Advancements and Benefits Over Traditional Methods

The advancements and benefits of COSMO-RS lie in its robust theoretical foundation:

- **Reduced Time and Cost:** COSMO-RS predicts molecular behavior in solvents with minimal user input, eliminating the need for extensive experimental solubility testing, saving time and resources [75].
- **Flexibility Across Systems:** The model is highly versatile, applicable to a wide range of solvent systems, including complex, multi-component mixtures, making it ideal for industries like pharmaceuticals [76].
- **Accurate Predictions:** COSMO-RS provides superior accuracy in predicting properties such as partition coefficients, vapor-liquid equilibria, and activity coefficients, outperforming traditional models (e.g., e.g., *Universal Quasi-Chemical Functional Group Activity Coefficients* and *Non-Random Two-Liquid model)* in complex systems [77].
- **Handling Complex Interactions:** The integration of quantum chemical insights allows COSMO-RS to handle strong hydrogen bonding and polar interactions, offering more reliable predictions for non-ideal molecular behavior [78].
- **Wide Applicability:** COSMO-RS is beneficial across various fields, including

pharmaceuticals, chemical engineering, and materials science, enhancing research and development through its robust theoretical foundation and lack of reliance on experimental data [79].

3. COSMOmic Extension for Drug Delivery Systems

COSMOmic stands for COnductor-like Screening MOdel for micelles and membranes. It is an advanced extension of the COSMO-RS model tailored to simulate the behavior of molecules, such as drugs, within complex biological environments like micelles, liposomes, and biological membranes. The goal of COSMOmic is to predict how molecules partition into and interact with these structured environments, making it highly relevant for drug design and delivery applications [16]. In detail, COSMOmic builds upon the COSMO-RS framework by incorporating the unique characteristics of layered, heterogeneous systems. Biological membranes, micelles, and liposomes are represented as structured, multi-layered environments, where each layer has distinct polar and non-polar regions. Quantum chemical calculations are used to generate sigma profiles that describe the surface charge distribution of both the drug molecules and the layers of the membrane or micelle. By doing so, COSMOmic can accurately predict how a drug molecule interacts with different regions of the membrane, whether it prefers to stay in the hydrophilic (polar) or hydrophobic (non-polar) regions, or how it might traverse the membrane, as shown in **Figure 13** [80]. This is particularly crucial in pharmaceutical research, where understanding the permeability and distribution of drugs across biological membranes influences drug efficacy and bioavailability. COSMOmic provides insights into the molecular-level behavior of drug compounds within these complex environments without the need for extensive experimental data, thus enabling faster, more cost-effective development of drug formulations. It is also valuable for predicting how drugs interact with delivery vehicles like micelles and liposomes, which are commonly used in targeted drug delivery systems. Overall, COSMOmic enhances the predictive power of COSMO-RS by extending its applicability to biologically relevant systems, making it a key tool in modern drug development [81].

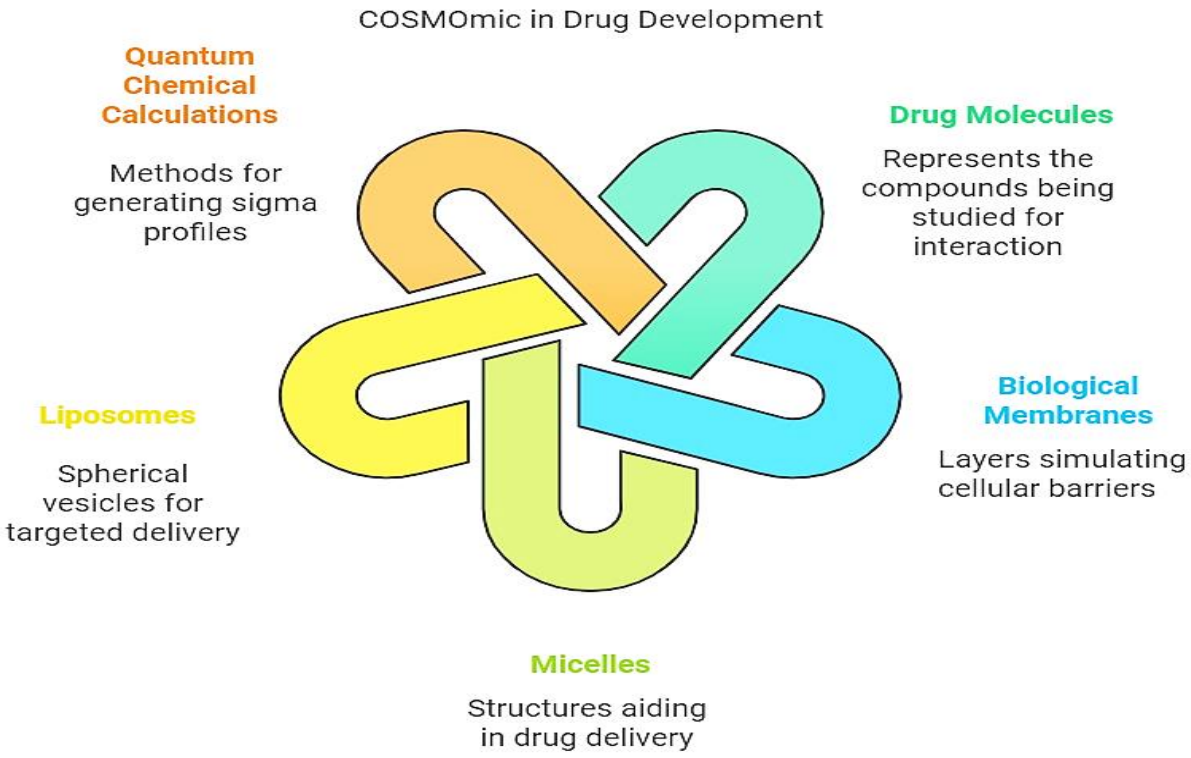


Figure 13 : COSMOmic in Drug development

3.1.Modeling Drug-Membrane Interactions

COSMOmic simulates drug partitioning and distribution within lipid bilayers by modeling the interactions between drug molecules and the different regions of the bilayer, which consists of both hydrophilic (polar) and hydrophobic (non-polar) layers. This is highly relevant for understanding and optimizing liposomal drug delivery formulations, where accurate predictions of drug behavior within these complex environments are crucial for ensuring drug efficacy and bioavailability. **see figure 14** [16].

- **Layered Membrane Model:** COSMOmic treats lipid bilayers or micelles as structured, multi-layered systems with distinct regions. Each layer of the bilayer has varying polarities the outer layers are hydrophilic (polar), while the inner layers are hydrophobic (non-polar). This structure is mimicked in COSMOmic to simulate how drugs interact with each specific region of the bilayer [82].
- **Quantum Chemical Input:** The model begins by performing quantum chemical calculations to generate **sigma profiles** for both the drug molecules and the lipid bilayer. These sigma profiles describe the surface charge distribution of the

molecules, capturing key interactions like hydrogen bonding, electrostatic forces, and van der Waals forces [83].

- **Predicting Drug Partitioning:** Using these sigma profiles, COSMOmic predicts how the drug partitions across the different layers of the bilayer. This includes determining whether the drug will favor the hydrophobic core of the membrane, reside in the hydrophilic outer regions, or distribute evenly across the layers. This information is crucial for determining drug permeability and stability in liposomal drug formulations [84].
- **Molecular Interactions and Distribution:** COSMOmic calculates how the drug interacts with the lipid molecules in each region of the bilayer. These calculations help predict whether the drug will be stably incorporated into the liposome or if it will preferentially stay in the surrounding aqueous environment, influencing how the drug is released from the liposome once it reaches its target [85].

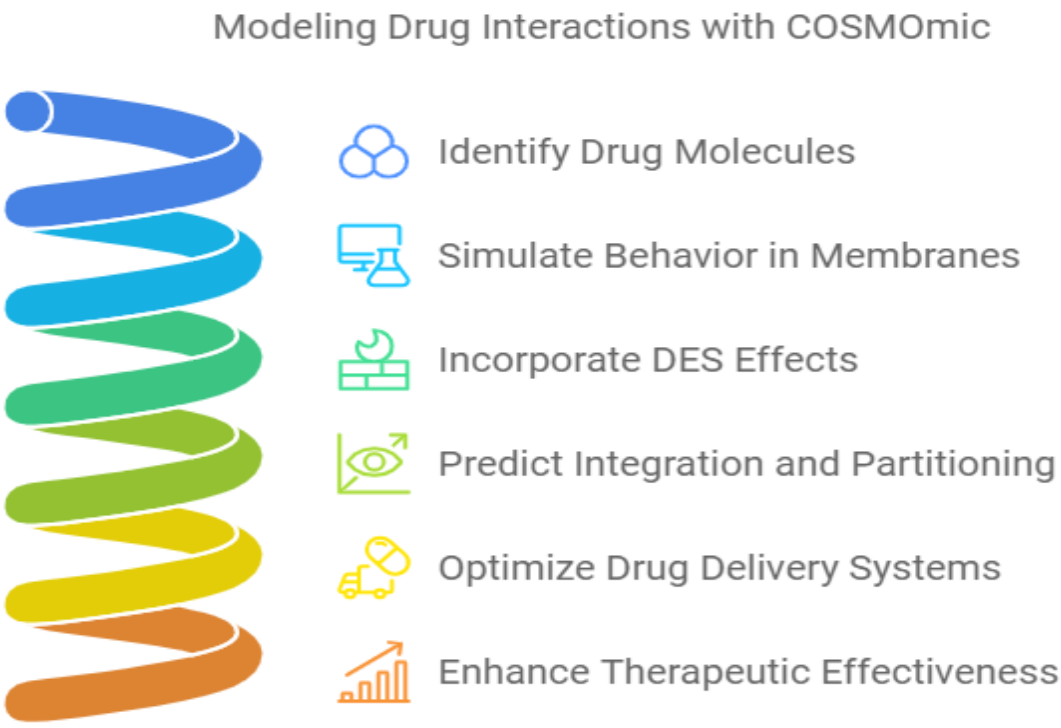


Figure 14: Modeling drug interaction with COSMOmic

3.2.Predicting Release Profiles

In liposomal drug delivery, understanding how a drug partition within the lipid bilayer is crucial for optimizing drug loading, release rates, and targeting effectiveness. COSMOmic, by simulating drug-lipid interactions, offers valuable insights into key aspects: it helps design the optimal lipid

composition to enhance drug encapsulation and stability; predicts release kinetics by modeling drug partitioning within the bilayer, allowing for controlled or sustained drug release; and improves drug efficacy and bioavailability by optimizing formulations for better absorption and distribution within the body. Overall, COSMOmic is a powerful tool that aids in refining liposomal formulations to improve encapsulation, control release profiles, and enhance therapeutic outcomes [86].

4. Comparative Advantage of COSMO-RS Over Experimental Methods

COSMO-RS presents numerous advantages over conventional experimental methods in drug development [87]. By leveraging quantum chemical and thermodynamic principles, it offers the ability to:

- **Non-Reactive Systems Simulation**: COSMO-RS predicts hazardous or unstable compound behavior safely without the need for physical samples.
- **Time and Cost Efficiency**: Replaces trial-and-error experiments with fast, accurate predictions, saving both time and money.
- **High Predictive Power**: Provides reliable predictions for solubility, partitioning, and complex molecular interactions, ideal for pharmaceutical screening.
- **Scale-Up Support**: Reduces risks associated with scaling up from laboratory experiments to industrial production by delivering consistent thermodynamic predictions.

Chapter 3: Enhancement Of Fa Delivery Using NADES In Liposomal Systems

1. Introduction

In the field of pharmaceutical sciences, liposomal systems have emerged as powerful nanocarriers for enhancing drug solubility, bioavailability, and therapeutic efficiency. However, challenges persist when it comes to incorporating hydrophobic bioactives like Ferulic Acid (FA) due to its poor aqueous solubility and limited membrane permeability. To address this issue, Natural Deep Eutectic Solvents (NaDES) have attracted considerable attention as environmentally friendly, tunable, and biocompatible solvents capable of enhancing drug solubilization.

This chapter presents a systematic study on the integration of NaDES with Dimyristoylphosphatidylcholine (DMPC) liposomes to optimize FA solubility and controlled release. The methodology combines computational predictions and experimental validations, establishing a framework for sustainable, efficient drug delivery systems**.**

2. Materials and Products

This study utilized high-purity, analytical-grade reagents and solvents obtained from certified suppliers such as Sigma-Aldrich and Merck to ensure maximum experimental reliability and reproducibility. Key materials included Ferulic Acid (FA), several biocompatible natural compounds (e.g., betaine, lactic acid, acetic acid, malonic acid, Levulinic acid) for the formulation of Natural Deep Eutectic Solvents (NaDES), and Dimyristoylphosphatidylcholine (DMPC) liposomes, selected for their suitability as lipid-based nanocarriers. The strategic selection of these components highlights the study's commitment to developing an environmentally friendly, tunable, and biocompatible drug delivery system.

Quantum chemical calculations were performed using TURBOMOLE (v7.4) to generate COSMO files detailed electrostatic maps of molecules in a virtual conductor environment. These served as critical inputs for COSMOtherm (version 18.0.0), a robust thermodynamic simulation suite that combines COSMO-RS and COSMOmic theories to predict solubility, molecular interactions, and membrane partitioning behavior under physiologically relevant conditions.

Additionally, a multi-platform data analysis strategy employing OriginPro, Microsoft Excel, and SPSS ensured the integrity of both experimental and computational outputs. These tools facilitated comprehensive statistical analyses and high-quality graphical representations, thereby reinforcing the robustness, reproducibility, and scientific validity of the result.

3. Computational Preparation of NADES and DMPC

Natural Deep Eutectic Solvents (NADES) represent an emerging class of green, biocompatible, and environmentally friendly solvents, formed by combining a hydrogen bond acceptor (HBA) with one or more hydrogen bond donors (HBD) in defined molar ratios. This combination results in a eutectic mixture whose melting point is significantly lower than that of the individual components, due to extensive hydrogen bonding networks. **see table 3**.

For this study, the selection of NaDES components was guided by specific criteria such as low toxicity, natural abundance, and the presence of functional groups conducive to stable hydrogen bonding. These properties not only ensure safety and sustainability but also enhance the solvent's capacity to dissolve bioactive compounds with poor water solubility.

To apply the COSMO-RS method, we first needed to prepare the molecular structures using a method called Density Functional Theory (DFT), which helps us find the most stable shape and electronic structure of molecules.

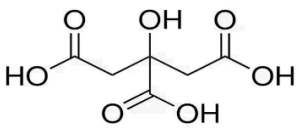
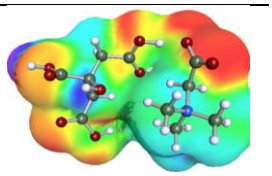
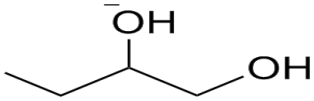
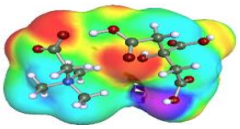
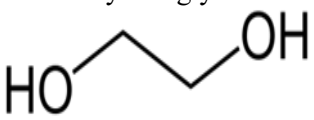
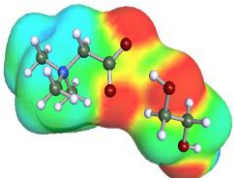
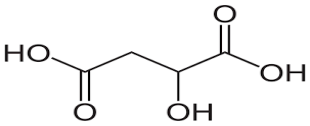
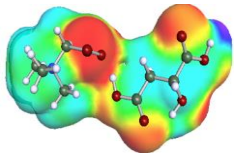
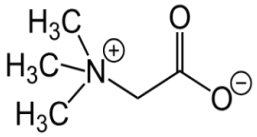
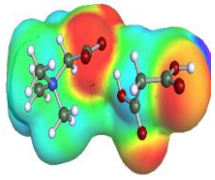
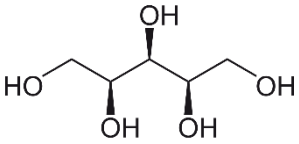
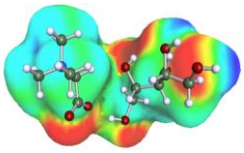
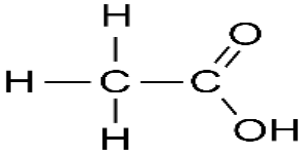
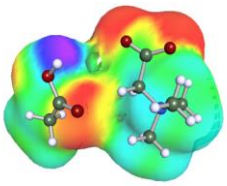
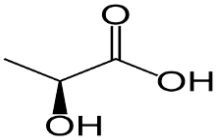
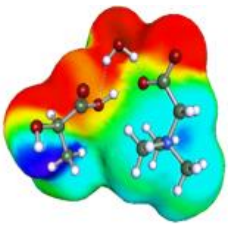
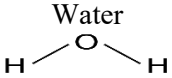
We used the **COSMO-BP-TZVP** template in the TmoleX software. This template provides settings specifically designed to generate the correct molecular files for COSMO-RS analysis. It includes:

The def-TZVP basis set: This is a high-quality mathematical tool that describes how electrons behave in atoms and molecules. "TZVP" stands for "Triple-Zeta Valence with Polarization," which means it gives a detailed and accurate picture of electron distributions.

The M06-2X functional: This is a specific formula within DFT that is very reliable for calculating noncovalent interactions (like hydrogen bonding and van der Waals forces) and energy-related properties. It's especially useful when studying molecular interactions in solvents or membranes.

Using these settings ensures that the molecular structures are realistic and accurate enough for further analysis. We also applied the COSMO solvation model, which mimics the effect of a solvent by placing the molecule inside a virtual environment that behaves like a perfect conductor. This generates a sigma profile a fingerprint showing how the molecule interacts with solvents used in COSMO-RS to predict solubility and other properties [88,89]

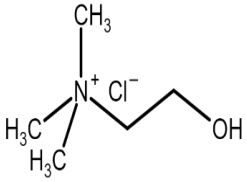
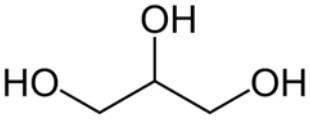
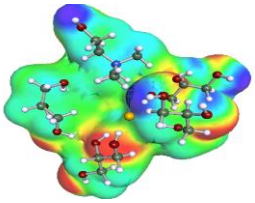
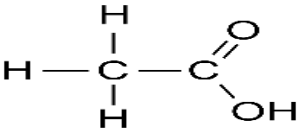
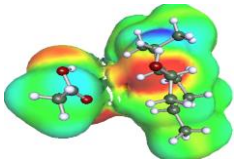
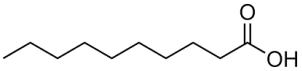
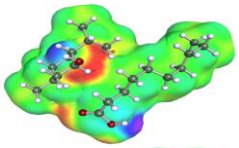
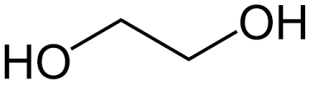
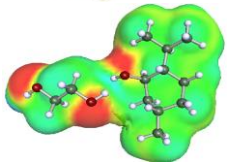
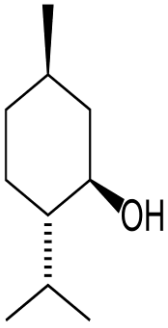
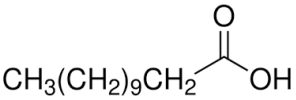
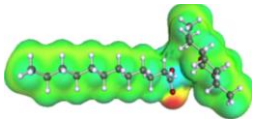
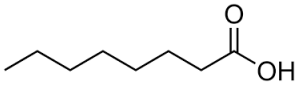
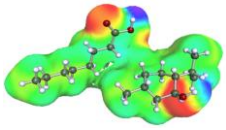
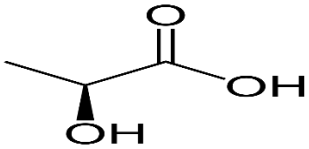
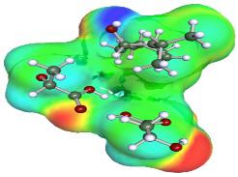
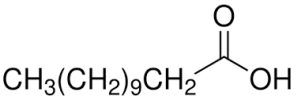
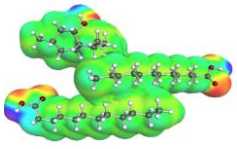
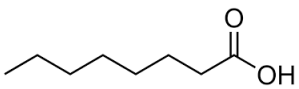
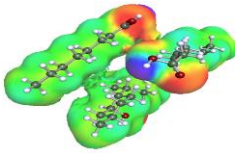
Table 3 Formulation of NaDES components using COSMO-RS theory

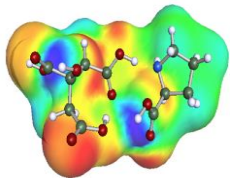
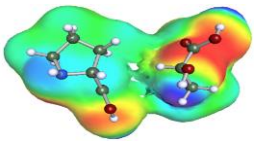
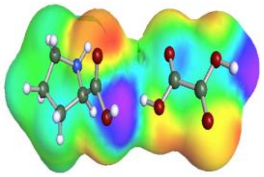
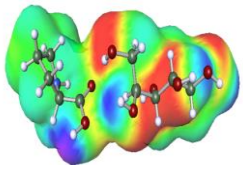
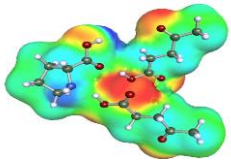
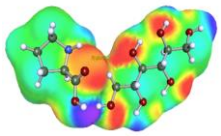
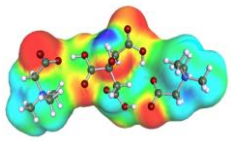
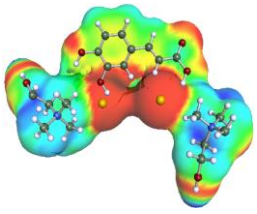
DES N°	Ratio	HBA	HBD	Structure
DES01	1:1	Betaine	Citric acid 	
DES02	1:1		1-2_butanediol 	
DES03	1:1		Ethylene glycol 	
DES04	1:1		Malic acid 	
DES05	1:1		Malonic acid 	
DES06	1:1		Xylitol 	
DES07	1:1		Acetic acid 	
DES08	1:1:1		Lactic acid 	
			Water 	

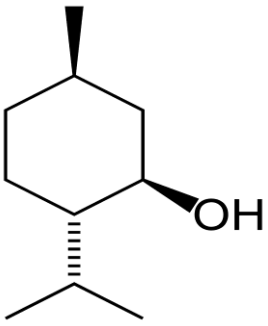
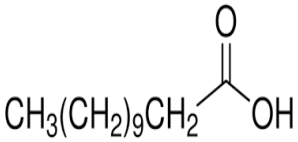
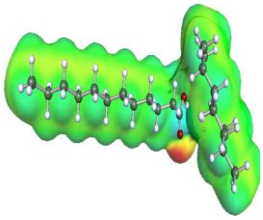
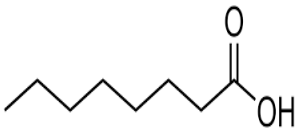
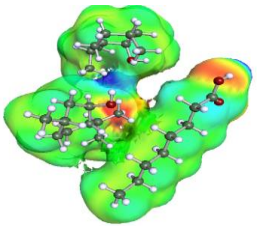
DES09	1:2	Betaine	Glycerol	
DES10	1:2		Lactic acid	
DES11	1:2		Levulanic acid	
DES12	1:2		Urea	
DES13	1:5		Lactic acid	
DES14	1:1	Choline chloride	1-2_butandiol	
DES15	1:1		Citric acid	
DES16	1:1		d-sorbitol	
DES17	1:1		Glutaric acid	

DES18	1:1	Choline chloride	Malonic acid	
DES19	1:1		Methylurea	
DES20	1:2		Acetamide	
DES21	1:2		Acetic acid	
DES22	1:2		Butyric acid	
DES23	1:2		Diethylene glycol	
DES24	1:2		Ethylene glycol	
DES25	1:2		Formic acid	
DES26	1:2		Glycerol	
DES27	1:2		Levulinic acid	

DES28	1:2	Choline chloride	Maleic acid	
DES29	1:2		Methyl acrylic acid	
DES30	1:2		Oxalic acid	
DES31	1:2		Phenol	
DES32	1:2		Propylene glycol	
DES33	1:2		Urea	
DES34	1:3		Propane 1,2diol	
DES35	1:3		Ethylene glycol	
DES36	1:3		Glycerol	

		Choline chloride	Glycerol	
DES37	1:4			
DES38	1:1		Acetic acid 	
DES39	1:1		Decanoic acid 	
DES40	1:1		Ethylene glycol 	
DES41	1:1	Menthol 	Lauric acid 	
DES42	1:1		Octanoic acid 	
DES43	1:2		Lactic acid 	
DES44	1:2		Lauric acid 	
DES45	1:2		Octanoic acid 	

DES46	1:1	L-Proline	Citric acid	
DES47	1:1		Lactic acid	
DES48	1:1		Oxalic acid	
DES49	1:1		Xylitol	
DES50	1:2		Levulanic acid	
DES51	1:2		D-sorbitol	
DES52	2:1	Betaine	Citric acid	
DES53	2:1	Choline chloride	Caffeic acid	

DES54	2:1	Menthol 	Lauric acid 	
DES55	2:1		Octanoic acid 	

By extracting the DMPC.log file from BIOVIA COSMOtherm (version 18.0.0), we obtained a detailed and high-fidelity dataset of thermodynamic and electrostatic descriptors, computed within the COSMO-RS (Conductor-like Screening Model for Real Solvents) framework. This output serves as a quantum chemically derived thermodynamic signature of the DMPC (dimyristoylphosphatidylcholine) molecule, encapsulating a wide array of essential physicochemical parameters. These include sigma profiles, sigma potentials, activity coefficients, solvation free energies (ΔG_solv), chemical potentials, as well as enthalpic and entropic contributions to both solvation and molecular interaction energies. Generated under the assumption of an idealized, virtual conductor environment, these parameters reflect the molecular surface polarization charge distribution and its influence on solvation phenomena. The comprehensive insights afforded by this output enable predictive modeling of lipid bilayer dynamics, membrane partitioning, and intermolecular interactions in a variety of solvent systems, including natural deep eutectic solvents (NaDES). Consequently, the DMPC.log data serves as a crucial computational resource for simulating membrane-associated processes under diverse physicochemical conditions, thereby advancing our understanding of biomimetic membrane behavior and solvation thermodynamics.

4. Sigma profile of NADES

The sigma profile of a solvent, as defined within the framework of COSMO-RS (Conductor-like Screening Model for Real Solvents), serves as a critical descriptor of molecular interactions. It provides a detailed representation of the distribution of surface charge densities (σ) across the solvent's molecular surface, offering profound insights into its interaction potential with solutes.

In the context of natural deep eutectic solvents (NADES), which are emerging as sustainable and biocompatible alternatives to conventional organic solvents, the significance of the sigma profile becomes even more pronounced. NADES are typically composed of hydrogen bond donors (HBDs), such as sugars, amino acids, or organic acids, and hydrogen bond acceptors (HBAs), such as choline chloride or urea. The interplay between these components defines the sigma profile of the resulting solvent, which in turn governs its ability to dissolve hydrophobic drugs. Understanding how the sigma profile influences solubility is not merely an academic exercise but a crucial step toward optimizing drug delivery systems for poorly soluble pharmaceuticals compounds [91].

The sigma profile can be dissected into three distinct regions: the hydrogen bond donor (HBD) region, characterized by negative σ values; the nonpolar region, where σ values hover near zero; and the hydrogen bond acceptor (HBA) region, marked by positive σ values. Each of these regions contributes uniquely to the solvent-solute interaction landscape. For instance, the HBD region facilitates the formation of stabilizing hydrogen bonds with solute molecules that possess hydrogen bond acceptor sites. Similarly, the HBA region complements solutes with hydrogen bond donor functionalities, while the nonpolar region facilitates hydrophobic interactions, which are particularly relevant for dissolving hydrophobic drugs. The relative proportions of these regions in the sigma profile of a NADES determine its overall polarity and hydrogen-bonding capacity, both of which are pivotal in dictating solubility behavior. By tailoring the composition of the NADES adjusting the ratios of HBDs and HBAs it is possible to engineer a sigma profile that aligns closely with the physicochemical properties of a target hydrophobic drug, thereby enhancing its solubility [92].

The scientific impact of this alignment is profound. Hydrophobic drugs, which often suffer from poor bioavailability due to their limited solubility in aqueous media, can achieve significantly improved dissolution rates when formulated with a NADES whose sigma profile is optimized for their specific molecular characteristics. For example, consider curcumin, a natural polyphenol with potent therapeutic properties but notoriously low water solubility. Studies have demonstrated that NADES composed of choline chloride and lactic acid exhibit remarkable efficacy in solubilizing curcumin. This can be attributed to the sigma profile of the NADES, which features a robust HBD region (from lactic acid) capable of forming strong hydrogen bonds

with curcumin's hydroxyl groups, as well as a balanced nonpolar region that accommodates curcumin's aromatic rings. Such complementary interactions reduce interfacial tension between the drug and the solvent, facilitating enhanced miscibility and dissolution [93].

Moreover, the tunability of NADES offers unparalleled flexibility in designing solvents for specific applications. In contrast to traditional organic solvents, whose physicochemical properties are fixed, NADES can be customized by varying their constituents and molar ratios. This adaptability allows researchers to fine-tune the sigma profile to match the requirements of a wide range of hydrophobic drugs. Computational tools like COSMO-RS further augment this process by enabling predictive modeling of sigma profiles and their compatibility with target solutes. By simulating the interactions between a drug and various NADES formulations, researchers can identify optimal combinations without resorting to exhaustive experimental trials. This not only accelerates the solvent screening process but also minimizes resource expenditure, making it a highly efficient approach in pharmaceutical research [94].

From a broader perspective, the ability to enhance the solubility of hydrophobic drugs using NADES has transformative implications for drug formulation and delivery. Poorly soluble drugs represent a significant challenge in the pharmaceutical industry, often necessitating the use of co-solvents, surfactants, or complexation agents, which may introduce toxicity or stability concerns. NADES, with their biocompatibility and green chemistry credentials, offer a safer and more sustainable alternative. Furthermore, their ability to dissolve hydrophobic drugs can lead to improved bioavailability, reduced dosing requirements, and enhanced therapeutic outcomes. This is particularly relevant for drugs administered via oral, transdermal, or parenteral routes, where solubility is a critical factor influencing absorption and overall efficacy. [90].

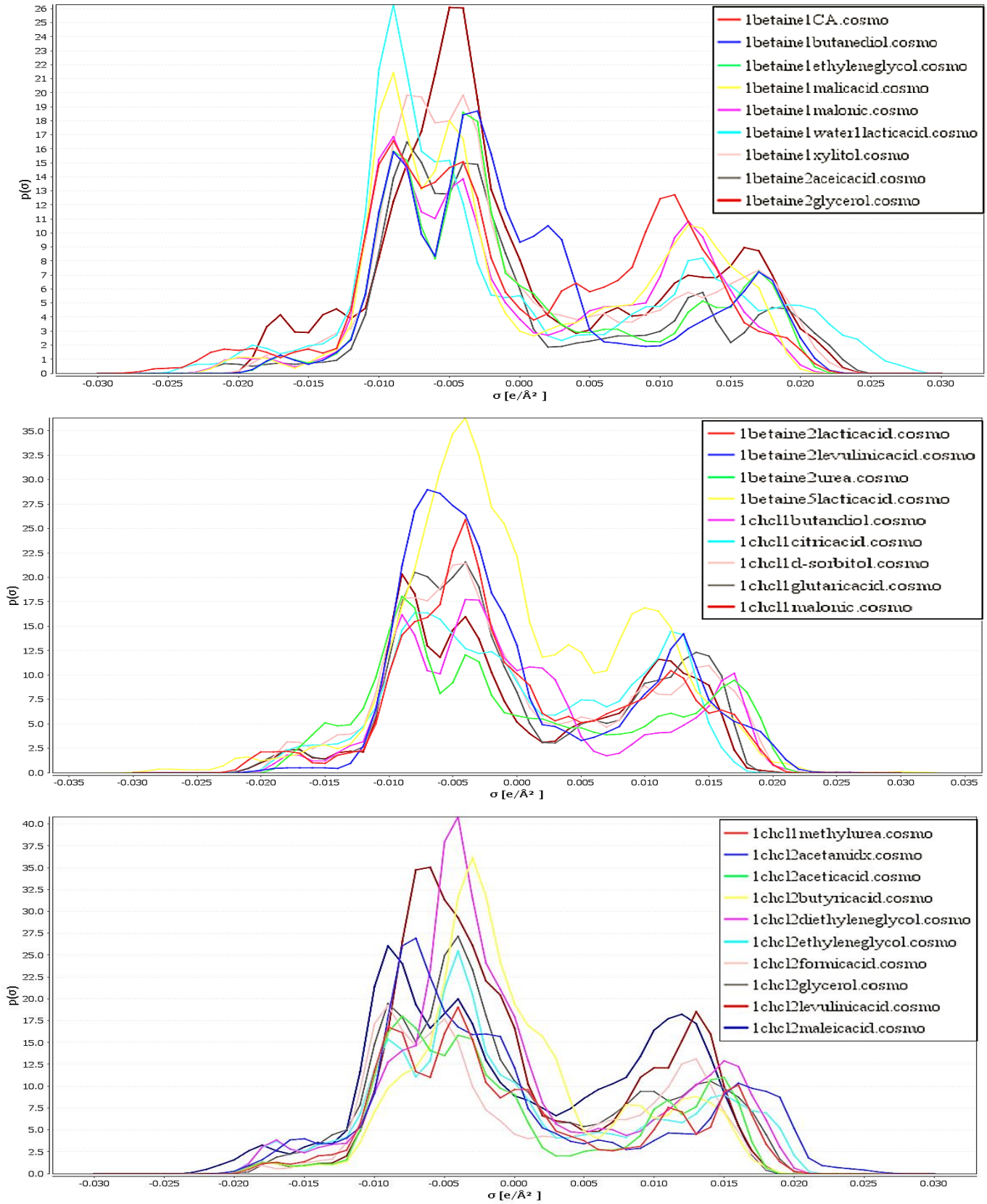


Figure 14: The sigma profile of NADES and ethanol

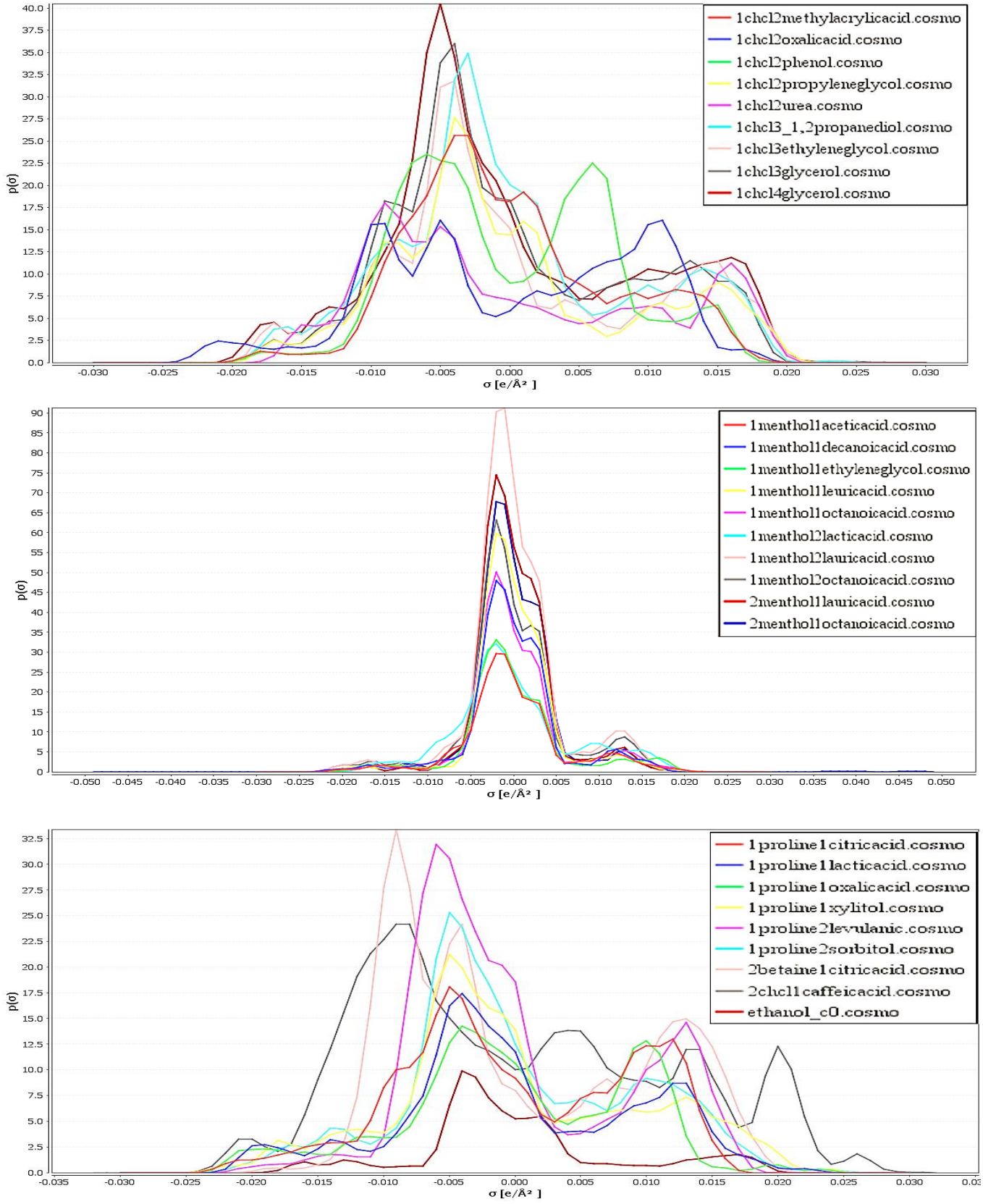


Figure 15: The sigma profile of NADES and ethanol

The sigma profiles in the figure 15 represent the distribution of molecular surface charge densities (σ, in units of e/A˚2) across the solvent's surface. These profiles are divided into three key regions:

- Negative σ values (-0.035 to -0.005): Hydrogen bond donor (HBD) sites.
- Near-zero σ values (-0.005 to +0.005): Nonpolar interactions.
- Positive σ values (+0.005 to +0.035): Hydrogen bond acceptor (HBA) sites.

Group 1: Nonpolar-Dominant DES Champions for Hydrophobic Drug Solubility

Nonpolar-dominant DES are characterized by a pronounced peak in the $\sigma < 0$ region of their sigma profiles. This indicates that their molecular surfaces are largely composed of nonpolar functional groups such as long alkyl chains or hydrophobic moieties. These DES systems likely include combinations based on long-chain fatty acids (like decanoic acid) or nonpolar hydrogen bond acceptors (HBAs), such as menthol or its analogues. The sigma profile suggests a low ability to engage in hydrogen bonding but a strong potential for dispersion forces and van der Waals interactions key to solubilizing hydrophobic drugs.

The figure 13 emphasizes that these DES types demonstrate excellent performance for dissolving drugs with similarly nonpolar sigma profiles, as they enable a “like-dissolves-like” interaction at the molecular level. This class of DES outperforms ethanol, a traditionally used co-solvent, in dissolving lipophilic drugs because ethanol’s polarity limits its affinity for nonpolar compounds. Therefore, for formulating poorly water-soluble drugs such as curcumin, or hydrophobic chemotherapeutics nonpolar-dominant DES present an effective solubility enhancement strategy. Their application is particularly promising in drug delivery systems where increasing bioavailability of hydrophobic agents is a critical challenge.

Group 2: Polar-Dominant DES – Ideal for Polar and Ionic Compounds

Polar-dominant DES exhibit a strong sigma profile peak in the $\sigma > 0$ region, typically centered around values that correspond to hydrogen bond donor (HBD) and acceptor (HBA) capabilities. These solvents are built from classic hydrophilic constituents such as choline chloride mixed with urea, glycerol, or sugars. Their polar nature enables them to form extensive hydrogen bonding networks, making them ideal for dissolving polar or ionic substances, including small

charged molecules, salts, and biologically relevant compounds like amino acids or peptides.

However, this same high polarity becomes a limitation when dealing with hydrophobic drugs. A mismatch between the sigma profile of a highly polar DES and a nonpolar drug result in poor solubility, as confirmed by the source file, which notes that such DES "may not effectively dissolve" hydrophobic drugs. Despite their biocompatibility and green chemistry appeal, polar-dominant DES should be avoided in formulations targeting lipophilic or amphiphilic drugs unless modified with co-solvents or emulsifiers. They shine best in specialized applications where the active pharmaceutical ingredient (API) is polar and benefits from hydrogen bonding stabilization.

Group 3: Balanced DES – Amphiphilic and Versatile Solvents

Balanced DES are characterized by bimodal sigma profiles that is, smaller peaks in both the nonpolar ($\sigma < 0$) and polar ($\sigma > 0$) regions. This indicates a roughly equal presence of hydrophobic and hydrophilic molecular regions within the solvent system. These DES are typically composed of short-chain acids (e.g., acetic or lactic acid), low molecular weight alcohols, or diols like ethylene glycol. Their intermediate sigma profile closely resembles that of ethanol, providing a compromise between nonpolar and polar interactions.

This category of DES offers moderate solubility across a wide range of drug types, especially those that are amphiphilic or moderately polar. While they may not provide the highest solubility for either extreme (highly polar or highly nonpolar drugs), they offer a balanced environment that suits a wide variety of pharmaceutical compounds. Their flexibility makes them a useful baseline in early-stage formulation screening, especially when the drug's polarity is uncertain or variable across different pH levels. Due to their dual solubilization capability, balanced DES are also promising candidates for multi-drug delivery systems that require compatibility with diverse APIs.

Ethanol: The Benchmark Solvent for Comparison

Ethanol's sigma profile features moderate peaks in both the nonpolar and polar regions, placing it in a mid-polarity range. This makes it a widely used and well-understood solvent in both

industrial and academic settings for drug solubilization. However, when compared with specifically tailored DES, ethanol often underperforms. For hydrophobic drugs, ethanol's limited nonpolar character restricts its solubilization potential, making nonpolar-dominant DES superior choices. Similarly, for very polar or ionic drugs, strongly polar DES outperform ethanol due to their enhanced hydrogen bonding capabilities.

Nonetheless, ethanol remains a useful benchmark for evaluating DES performance. Balanced DES mimic ethanol's polarity and offer similar, if not better, versatility, often with improved safety, environmental compatibility, and tunability. Ethanol's position as a "middle-ground" solvent thus helps contextualize the relative strengths of the DES classes described above.

5. Solubility of FA in NADES

After preparing the molecular structure of Ferulic Acid (FA) and generating its corresponding COSMO files using BIOVIA COSMOtherm software, we systematically screened and compared the solubility profiles of several Natural Deep Eutectic Solvent (NaDES) formulations against conventional ethanol, which served as the reference solvent. This computational solubility screening, based on the COSMO-RS framework, was designed to identify NaDES systems with superior solubilizing capabilities for FA, the insights obtained from this screening process are instrumental in the rational selection of NaDES formulations, which can facilitate their adoption in pharmaceutical applications and lipid-based drug delivery platforms.

The solubility of Ferulic Acid (FA) ($C_{10}H_{10}O_4$; MW = 194.19; >98% purity) in ethanol, approximately 10 mg/mL at elevated temperatures (≥50°C), serves as a critical benchmark for evaluating the solubilization efficiency of alternative solvents. This reference point allows for a quantitative comparison of the solubility profiles of various NaDES, aiding in the identification of greener, more effective solubilizing systems that can enhance the bioavailability and controlled release of FA in pharmaceutical contexts [95-96].

In this study, two fundamental solubility parameters **Weight Solubility in Liquid Equilibrium (WSLE)** and the **Logarithm of Mole Fraction Solubility in Liquid Equilibrium ($\log_{10}$(x_SLE))** were employed to rigorously evaluate and compare the solubilizing performance of various Natural Deep Eutectic Solvent (NaDES) formulations for Ferulic Acid (FA). These

parameters provide complementary insights, with WSLE offering a mass-based perspective relevant for practical formulation, and $\log_{10}$(x_SLE) offering a mole-based, thermodynamically meaningful metric suitable for computational and theoretical modeling [97].

The **Weight Solubility in Liquid Equilibrium (WSLE)** quantifies the amount of FA (in grams) that can be dissolved in a given DES system under equilibrium conditions, normalized by the total mass of the resulting solution. It is mathematically defined as:

$$W_{SLE} = \frac{Mass\ of\ FA\ (g)}{\text{Total mass of solution (g)}} \quad (1)$$

This parameter provides a straightforward and experimentally accessible measure of solubility, which is especially important for assessing the drug-loading capacity of solvents in pharmaceutical applications. A higher WSLE value indicates superior solubility performance, indicating the solvent's capacity to dissolve a greater proportion of the target compound. This is critical in the context of formulation development, where maximizing the solute content within a minimal solvent volume is desirable for effective dosage design, encapsulation efficiency, and bioavailability enhancement.

On the other hand, the **Logarithm of Mole Fraction Solubility in Liquid Equilibrium ($\log_{10}$(x_SLE))** provides a more fundamental representation of solubility based on the ratio of solute to total moles in the solution. This is defined by the following equations:

$$log_{10}(x_{SLE}) = \frac{\text{Moles of FA}}{Total\ moles\ of\ (FA+DES)} \quad (2)$$

This mole-based parameter is particularly suited for computational chemistry and thermodynamic modeling, as it reflects the intrinsic molecular-level interactions between solute and solvent. The logarithmic transformation is necessary because mole fraction values are typically very small (often below 0.01), and taking the logarithm allows for easier comparative analysis and graphical representation. In this context, **less negative $\log_{10}$(x_SLE)** values correspond to **higher solubility**, indicating stronger and more favorable interactions between FA and the DES components, such as hydrogen bonding, polarity matching, or van der Waals attractions.

Together, WSLE and $\log_{10}$(x_SLE) form a comprehensive framework for assessing solubility: WSLE addresses practical, formulation-focused concerns, while $\log_{10}$(x_SLE) provides a deeper understanding of molecular affinity and thermodynamic compatibility. These dual metrics were instrumental in identifying the most promising NaDES candidates with enhanced solubilization potential compared to ethanol, thereby supporting the rational development of green and efficient solvent systems for FA encapsulation in lipid-based nanocarriers.

Table 4 Evaluation of the solubility behavior of FA across a range of NADES with ethanol serving as the reference solvent.

DES N°	WSLE	$log_{10}(x\_SLE)$	NADES VS Eth	Key insights
DES01	0.00030	-3.31751	0.02x	Very low solubility; minimal enhancement over ethanol.
DES02	0.05806	-1.20949	4.53x	Moderate solubility; significantly higher than ethanol.
DES03	0.03675	-1.46833	2.87x	Balanced solubility; shows good improvement over ethanol.
DES04	0.00145	-2.72652	0.11x	Weak solubility; much lower than ethanol.
DES05	0.00092	-2.97956	0.07x	Very low solubility; negligible enhancement over ethanol.
DES06	0.04565	-1.20613	3.56x	High solubility; demonstrates strong solubilization potential.
DES07	0.28067	-0.58076	**21.9x**	**Highest solubility; far exceeds ethanol's performance.**
DES08	0.23616	-0.57846	18.4x	Excellent solubility; second-highest solubilization capacity.
DES09	0.00987	-1.81723	0.77x	Moderate solubility; slightly below ethanol's performance.
DES10	0.00165	-2.59706	0.13x	Weak solubility; much lower than ethanol.
DES11	0.05821	-0.99965	4.54x	Good solubility; shows significant improvement over ethanol.
DES12	0.01156	-1.85109	0.90x	Comparable solubility to ethanol; slightly below baseline.
DES13	0.00057	-2.77937	0.04x	Very low solubility; minimal enhancement over ethanol.
DES14	0.00637	-2.12319	0.49x	Limited solubility; less effective than ethanol.
DES15	0.00034	-3.23998	0.03x	Poor solubility; negligible enhancement over

				ethanol.
DES16	0.00082	-2.86762	0.06x	Minimal solubility; ineffective for improving solubility.
DES17	0.00097	-2.86628	0.07x	Very low solubility; minimal enhancement over ethanol.
DES18	0.00034	-3.36375	0.03x	Negligible solubility; ineffective for solubilization.
DES19	0.00729	-2.09582	0.57x	Weak solubility; modest improvement over ethanol.
DES20	0.16466	-0.68322	12.8x	High solubility; demonstrates excellent solubilization capacity.
DES21	0.00232	-2.62302	0.18x	Low solubility; much lower than ethanol.
DES22	0.00043	-3.15405	0.03x	Extremely low solubility; negligible enhancement over ethanol.
DES23	0.00216	-2.40866	0.17x	Weak solubility; less effective than ethanol.
DES24	0.00188	-2.59226	0.15x	Very low solubility; minimal enhancement over ethanol.
DES25	0.00039	-3.32868	0.03x	Negligible solubility; ineffective for solubilization.
DES26	0.00121	-2.69624	0.09x	Weak solubility; much lower than ethanol.
DES27	0.00072	-2.86193	0.06x	Minimal solubility; ineffective for improving solubility.
DES28	0.00014	-3.52167	0.01x	Extremely low solubility; unsuitable for practical use.
DES29	0.00035	-3.24527	0.03x	Very low solubility; ineffective for solubilization.
DES30	0.00025	-3.38324	0.02x	Negligible solubility ; minimal enhancement over ethanol.
DES31	0.00025	-3.38218	0.02x	Extremely low solubility; unsuitable for practical use.

DES32	0.00284	-2.37007	0.22x	Weak solubility; requires optimization for better performance.
DES33	0.01274	-1.77043	0.99x	Comparable solubility to ethanol; slightly below baseline.
DES34	0.00074	-2.85323	0.06x	Minimal solubility; ineffective for improving solubility.
DES35	0.00101	-2.77027	0.08x	Very low solubility; ineffective for solubilization.
DES36	0.00073	-2.80847	0.06x	Minimal solubility; ineffective for improving solubility.
DES37	0.00068	-2.75077	0.05x	Very low solubility; minimal enhancement over ethanol.
DES38	0.00016	-3.75140	0.01x	Extremely low solubility; unsuitable for practical use.
DES39	0.00004	-4.14408	0.00x	Negligible solubility; ineffective for solubilization.
DES40	0.00030	-3.46875	0.02x	Very low solubility; minimal enhancement over ethanol.
DES41	0.00002	-4.52315	0.00x	Negligible solubility; unsuitable for practical use.
DES42	0.00009	-3.87873	0.01x	Extremely low solubility; ineffective for solubilization.
DES43	0.00057	-3.00807	0.04x	Very low solubility; ineffective for solubilization.
DES44	0.00003	-4.10056	0.00x	Negligible solubility; ineffective for solubilization.
DES45	0.00005	-3.91078	0.00x	Extremely low solubility; unsuitable for practical use.
DES46	0.00025	-3.40788	0.02x	Very low solubility; minimal enhancement over ethanol.
DES47	0.00039	-3.38343	0.03x	Minimal solubility; ineffective for improving

				solubility.
DES48	0.00097	-2.98737	0.07x	Very low solubility; ineffective for solubilization.
DES49	0.00071	-3.00819	0.06x	Minimal solubility; ineffective for improving solubility.
DES50	0.00086	-2.81395	0.07x	Very low solubility; minimal enhancement over ethanol.
DES51	0.00036	-3.25688	0.03x	Extremely low solubility; unsuitable for practical use.
DES52	0.00119	-2.58182	0.09x	Weak solubility; requires optimization for better performance.
DES53	0.00125	-1.62943	0.10x	Moderate improvement; potential for specific applications.
DES54	0.00001	-4.87195	0.00x	Negligible solubility; ineffective for solubilization.
DES55	0.00001	-4.55887	0.00x	Extremely low solubility; unsuitable for practical use.
Reference	0.01282	-2.51276	Eth (Baseline)	Reference solvent; moderate solubility but limited compared to top-performing DES.

Table 4 and Figure 16 offer an in-depth representation of the solubility behavior of Ferulic Acid (FA) in a diverse set of Deep Eutectic Solvent (DES) formulations, all evaluated at a controlled temperature of 298.15 K. These visual and tabulated datasets encapsulate key quantitative insights into how various DES compositions formed through different combinations of hydrogen bond donors (HBDs) and acceptors (HBAs) influence the solubilization capacity for FA.

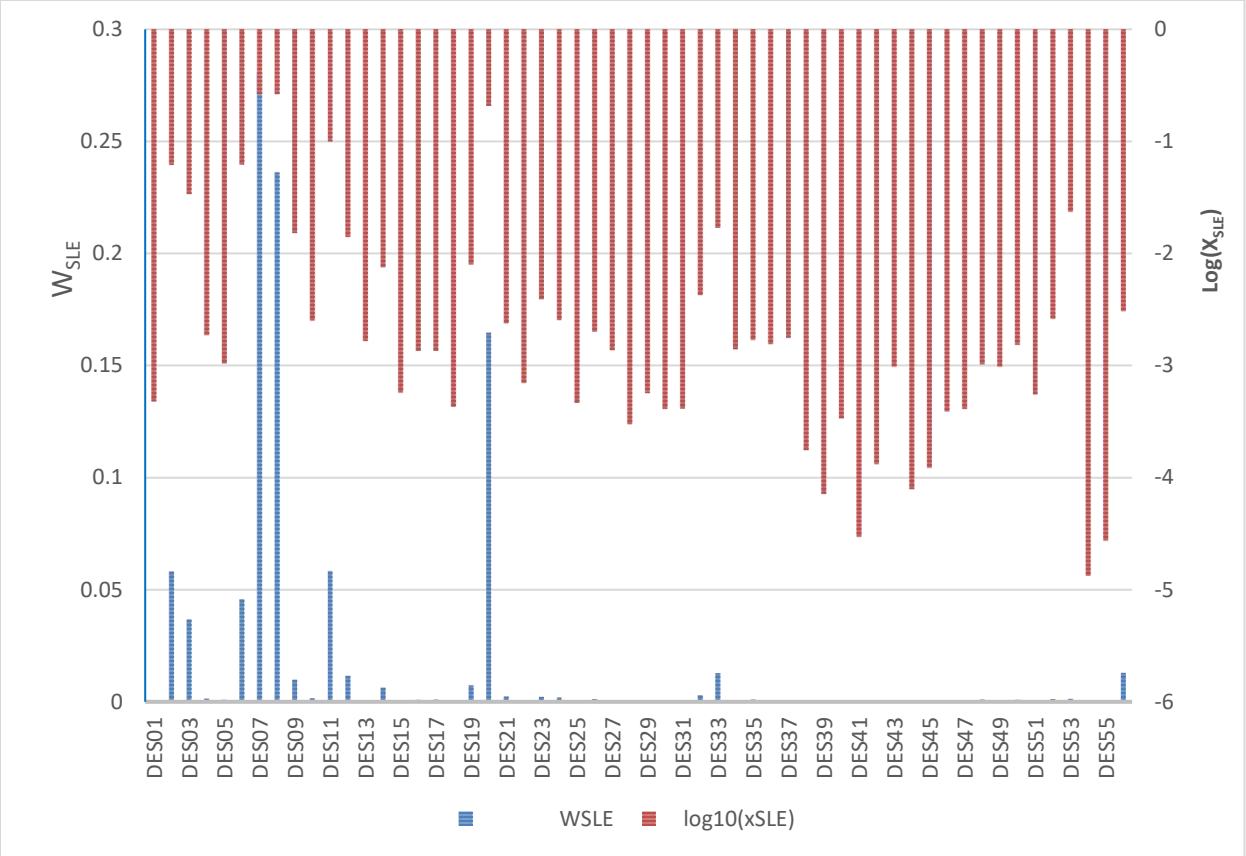


Figure 16: Comparative Solubility Analysis of Ferulic Acid in (NADES) and Ethanol

Molecular interactions are pivotal in determining the solubility of ferulic acid (FA) in deep eutectic solvents (DES), and the COSMO-RS model serves as an invaluable computational tool for predicting and analyzing these complex interactions. By treating each DES as a unique chemical entity, this framework enables a detailed analysis of three critical factors hydrogen bonding, polarity, and solvation capacity that are essential for optimizing DES performance in pharmaceutical applications. FA, a polar molecule characterized by hydroxyl (-OH) and carboxyl (-COOH) functional groups, forms robust hydrogen bonds that significantly influence its stability and solubility across various solvents. The COSMO-RS model provides mechanistic insights into these interactions by examining charge distribution, hydrogen bonding networks, and molecular packing efficiency, elucidating how partial charges on oxygen atoms and molecular configurations modulate FA's behavior in different environments.

Among the evaluated DES formulations, DES07 exhibits the highest solubility, with a Weight Solubility in Liquid Equilibrium (WSLE) of 0.28067 and a $\log_{10}$(x_SLE) of -0.58076. This exceptional performance is attributed to acetic acid's small size, flexibility, and proton-donating

capacity, which facilitate strong hydrogen bonding with FA's functional groups. Additionally, the polarity of acetic acid promotes the formation of solvation shells, reducing crystallization tendencies and making DES07 particularly effective for solubilizing hydrophobic drugs. Similarly, DES20 ranks second in solubility, with a WSLE of 0.16466 and a $\log_{10}$(x_SLE) of -0.68322. This formulation benefits from the complementary roles of acetamide and choline chloride, which together establish a highly polar environment that facilitates the solubilization of FA. The cationic nature of choline chloride plays a crucial role in stabilizing the overall system, while acetamide, through its strong polarity, hydrogen-bonding capacity, and van der Waals interactions with the aromatic system, contributes to the stabilization of the nonpolar regions, thereby promoting the formation of stable complexes. DES08 demonstrates solubility comparable to DES07, with a WSLE of 0.23616 and a $\log_{10}$(x_SLE) of -0.57846. The presence of water in this formulation strengthens hydrogen bonding between FA and lactic acid, further enhancing solubilization. Additionally, betaine contributes to system stability, preventing precipitation and making DES08 ideal for liposomal drug delivery systems that require both high stability and solubility. In contrast, DES11 shows a significant but moderate solubility increase (WSLE = 0.05821, $\log_{10}$(x_SLE) = -0.99965), driven by Levulinic acid's extensive hydrogen bonding interactions with FA. This formulation strikes a balance between solubility and viscosity, making it suitable for applications requiring lower viscosity despite slightly reduced solubility compared to DES07 and DES20.

The solubility of DES06 is moderate to high (WSLE = 0.04565, $\log_{10}$(x_SLE) = -1.20613). While xylitol's numerous hydroxyl groups promote hydrogen bonding, its higher viscosity restricts molecular mobility, reducing the frequency of solute-solvent interactions. Similarly, DES02, based on butanediol, achieves a WSLE of 0.05806 and a $\log_{10}$(x_SLE) of -1.20949. Its balanced molecular size and multiple hydroxyl groups enable significant hydrogen bonding with FA, contributing to its performance. Conversely, DES03, formulated with ethylene glycol, exhibits lower solubility (WSLE = 0.03675, $\log_{10}$(x_SLE) = -1.46833). Ethylene glycol's smaller size limits its ability to form hydrogen bonds, resulting in relatively poor FA solubility. These findings underscore the critical importance of selecting DES components with appropriate molecular structures to maximize the solubility of bioactive compounds like FA.

Although experimental solubility data were not directly measured in this study, the COSMO-RS predictions exhibit strong agreement with previously reported experimental results, such as those

presented by Jeliński et al. (2024) [98], reinforcing the reliability of the model. For instance, DES54 and DES55 exhibit the lowest solubility due to their hydrophobic and sterically hindered components. The lengthy, nonpolar carbon chains of lauric and octanoic acids, along with the bulky structure of menthol, impede adequate hydrogen bonding with FA. These hydrophobic elements reduce the overall polarity of the DES and introduce steric barriers, hindering solubility enhancement. Similarly, DES05 and DES15, containing citric and malonic acids, demonstrate limited solubility despite their multiple acidic functional groups. Their complex and branched architectures introduce steric hindrance, inhibiting optimal interaction with FA. This highlights that solubility enhancement depends not only on the presence of functional groups but also by their spatial arrangement and molecular flexibility of the system.

Polyol-based DES formulations, such as DES09 and DES06 (WSLE = 0.00987 and 0.04565, respectively), leverage the numerous hydroxyl groups in glycerol and xylitol to form strong hydrogen bonds with FA. However, their higher viscosity restricts molecular mobility, reducing the frequency and effectiveness of solute-solvent interactions. Achieving an optimal balance between viscosity and hydrogen bonding capacity is crucial for maximizing solubility in polyol-based DES. Urea-based DES, exemplified by DES33 (WSLE = 0.01274), benefits from urea's compact, flexible structure and substantial hydrogen bond donor and acceptor properties, enabling effective solute-solvent interactions. Variability in the solubility of urea-based DES suggests that further optimization can be achieved by fine-tuning the ratio of hydrogen bond donors to acceptors.

Collectively, these findings emphasize the necessity of carefully engineering DES to balance molecular properties such as polarity, hydrogen bonding potential, and steric effects to optimize solubility for specific applications. The implications of this research extend to fields such as drug delivery, where enhancing the solubility of active pharmaceutical ingredients is crucial, as well as to the design of green solvents for sustainable chemical processes. By providing a deeper understanding of the interplay between molecular interactions and solubility, this study lays a robust foundation for advancing pharmaceutical innovation and developing environmentally friendly drug delivery systems.

Our findings are in line with sigma-profile-driven solubility theory. Even though ferulic acid is largely nonpolar, it also contains polar groups that require dual solubilization strategies. These DES systems strike the right polarity balance, enabling efficient multi-point molecular

interaction, and therefore demonstrate superior solubility behavior.

6. Optimizing Ferulic Acid controlled release within DMPC

After determining the most effective Deep Eutectic Solvent (DES) for solubilizing Ferulic Acid (FA), the COSMOmic model was applied to investigate its release dynamics and molecular interactions within the Dimyristoylphosphatidylcholine (DMPC) bilayer. This model simulates the diffusion of molecules from the aqueous phase through the polar headgroup region into the hydrophobic core, **with the opposite leaflet treated as a symmetric mirror representing a half-bilayer (33Å) rather than a complete liposome**. This analysis encompassed the determination of FA's partition coefficient (logP) to evaluate its affinity for the lipid phase, the calculation of membrane permeability (logPerm) to estimate its transbilayer transport efficiency, and the generation of free energy profiles to characterize its spatial distribution across the membrane. These computational investigations offer deep mechanistic insights into the solubility, localization, and diffusional behavior of FA in both solvent systems and biologically relevant membrane environments, thereby informing rational design of effective delivery systems [90].

6.1. ***Stability of NADES and FA in the DMPC:***

The computational data derived from COSMO-RS simulations provide a granular thermodynamic profile of ferulic acid (FA) within various NaDES-DMPC liposomal environments, offering insight into the molecular mechanisms governing solubility, partitioning, and membrane compatibility. For each DES-lipid mixture, we evaluated several critical parameters:

Chemical Potential (μ, kcal/mol): This represents the free energy change associated with adding an infinitesimal amount of FA to the mixture. A lower (more negative) chemical potential reflects greater thermodynamic stability and stronger solute-solvent interactions, indicating that the FA molecule is more favorably solvated in the corresponding DES-lipid environment.

Log_{10}(Partial Pressure [mbar]): This logarithmic value indicates the volatility of FA in the system. Lower partial pressure values imply reduced vapor-phase escape, corresponding to

stronger retention of FA within the lipid-NaDES matrix, which is essential for sustained drug release and minimized premature evaporation or degradation.

Free Energy in the Mixture (ΔG_mix, kcal/mol): This is a composite thermodynamic descriptor representing the overall Gibbs free energy of mixing FA into the DES-lipid system. More negative ΔG_mix values denote a spontaneous and energetically favorable solvation process, aligning with improved solubilization efficiency.

Total Mean Interaction Energy (E_int, kcal/mol): These aggregates all pairwise interactions between FA and the surrounding solvent/lipid environment. A more negative total interaction energy reflects stronger binding forces and cohesive interactions that stabilize FA within the formulation.

Misfit Interaction Energy (E_misfit): This term quantifies the electrostatic and steric mismatch between FA and its surrounding medium, derived from the misalignment of their surface polarization charge densities. Lower misfit energy suggests greater molecular complementarity, which is crucial for stable encapsulation.

Hydrogen-Bond Interaction Energy (E_H-bond): This isolates the contribution of hydrogen bonding interactions, a dominant mechanism in both DES and lipid interactions with polar bioactives like FA. Higher negative values indicate strong H-bond networks, which significantly aid in solvation and stabilization.

Van der Waals (VdW) Interaction Energy (E_VdW): Reflecting non-specific dispersion forces, this component becomes especially important in the hydrophobic tail regions of the lipid bilayer or in DESs with nonpolar components. Favorable VdW interactions support FA insertion into the bilayer's hydrophobic core.

Together, these thermodynamic and interaction descriptors enable a multi-dimensional understanding of how each DES formulation influences FA behavior inside the DMPC liposomal matrix. The results demonstrate that optimizing the balance between polar (H-bonding, electrostatic) and nonpolar (VdW) interactions is essential to enhancing drug retention, solubility, and compatibility with the lipid membrane. This systematic profiling guides the

rational selection of DES components to tailor nanoformulations for hydrophobic or amphiphilic therapeutic agents.

Table 5 analyses the interaction energies between FA and DESs with optimal solubility when incorporated into DMPC bilayers.

Table 5 The analysis of the interaction energies between FA and DESs in the DMPC bilayer

Mix N°	Mixtures (within liposome)	Chemical Potential (kcal/mol)	Log10(partial pressure [mbar])	Free Energy in Mix (kcal/mol)	Total Mean Interaction Energy (kcal/mol)	Misfit Interaction Energy (kcal/mol)	H-Bond Interaction Energy (kcal/mol)	VdW Interaction Energy (kcal/mol)
Mix 01	FA	-2.26111	-9.02324	-431701.26	-17.80361	3.85799	-11.21295	-10.43691
	DES 02	4.44658	-12.66401	-446287.15	-14.55235	5.42775	-9.10949	-12.01161
Mix 02	FA	-1.84450	-8.71787	-431700.84	-17.01440	4.06784	-10.63963	-10.43088
	DES 03	5.10013	-14.55292	-396953.24	-12.84677	5.11227	-8.54210	-10.55793
Mix 03	FA	-2.27574	-9.03397	-431701.27	-18.19641	3.88738	-11.94642	-10.12564
	DES 06	3.76206	-14.55292	-612572.18	-20.25667	6.18265	-14.97434	-12.60599
Mix 04	FA	-4.44735	-10.62577	-431703.44	-18.86334	4.59029	-13.08977	-10.35212
	DES 07	5.56314	-13.33018	-396217.47	-14.20828	6.68750	-12.17711	-9.85966
Mix 05	FA	-4.50182	-10.66570	-431703.50	-20.14938	5.39656	-15.27951	-10.25470
	DES 08	2.32924	-32.31477	-516022.01	-35.68266	9.34788	-33.89052	-12.28103
Mix 06	FA	-2.69443	-9.34087	-431701.69	-17.34210	4.08946	-11.15640	-10.26342
	DES 11	7.08125	-17.61644	-780869.13	-12.88345	9.53332	-6.22356	-17.33421
Mix 07	FA	-3.49188	-9.92541	-431702.49	-19.23442	4.32817	-12.82269	-10.72816
	DES20	5.01241	-24.37986	-757712.64	-23.39892	9.41601	-17.41755	-16.53837

Mix 01: FA with DES 02

Ferulic Acid (FA) in this mixture demonstrates favorable thermodynamic stability, as reflected by a low chemical potential of -2.26111 kcal/mol. The negative $\log_{10}$(partial pressure) of -9.02324 confirms its low volatility and high encapsulation efficiency within the DMPC liposomal membrane. FA's integration is thermodynamically advantageous, shown by the highly negative free energy of -431,701.26 kcal/mol. Strong hydrogen bonding (-11.21 kcal/mol) and substantial van der Waals (VdW) interactions (-10.44 kcal/mol) yield a total interaction energy of -17.80 kcal/mol. These attributes indicate strong membrane affinity, outperforming DES 02, which exhibits a higher chemical potential (4.44658 kcal/mol), reduced hydrogen bonding (-9.11 kcal/mol), and higher misfit energy, suggesting lower structural compatibility with the lipid bilayer. Therefore, DES 02 may enhance solubility but remains less stable within the membrane environment.

Mix 02: FA with DES 03

FA exhibits slightly reduced thermodynamic stability in this environment, with a chemical potential of -1.84450 kcal/mol. Nonetheless, it retains low volatility ($\log_{10}$ partial pressure: -8.71787) and maintains high encapsulation potential. The total free energy remains highly negative at -431,700.84 kcal/mol. However, the hydrogen bonding energy slightly decreases to -10.64 kcal/mol, and VdW interactions remain stable at -10.43 kcal/mol, culminating in a total interaction energy of -17.01 kcal/mol the lowest among all mixes. DES 03 shows weaker interaction energies and high misfit values, pointing to poor membrane integration. This suggests that DES 03 introduces unfavorable interactions, compromising bilayer affinity and reducing both FA and DES stability within the system.

Mix 03: FA with DES 06

In this formulation, FA exhibits improved thermodynamic stability, indicated by a chemical potential of -2.27574 kcal/mol and low volatility ($\log_{10}$ partial pressure: -9.03397). The total free energy remains strongly negative at -431,701.27 kcal/mol. Enhanced hydrogen bonding (-11.95 kcal/mol) and steady VdW interactions (-10.13 kcal/mol) contribute to a high total interaction energy of -18.20 kcal/mol. DES 06 presents stronger binding affinity (-20.26 kcal/mol), characterized by significant hydrogen bonding (-14.97 kcal/mol) and VdW forces (-12.61 kcal/mol). However, the high misfit energy (6.18 kcal/mol) suggests it disrupts bilayer structure, indicating that although it can enhance drug retention, it may compromise membrane stability, making it suitable for formulations requiring stronger bilayer interactions or controlled disruption.

Mix 04: FA with DES 07

FA achieves one of its most stable thermodynamic profiles in Mix 04, with a remarkably low chemical potential of -4.44735 kcal/mol. The system is thermodynamically favored (ΔG = -431,703.44 kcal/mol), supported by robust hydrogen bonding (-13.09 kcal/mol) and consistent VdW interactions (-10.35 kcal/mol). The total interaction energy reaches -18.86 kcal/mol. In contrast, DES 07 shows higher chemical potential (5.56 kcal/mol), weaker dispersion forces (-9.86 kcal/mol), and elevated misfit energy (6.69 kcal/mol), reflecting its limited structural compatibility and stability within the lipid bilayer. Thus, FA remains dominant in anchoring interactions, while DES 07 may serve to adjust fluidity or release kinetics without deeply integrating into the bilayer.

Mix 05: FA with DES 08

This mix features the most stable FA configuration, highlighted by the lowest chemical potential (-4.50182 kcal/mol) and a $\log_{10}$ partial pressure of -10.66570, indicating excellent encapsulation. The free energy of -431,703.50 kcal/mol remains highly favorable. FA demonstrates its strongest hydrogen bonding capacity here (-15.28 kcal/mol), while maintaining stable VdW interactions (-10.25 kcal/mol). These values yield a total interaction energy of -20.15 kcal/mol. DES 08 contributes a dramatically high hydrogen bonding energy (-33.89 kcal/mol) and substantial VdW forces (-12.28 kcal/mol), but its high misfit energy (9.35 kcal/mol) raises concerns about membrane destabilization. Consequently, DES 08 is suitable for systems requiring enhanced permeability or drug release through temporary bilayer disruption.

Mix 06: FA with DES 11

FA maintains robust thermodynamic behavior in this combination, with a chemical potential of -2.69443 kcal/mol and moderate volatility ($\log_{10}$ partial pressure: -9.34087). Its free energy remains significantly negative at -431,701.69 kcal/mol. The molecule engages in effective hydrogen bonding (-11.16 kcal/mol) and stable VdW interactions (-10.26 kcal/mol), generating a total interaction energy of -17.34 kcal/mol. DES 11, despite its high chemical potential (7.08 kcal/mol), shows strong dispersion forces (-17.33 kcal/mol) and relatively low misfit energy (9.53 kcal/mol), suggesting favorable integration into the lipid bilayer. This balance makes the system suitable for applications emphasizing stability, membrane compatibility, and enhanced delivery.

Mix 07: FA with DES 20

FA presents strong thermodynamic characteristics in this system, with a chemical potential of -3.49188 kcal/mol and a very favorable free energy of -431,702.49 kcal/mol. Enhanced hydrogen

bonding (-12.82 kcal/mol) and significant VdW interactions (-10.73 kcal/mol) yield a total interaction energy of -19.23 kcal/mol. DES 20 offers high stability via strong H-bonding (-17.42 kcal/mol) and VdW interactions (-16.54 kcal/mol), but its misfit energy (9.99 kcal/mol) suggests that it alters the bilayer structure. While this may compromise membrane rigidity, it benefits formulations targeting deep membrane integration, improved permeability, and enhanced drug encapsulation.

Across all studied lipid-DES mixtures, Ferulic Acid demonstrates consistently favorable thermodynamic stability and strong interaction with lipid bilayers. DESs such as 08 and 20 significantly enhance overall interaction energies, favoring systems that require higher permeability or membrane modulation. DES 06 and 11 provide robust binding while maintaining better bilayer compatibility, suitable for drug stabilization. Conversely, DES 03 and 07 show limited stability and compatibility, suggesting their role is more appropriate in systems demanding low membrane interference. These findings offer a systematic framework for selecting DES candidates tailored to specific drug delivery goals, enhancing formulation performance in pharmaceutical and nanobiotechnological applications.

6.2. *Encapsulation of FA and DESs in DMPC layers*

Analyzing the free energy profiles associated with the encapsulation of ferulic acid (FA) in DES-modified DMPC liposomes (as depicted in Figure 18) offers profound insights into the energetic landscape governing drug stabilization and release behavior. The Gibbs free energy of encapsulation (ΔG_encap) serves as a critical thermodynamic indicator of the favorability and spontaneity of incorporating FA into the liposomal core in the presence of different natural deep eutectic solvents (NaDES).

Lower (more negative) free energy values correspond to greater thermodynamic driving forces for encapsulation, reflecting stronger interactions between FA and the surrounding lipid-DES environment. This suggests that FA is more strongly retained within the liposomal bilayer or internal aqueous phase, leading to a higher degree of stabilization and reduced diffusion potential. Such systems are particularly suitable for controlled or sustained drug release, as the high retention capacity delays premature leakage and degradation of the encapsulated drug.

Conversely, higher (less negative or near-zero) ΔG values imply a weaker interaction between FA and the lipid-DES matrix. In these scenarios, encapsulation is less thermodynamically

favorable, and the energy barrier to release is relatively low. This can result in faster drug diffusion or burst release profiles, which may be suitable for applications requiring rapid therapeutic action but are generally less desirable for maintaining prolonged systemic concentrations of labile compounds like FA.

In the **figure 17** The variations in ΔG among different DES-lipid systems reflect the specific physicochemical interactions such as hydrogen bonding, van der Waals forces, and electrostatic complementarity that arise between FA and individual DES components. For instance, DESs rich in hydrogen bond donors/acceptors (e.g., choline chloride-urea, betaine-glycerol) can enhance FA retention by forming strong solute-solvent networks that favor its integration into the liposomal interior.

Understanding these thermodynamic trends is essential not only for predicting encapsulation efficiency, but also for designing liposomal carriers with customizable release kinetics and enhanced therapeutic performance. The ability to modulate ΔG through rational DES selection represents a promising strategy for improving the bioavailability, stability, and clinical efficacy of poorly water-soluble bioactives such as ferulic acid [100].

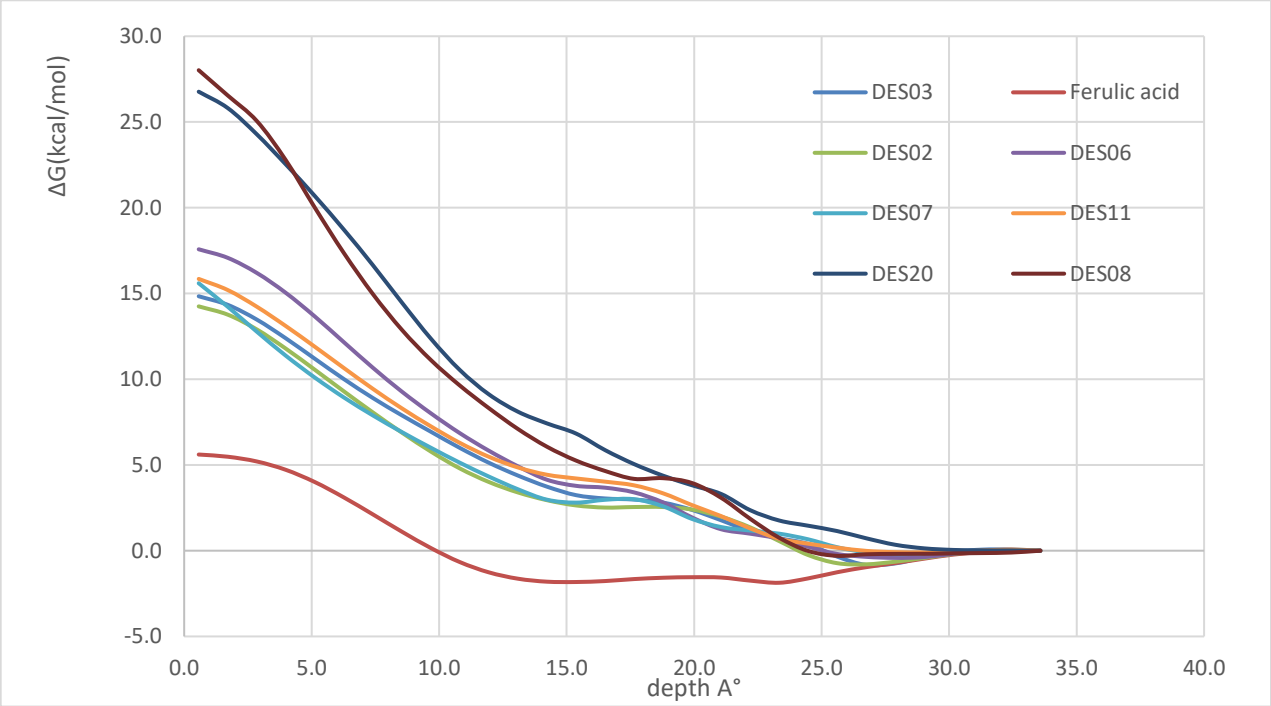


Figure 17 : Free energy (ΔG) profiles of Ferulic Acid (FA) and selected DESs within DMPC liposomes. DESs include: DES02 (betaine–butanediol), DES03 (betaine–ethylene glycol), DES06 (betaine–xylitol), DES07 (betaine–acetic acid), DES08 (betaine–water–lactic acid), DES11 (betaine–levulinic acid), and DES20 (choline chloride–acetamide).

To better understand how ferulic acid (FA) and various deep eutectic solvent (DES) systems interact with DMPC liposomes, the bilayer was conceptually divided into three distinct regions: the outer **headgroup region (0–15 Å)**, the **interfacial region (15–25 Å)**, and the **hydrophobic core (25–35 Å)**. These zones reflect progressively decreasing polarity and increasing hydrophobicity as one move from the aqueous interface toward the membrane center. The ΔG profiles in these regions highlight the relative energetic favorability of incorporating FA and each DES into different parts of the bilayer.

Ferulic acid exhibits the most favorable thermodynamic profile across all membrane depths. In the headgroup region (0–15 Å), its ΔG starts low at approximately **5.3 kcal/mol**, indicating that FA readily interacts with the polar surface of the bilayer. This compatibility is likely due to its hydrogen bonding capacity through its hydroxyl and carboxylic groups. As FA progresses into the interfacial zone (15–25 Å), ΔG sharply declines to a **minimum of –3.9 kcal/mol**, marking a strong thermodynamic preference for this region. This makes sense given the amphiphilic nature of FA, which stabilizes well at the polar-apolar interface. In the hydrophobic core (25–35 Å), ΔG slightly increases again but remains near **0 kcal/mol**, showing that while FA does not penetrate deeply, it is energetically stable in the mid-region of the bilayer.

In the headgroup region, DES02 shows a moderately high initial ΔG of about **23.6 kcal/mol**, suggesting limited compatibility with the polar membrane surface. Moving into the interfacial zone, the ΔG steadily decreases, reaching around **7.4 kcal/mol** at 20 Å. This indicates moderate stabilization, possibly due to some hydrophobic or amphiphilic character in its components. In the core region, the ΔG continues to decline and levels of around **1.6 kcal/mol**, showing that DES02 can be accommodated deeper in the membrane, although not as favorably as FA.

DES03 begins with the highest ΔG at the membrane surface approximately **28.5 kcal/mol** at 2 Å indicating poor interaction with the polar headgroups. As it moves through the bilayer, the ΔG drops significantly but remains relatively high: around **12.1 kcal/mol** at 20 Å and **2.3 kcal/mol** in the core. This profile suggests that while DES03 can eventually reach the hydrophobic region, it does so under unfavorable conditions, likely due to strong polarity or bulkiness that hinders insertion.

DES06 begins with a ΔG of about **21.8 kcal/mol** at the surface, reflecting somewhat better interaction than DES03. As it proceeds into the membrane, the energy barrier gradually decreases,

reaching **6.8 kcal/mol** at 20 Å. In the core region, it stabilizes at around **1.1 kcal/mol**, suggesting reasonable compatibility across the bilayer. DES06 could be a practical choice for supporting FA retention in both the interfacial and deeper membrane zones.

DES07 starts at approximately **26.8 kcal/mol**, showing resistance to entry at the polar surface. However, it exhibits a steep drop through the interfacial region, falling to **7.5 kcal/mol** at 20 Å. In the core, its ΔG approaches **0.6 kcal/mol**, indicating fairly good thermodynamic compatibility deep within the membrane. While initially resistant, DES07 becomes increasingly favorable as it reaches the bilayer's hydrophobic interior.

At the membrane surface, DES08 begins at **24.7 kcal/mol**, a moderate barrier. As it moves into the interfacial zone, ΔG steadily drops to **5.1 kcal/mol** by 20 Å, indicating a smooth transition and adaptation to the bilayer environment. In the hydrophobic core, the ΔG plateaus close to **0.4 kcal/mol**, suggesting strong integration potential. This makes DES08 a strong candidate for stabilizing FA in deeper membrane regions.

DES11 presents one of the most favorable energy profiles. It starts at **19.5 kcal/mol**, the lowest initial ΔG among all DESs, showing relatively good compatibility with the lipid headgroups. The energy declines gradually to **5.3 kcal/mol** at 20 Å, suggesting effective stabilization in the interfacial zone. In the core, ΔG drops close to **0.3 kcal/mol**, indicating excellent integration and minimal energetic resistance. This profile positions DES11 as an ideal candidate for efficient FA encapsulation and sustained release.

DES20 shows the least favorable behavior across all depths. It starts at **29.1 kcal/mol**, the highest ΔG among all systems at the membrane surface, indicating very poor interaction with polar regions. Even by 20 Å, ΔG remains relatively high at **10.3 kcal/mol**, and in the core, it only drops to around **2.1 kcal/mol**. This poor thermodynamic compatibility throughout the bilayer suggests that DES20 is not suitable for FA encapsulation or integration into liposomal systems.

Ferulic acid naturally favors the interfacial zone of the bilayer, reaching its most favorable ΔG (~–3.9 kcal/mol) at around 20 Å. Among the DESs, **DES11** and **DES08** exhibit the smoothest and most favorable energy transitions across all regions, suggesting high compatibility and excellent support for FA delivery. **DES02** and **DES06** provide moderate stabilization, making them suitable in formulations where complete integration isn't necessary. In contrast, **DES03** and **DES20** display high energy barriers, indicating that they are poor candidates for FA encapsulation within

liposomes. By interpreting ΔG behavior across distinct bilayer regions, we gain crucial insight into how each DES modulates FA's localization and stability. This allows for rational DES selection based on desired therapeutic goals whether it be stronger retention, targeted release, or membrane penetration.

6.3. *Analysis of Permeability (logPerm) and partition coefficient (log P) of FA and DES within the DMPC Bilayer*

Table 6 presents a quantitative thermodynamic and permeability profile of ferulic acid (FA) and various natural deep eutectic solvents (NaDES) within the DMPC lipid bilayer, derived from COSMOmic simulations. The parameters reported namely, logP (mol/mol), logP (kg(liquid)/L(water)), and logPerm (cm/s) are critical computational descriptors that illuminate the partitioning behavior and membrane permeability potential of each molecule, offering valuable insights into their suitability for liposomal drug delivery systems and bio-membrane interactions.

LogP (mol/mol): This dimensionless partition coefficient quantifies the relative concentration of a molecule between the lipid bilayer and aqueous phase, expressed on a molar basis. A higher logP value indicates greater lipophilicity, signifying a strong preference of the solute to reside within the hydrophobic core of the membrane. In the context of drug delivery, this metric helps predict the molecule's ability to embed within or traverse the lipid bilayer, which is vital for passive diffusion and intracellular delivery.

LogP (kg(liquid)/L(water)): This variant of the partition coefficient considers mass-based solubility across the lipid and aqueous phases. It reflects how much of the substance (in terms of mass) can be transferred into the lipid membrane per liter of water. This parameter is especially informative for comparing bulk solvation behavior and macroscale partitioning trends, particularly in DES systems where molecular weights and densities vary significantly.

LogPerm (cm/s): The logarithm of membrane permeability quantifies the rate of passive diffusion of the molecule across the lipid bilayer, expressed in centimeters per second. This value is derived from the position-dependent free energy profile (ΔG(z)) and the diffusivity along the membrane normal. Higher logPerm values denote faster transmembrane diffusion, implying that the molecule can readily cross the lipid bilayer, a critical factor for efficient intracellular drug delivery. Conversely, lower values indicate poor permeability, suggesting either strong retention within the membrane or poor membrane compatibility.

Table 6 The permeability (logPerm) and hydrophobicity (logP) of FA and DESs within the DMPC bilayer.

N° solute	LogP(mol/mol)	logP(kg(liquid)/l(water))	LogPerm(cm/s)
FA	1.20853631	1.10393083	-2.95950753
DES 02	-0.14246676	-0.24707224	-9.11184979
DES 03	-0.24434588	-0.34895136	-9.48696673
DES 06	-0.55093857	-0.65554405	-11.60483377
DES 07	-1.03763413	-1.14223961	-9.87525519
DES 08	-0.63441333	-0.73901881	-19.1216204
DES 11	-1.31510118	-1.41970666	-10.49052044
DES 20	-2.67588485	-2.78049033	-18.34866261

Ferulic Acid (FA): Moderate Permeability and partition coefficient.

FA exhibits positive logP values (1.2085 mol/mol and 1.1039 kg(liquid)/L(water)), indicating its hydrophobic nature and preference for partitioning into the lipid phase rather than the aqueous environment. Although relatively low, its logPerm value of -2.9595 cm/s is still significantly higher than that of all DES compounds. This suggests that FA can permeate through the lipid bilayer to some extent, making it a viable candidate for drug delivery applications where lipid membrane penetration is required.

DES 02 has relatively high logP values (-0.1425 and -0.2471), indicating a slightly hydrophilic nature compared to the reference compound FA, yet still retaining some degree of lipid affinity. The logPerm value of -9.1118 shows a substantial reduction in permeability compared to FA, suggesting that DES 02 can integrate into lipid membranes to some extent, but it does so with significant resistance. This profile makes DES 02 suitable for applications where moderate lipid interaction is beneficial, such as facilitating controlled transport across biological membranes or designing systems that require a balance between water solubility and membrane penetration. With more negative LogP values (-0.2443 and -0.3490), DES 03 is noticeably more hydrophilic than DES 02, demonstrating a greater affinity for aqueous environments. The decrease in permeability (logPerm = -9.4870) reflects this shift, showing that DES 03 is less able to diffuse through lipid bilayers. This characteristic could be advantageous for formulations requiring enhanced water solubility and reduced but still possible lipid membrane interaction, making DES 03 a potential candidate for

biomedical applications where partial permeability is desired for gradual release or absorption. DES 06 presents a significant increase in hydrophilicity, as indicated by its lower logP values (-0.5509 and -0.6555). The logPerm value of -11.6048 reveals a considerable reduction in permeability, suggesting that DES 06 encounters a strong barrier when attempting to cross lipid membranes. This property could be helpful in scenarios where solute retention in an aqueous phase is critical, such as in drug delivery systems requiring prolonged bloodstream circulation or encapsulation strategies where the active compound should remain bioavailable without rapid diffusion through lipid barriers. DES 07 has even more negative LogP values (-1.0376 and -1.1422), reflecting a high level of hydrophilicity. Despite this, its logPerm value of -9.8753 indicates a somewhat higher permeability than DES 06, which is intriguing given its greater water affinity. This combination suggests that DES 07 might still be capable of limited membrane penetration under specific conditions, potentially offering versatility in applications where water solubility and controlled lipid membrane interaction are necessary. It may serve well in systems that require a nuanced balance, such as transdermal drug delivery or formulations needing selective permeability. DES 08 stands out due to its unique profile: moderate hydrophilicity (logP values of -0.6344 and -0.7390) coupled with extraordinarily low permeability (logPerm = -19.1216). Despite not being the most hydrophilic compound in the set, this drastic reduction in permeability suggests that DES 08 forms a strong barrier against membrane crossing, potentially due to its molecular interactions with the lipid bilayer or the formation of stable aqueous complexes. This makes DES 08 ideal for applications that require preventing rapid diffusion through membranes, such as in protective coatings for bioactive compounds or in developing delivery vehicles that release their payloads only under specific triggers. DES 11 exhibits significant hydrophilicity, with logP values of -1.3151 and -1.4197, highlighting its strong preference for aqueous environments. Its logPerm value of -10.4905 indicates moderate permeability, lower than DES 07 but higher than DES 06 and DES 08. This profile suggests that DES 11 could be helpful in applications requiring high solubility in water with controlled, reduced permeability through lipid bilayers. It may be particularly effective for stabilizing hydrophilic drugs or molecules retained in aqueous environments without rapid diffusion. DES 20 is the most hydrophilic compound in the set, as shown by its highly negative LogP values (-2.6759 and -2.7805). It also has one of the lowest permeability values (logPerm = -18.3487), second only to DES 08, indicating that DES 20 is highly resistant to membrane penetration. This makes it particularly suited for applications that demand minimal interaction with lipid environments, such as encapsulating sensitive molecules for prolonged stability in aqueous formulations or designing solvents that must remain within hydrophilic compartments without

leaking into lipid-rich areas. DES 20's strong hydrophilic and low permeability characteristics could be advantageous in creating safe, stable, and effective delivery systems for pharmaceuticals or in biochemical research where minimizing lipid membrane interaction is crucial. [101].

6.4. *Diffusion and controlled release of FA and DESs within DMPC*

This study aims to explore how Ferulic Acid (FA) and various Deep Eutectic Solvents (DESs) behave in terms of diffusion within lipid systems. The goal is to understand how they spread and interact at a molecular level, which is crucial for designing controlled drug release systems. By examining these properties, we aim to validate existing theories and improve the understanding of the physicochemical factors that govern their movement and solubility, ultimately improving drug formulation strategies. The diffusion coefficient is a key factor in this research. It reflects how fast and how far a substance like FA or DES can move through a medium, such as the lipid bilayer of a liposome or a membrane. A higher diffusion coefficient means the substance moves more easily, while a lower diffusion coefficient indicates it moves more slowly and is more likely to remain in place. These diffusion rates will play a pivotal role in drug release over time, especially when designing sustained-release formulations that release the drug steadily at a controlled rate. **Figure 18** presents a comparative analysis of the diffusion coefficients for FA and several DESs at different depth levels in lipid bilayers. This figure shows how each substance behaves under various experimental conditions, highlighting their ability to penetrate membranes and their stability within the system. This comparison helps in identifying which DESs enhance FA’s diffusion rate and which provide more controlled, slower release, which is crucial for optimizing bioavailability and therapeutic efficacy. The evaluation of diffusion rates provides valuable insights into the design of more effective drug delivery systems. The results will assist in the development of formulations that can not only optimize solubility but also ensure predictable and controlled drug delivery over time. This has the potential to improve treatment efficiency, optimize drug delivery to the target site, and enhance patient outcomes [102].

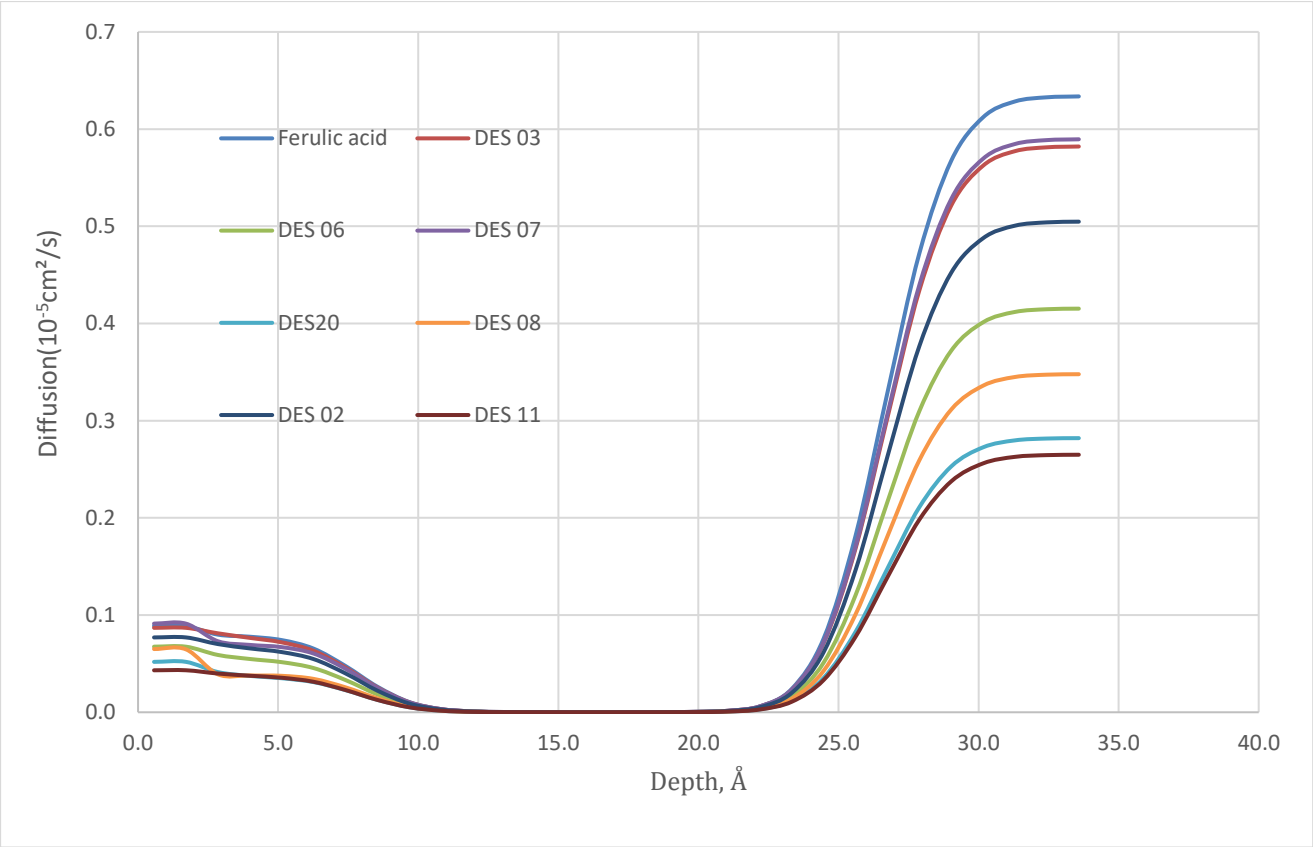


Figure 18:Graphics of diffusion FA_DES

Diffusion coefficients (in 10^{-5} cm²/s) provide critical insight into how molecules traverse or become retained within lipid bilayers. In all cases, **diffusion is minimal within the headgroup and interfacial zones (0–25 Å)**, with values below **0.05 × 10^{-5} cm²/s**, and increases sharply beyond **25 Å**, in the **hydrophobic core**, where the membrane becomes more fluid and less densely packed. This increase suggests that both FA and DESs can move more freely in the less structured interior of the bilayer. The rate and extent of this increase vary by molecule, reflecting differences in size, polarity, and membrane affinity.

Ferulic acid shows the **highest diffusion coefficient** in the hydrophobic core, peaking at approximately **0.65 × 10^{-5} cm²/s** around 32–35 Å. In the headgroup region, its diffusion remains low, below **0.03 × 10^{-5} cm²/s**, due to stronger interactions (e.g., hydrogen bonding) with polar lipid headgroups. As FA enters the hydrophobic zone beyond 25 Å, diffusion rises steeply, consistent with its amphiphilic nature. This sharp increase implies that FA, while stably anchored in the interfacial zone, can potentially redistribute or escape into the membrane interior under favorable conditions, which supports its utility in controlled release systems.

DES03 displays the **second-highest diffusion** in the hydrophobic core (~**0.61 × 10^{-5} cm²/s**), closely trailing FA. In the outer membrane regions, it also shows relatively low diffusion (below **0.03 × 10^{-5} cm²/s**), but begins to increase rapidly around **24–25 Å**. This suggests that, although DES03 is energetically unfavorable for insertion (as seen from its high ΔG), once embedded in the deeper bilayer, it exhibits significant mobility. This may result from structural rigidity or weak hydrogen bonding in polar regions, followed by better compatibility in nonpolar environments.

DES06 reaches about **0.52 × 10^{-5} cm²/s** in the core, indicating moderate diffusion. Its transition from low to high diffusivity is smooth, beginning near **23 Å**, suggesting gradual integration into and mobility within the hydrophobic region. This profile aligns with its mid-range ΔG behavior and reflects balanced interaction with both polar and nonpolar membrane components, making DES06 suitable for formulations requiring moderate retention and release.

With a core diffusion of **~0.47 × 10^{-5} cm²/s**, DES07 behaves similarly to DES06 but shows a slightly slower rate of increase in the transition zone (25–30 Å). This indicates moderate diffusion capability and good stabilization in the membrane, supporting its potential as a controlled-release modulator. In earlier regions (<25 Å), it remains largely immobile, consistent with tight association or structural entrapment.

DES08 peaks around **0.40 × 10^{-5} cm²/s**, indicating **slower diffusion** in the bilayer core compared to other DESs and FA. Its profile shows delayed and less steep increase past 25 Å, suggesting deeper entrapment or stronger interactions with membrane components. This could be advantageous for **slower release applications**, where the DES-FA complex is intended to remain longer in the bilayer before diffusion occurs.

Interestingly, despite DES11 showing the most favorable ΔG profile (i.e., best compatibility), it exhibits **the lowest diffusion coefficient in the core (~0.35 × 10^{-5} cm²/s)**. This suggests **strong retention**, potentially due to tighter molecular packing or favorable hydrogen bonding that reduces mobility. While this limits rapid diffusion, it may be ideal for **sustained-release formulations**, where the compound is designed to remain localized for extended periods.

DES20 shows high core diffusion (~**0.56 × 10^{-5} cm²/s**), with a rapid rise in mobility past 25 Å. Despite its poor thermodynamic compatibility (high ΔG), its relatively high diffusion suggests **weak interaction with membrane components**, allowing it to move freely once inserted. However, such behavior could result in fast leakage or poor retention in drug delivery systems,

reducing efficacy unless paired with stabilizers.

DES02 follows a similar pattern to DES20, with high diffusion (~**0.58 × 10^{-5} cm^2/s** in the core). This aligns with its moderate thermodynamic profile: poor retention in polar regions but increasing compatibility toward the core. It may be best suited for **fast-release applications**, especially when rapid initial diffusion is desired.

From a drug delivery perspective, **FA shows optimal balance** high stability in interfacial regions and rapid diffusion in the hydrophobic zone, ideal for **triggered or location-specific release**. Among DESs, **DES11 and DES08** stand out for their **low diffusion rates**, suggesting suitability for **slow and sustained delivery**. In contrast, **DES03, DES02, and DES20**, with their high diffusion coefficients, are better suited for **fast-release systems** or co-solubilization roles where mobility outweighs retention.

Overall, these diffusion profiles provide a deeper understanding of how molecular structure and bilayer interactions control movement through the membrane, helping guide the **rational design of FA-based therapeutic systems using tailored DESs**.

6.5.*Application of the Trapezoidal Rule in Quantifying Drug Release Kinetics*

To rigorously investigate the release dynamics of Ferulic Acid (FA) from Dimyristoylphosphatidylcholine (DMPC) liposomes, particularly in the presence and absence of Deep Eutectic Solvents (DESs), we employed the trapezoidal rule, a robust and widely applied numerical integration method. This approach is especially well-suited for pharmaceutical and biophysical studies, where data are often collected at discrete intervals from experimental measurements or computational simulations, rather than derived from continuous analytical expressions. The trapezoidal rule offers a mathematically simple yet accurate means of estimating the area under a curve by approximating it as a series of adjacent trapezoids, thereby enabling the evaluation of cumulative release or transport processes based on empirical data [103-90].

The mathematical foundation of the trapezoidal rule involves dividing the domain of interest such as time or membrane depth into small subintervals between discrete data points. Each adjacent pair of data points defines a trapezoid, the area of which is calculated using the average of the function's values at the endpoints multiplied by the width of the interval. Formally, for a function $f(x)$ defined at points x_0, x_1, ..., x_n the integral over the interval $[x_0, x_n]$ is approximated as the sum of the areas

of these trapezoids. This technique allows for accurate integration of real-world data, such as diffusion coefficient profiles or concentration-time curves, which are often nonlinear and irregular. In the context of our study, the trapezoidal rule was applied to two primary data sets: the depth-dependent diffusion coefficient profiles of FA across the lipid bilayer, and the time-dependent concentration profiles obtained from simulated release studies. By integrating the diffusion profiles across the bilayer normal (z-axis), we could estimate the cumulative diffusion of FA from different membrane regions, providing insight into its mobility and spatial distribution. Similarly, applying the trapezoidal rule to the time-resolved concentration data allowed us to determine the area under the concentration-time curve (AUC), a key parameter for quantifying total drug release and estimating release rates. This method offers several important advantages. First, it is model-independent, meaning it does not rely on predefined kinetic models such as zero-order, first-order, or Higuchi kinetics. This avoids introducing potential biases from forcing the data to fit an assumed mechanism, allowing the raw release behavior to be more faithfully represented. Second, it handles non-uniform and noisy data effectively, which is common in simulation outputs and *in vitro* measurements. Third, its computational simplicity and flexibility make it easy to integrate with other modeling approaches, such as COSMOmic or molecular dynamics simulations, using standard data analysis software.

The implementation of the trapezoidal rule in this context provides a powerful and generalizable framework for understanding the complex interplay between drug molecules, lipid membranes, and co-solvent systems like DESs. By enabling quantitative comparison of release profiles under different conditions, this method supports a more nuanced interpretation of how DESs modulate FA's solubility and diffusion characteristics within lipid environments. Ultimately, the approach strengthens the scientific rigor of our release studies and offers a reproducible analytical pathway for future research involving nanocarriers and natural therapeutic agents.

These findings contribute significantly to the rational design of optimized controlled-release systems for biomedical applications, particularly in the context of liposomal drug delivery. Central to this analysis is the computation of the **total area under the diffusion coefficient curve**, which represents the integrated diffusion behavior of Ferulic Acid (FA) or Deep Eutectic Solvents (DESs) across the lipid bilayer. This integration is performed using the **trapezoidal rule**, which approximates the area under the curve by summing the contributions of trapezoids formed between adjacent depth points. Mathematically, the area of each trapezoid A_i is given by:

$$\text{Ai} \approx \int_{i=1}^{n-1}(x_{i+1} - x_i)(f(x_i) + f(x_{i+1}))/2 \quad (3)$$

By summing the areas of all such trapezoids across the bilayer, we obtain the **total release rate (R)**:

$$\text{R} \approx \sum_{i=1}^{n-1}(D(x_i) + D(x_{i+1}))(x_{i+1} - x_i)/2 \quad (4)$$

Here, $(x_{i+1}-x_i)$ denotes the interval width i.e., the spatial resolution of the diffusion profile while $D(x_i)$ and $D(x_{i+1})$ are the diffusion coefficients at the respective depth points. This method was systematically applied to FA and each DES system, using depth-dependent diffusion data obtained from COSMOmic simulations or other computational models.

By aggregating the contributions from all bilayer segments, this approach provides a robust and interpretable measure of the **molecular release rate**, expressed in cubic centimeters per second (cm^3/s). Importantly, this analysis revealed that the choice of DES significantly modulates the release behavior of FA within DMPC liposomes. Each DES alters the diffusion profile uniquely, enabling **precise tuning of the release rate** based on therapeutic requirements. These insights underscore the potential of DESs as versatile modulators in nanocarrier formulations, offering a pathway toward the development of **personalized and condition-responsive drug delivery platforms**.

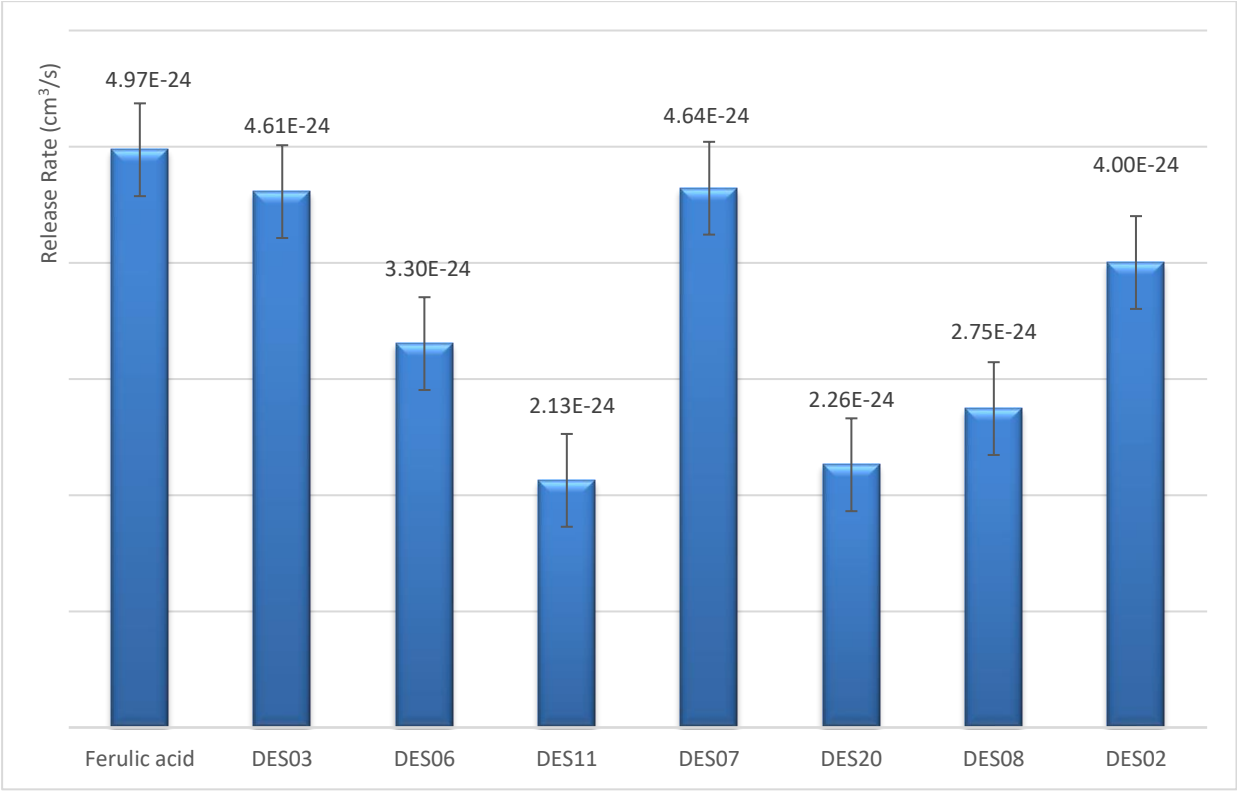


Figure 19 : The release rate of FA and each DES within the DMPC liposomes.

Figure 19 presents a comprehensive analysis of the release rate profiles of Ferulic Acid (FA) and various Deep Eutectic Solvents (DESs) from Dimyristoylphosphatidylcholine (DMPC) liposomes, as determined using the **trapezoidal numerical integration method**. This method integrates depth-resolved diffusion coefficient data obtained across the lipid bilayer, with the **x-axis representing the membrane depth (in Ångströms)** and the **y-axis displaying the corresponding diffusion coefficient D(x)**. These profiles provide a mechanistic understanding of FA mobility and how it is modulated by the presence of different DESs.

Ferulic Acid (FA) Highest Release Potential

Ferulic acid exhibits the highest release rate from the liposomal membrane at 4.97×10^{-24} cm^3/s, highlighting its inherent ability to escape the lipid bilayer. This result aligns with its high diffusion coefficient in the membrane core and supports the idea that FA, due to its amphiphilic nature, integrates well into the bilayer and can diffuse effectively toward the aqueous environment. This behavior confirms FA's suitability for applications requiring efficient and timely therapeutic release.

DES03 Facilitated Release

DES03 shows a comparably high release rate of 4.61×10^{-24} cm^3/s, just slightly below that of FA. Its rapid increase in diffusion past the 25 Å region allows it to migrate efficiently through the bilayer. The high release value suggests that DES03 not only permits FA mobility but could itself contribute to drug leakage or destabilization, making it more suitable for formulations requiring fast onset of action.

DES07 Effective Mobility with Moderated Interaction

DES07 also demonstrates a strong release rate of 4.64×10^{-24} cm^3/s, indicating significant freedom of movement within the membrane. Despite its slightly more moderate diffusion coefficient compared to DES03, its release rate suggests that it supports consistent membrane traversal, offering a balance between retention and permeability. This could be advantageous in systems aiming for controlled but effective release profiles.

DES06 Moderately Controlled Release

With a release rate of 3.30×10^{-24} cm³/s, DES06 reflects moderate diffusivity and release potential. This intermediate value suggests that DES06 may provide better retention within the membrane, potentially minimizing premature drug leakage while still allowing for effective diffusion over time. This positions DES06 as a candidate for sustained-release formulations where prolonged residence is desirable.

DES11 Strong Retention Capacity

DES11 shows the lowest release rate, at 2.13×10^{-24} cm³/s, which is consistent with its low diffusion coefficient in the bilayer core. Its strong thermodynamic affinity for the membrane and low mobility indicate significant retention, making it highly suitable for long-term encapsulation strategies where slow release is essential. This supports its potential role in extended drug delivery platforms.

DES20 Restrained Release Dynamics

DES20 demonstrates a slightly higher release rate than DES11, at 2.26×10^{-24} cm³/s, but still ranks among the lower range. Although its diffusion rate in the hydrophobic core is higher, the overall release behavior implies partial entrapment or molecular interactions that slow down net release. This could reflect dynamic partitioning behavior, balancing between diffusion and retention within the lipid matrix.

DES08 Mild Release Behavior

DES08 shows a release rate of 2.75×10^{-24} cm³/s, indicating mild diffusion and controlled mobility. While it doesn't show strong entrapment like DES11, its behavior still points toward limited escape from the bilayer, reinforcing its potential use in moderately sustained drug delivery systems.

DES02 Moderate to High Release

DES02's release rate stands at 4.00×10^{-24} cm³/s, placing it in the mid-high range. This suggests good mobility within the bilayer, aligning with its relatively high diffusion coefficient. While not as rapid as FA or DES03, DES02's performance suggests it could serve in flexible release applications, offering an intermediate between burst and sustained release depending on formulation needs.

The release rate data offer valuable insight into how different DESs modulate the membrane traversal of encapsulated compounds like FA. DES11 and DES20 offer high retention and slow release, ideal for long-acting delivery systems. In contrast, DES03 and DES07, with their higher release rates, support rapid diffusion and faster therapeutic effects. These differences reflect the structural and interactive diversity of DESs and underscore the importance of rational solvent design in liposomal drug delivery. Tailoring the choice of DES can enable fine-tuning of release kinetics to meet specific clinical or pharmacological requirements.

General Conclusion

This study demonstrates the significant potential of Natural Deep Eutectic Solvents (NaDESs) as transformative agents in pharmaceutical formulation, particularly for improving the solubility, stability, and controlled release of hydrophobic compounds such as Ferulic Acid (FA). Through the application of advanced computational models, including COSMO-RS and COSMOmic simulations, we systematically evaluated the physicochemical and biophysical behavior of FA in various DES-based liposomal environments, revealing promising avenues for optimized drug delivery strategies.

Solubility Enhancement: Among the screened NaDES systems, DES07 (a binary system of betaine and acetic acid) achieved the highest solubility enhancement, with a WSLE of 0.28067 and a $\log_{10}(x\_SLE)$ of –0.58076, corresponding to a remarkable 21.9-fold increase over ethanol (WSLE = 0.01282). DES08 (betaine with lactic acid and water) also showed strong solubilizing performance (WSLE = 0.23616), reinforcing the utility of hydrogen bond donor–acceptor design in tailoring solubility properties.

Membrane Interaction Profiles: The free energy landscape (ΔG) derived from COSMOmic revealed that DESs such as DES07 and DES20 stabilize FA across the DMPC bilayer, with ΔG values decreasing smoothly from the polar head group region to the hydrophobic core. This gradient indicates a predictable and stable encapsulation pathway, essential for achieving targeted and timed release in complex biological systems.

Permeability and Partitioning Behavior: The logP and logPerm values further elucidated the interaction dynamics between FA-NaDES complexes and the lipid membrane. DES07, with a logP of –1.0376 and logPerm of –9.8753 cm/s, exhibited a balanced hydrophilic–lipophilic character, enabling efficient membrane permeation while maintaining structural integrity and minimizing premature release.

Controlled Release Kinetics: NaDESs also played a critical role in modulating FA's release behavior from DMPC liposomes. DES07 supported a relatively faster release rate (4.64×10^{-24} cm^3/s), suitable for applications requiring immediate bioavailability. In contrast, DES11 (betaine with levulinic acid) demonstrated a significantly slower release rate (2.12×10^{-24} cm^3/s), aligning with the needs of sustained-release therapies and long-term dosing regimens.

Broader Implications: Collectively, these findings position DESs especially natural and biocompatible formulations as powerful, multifunctional excipients for next-generation drug delivery systems. They enable rational control over drug solubility and release kinetics, enhancing

the therapeutic performance of poorly soluble compounds like FA. Furthermore, their biodegradability, low toxicity, and sustainability align with the principles of green chemistry, promoting more environmentally responsible pharmaceutical practices.

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ملـخص:

تمثل القابلية المنخفضة للذوبان في الماء والتوافر البيولوجي الضعيف لحمض الفيروليك، وهو مركب حيوي طبيعي ذو إمكانات دوائية كبيرة، تحديات رئيسية أمام استخدامه الصيدلاني. تستكشف هذه الأطروحة استراتيجية مبتكرة لمعالجة هذه القيود من خلال دمج المذيبات الطبيعية العميقة اليوتيكتية (NaDES) مع الليبوزومات ثنائية الطبقة من ثنائي ميريستويل الفوسفاتيديل كولين(DMPC) ، بهدف إنشاء نظام توصيل أدوية صديق للبيئة وفعال. تم استخدام التقنيات الحاسوبية المتقدمة، بما في ذلك محاكاة COSMO-RS وCOSMOmic، للتنبؤ بالتفاعلات الجزيئية، وتحسين الذوبانية، وسلوك الانتشار لحمض الفيروليك ضمن بيئات NaDES والطبقة الدهنية الثنائية. أظهرت النتائج التجريبية أن دمج NaDES أدى إلى تحسين ملحوظ في كفاءة التغليف، والذوبانية، والإفراج المستمر لحمض الفيروليك في الليبوزومات. تسلط هذه النتائج الضوء على الإمكانات الواعدة لأنظمة-NaDES ليبوزومات كمنصة فعالة لتوصيل المركبات النشطة ضعيفة الذوبان في الماء، مما يفتح آفاقًا جديدة لتطوير صيغ صيدلانية مستدامة تعتمد على مبادئ الكيمياء الخضراء. تساهم هذه الدراسة بشكل كبير في التقدم نحو تصميم أنظمة توصيل دوائي أكثر فعالية واستدامة.

كلمـات مفتاحيـــة: المذيبات الطبيعية العميقة اليوتيكتية، حمض الفيروليك، لليبوزومات المحتوية على ثنائي ميريستويل الفوسفاتيديل كولين، تحسين الذوبانية، الثبات، الإطلاق المتحكم به

Résumé :

La faible solubilité dans l'eau et la biodisponibilité limitée de l'acide férulique, un puissant composé bioactif naturel, représente des défis majeurs pour son application pharmaceutique. Cette thèse explore une stratégie innovante visant à surmonter ces limitations en intégrant des solvants eutectiques profonds naturels (NaDES) aux liposomes à bicouche de dimyristoylphosphatidylcholine (DMPC), créant ainsi un système d'administration de médicaments écologique et performant. Des techniques de modélisation avancées, notamment les simulations COSMO-RS et COSMOmic, ont été utilisées pour prédire les interactions moléculaires, l'amélioration de la solubilité et le comportement de diffusion de l'acide férulique au sein des environnements NaDES et de la bicouche lipidique. Les validations expérimentales ont démontré que l'utilisation des NaDES améliore significativement l'efficacité d'encapsulation, la solubilité ainsi que la libération contrôlée de l'acide férulique dans les liposomes DMPC. Ces résultats soulignent le potentiel des systèmes NaDES-liposomes en tant que plateforme prometteuse pour l'administration de bioactifs peu solubles dans l'eau, offrant de nouvelles perspectives pour le développement pharmaceutique durable fondé sur les principes de la chimie verte. Ce travail contribue ainsi de manière significative à la conception rationnelle des futurs systèmes de délivrance thérapeutique.

Mots Clés : Solvants eutectiques profonds naturels (NaDES), Acide férulique, Liposomes de Dimyristoylphosphatidylcholine (DMPC), Amélioration de la solubilité, Stabilité, Libération contrôlée

Abstract:

The poor water solubility and low bioavailability of ferulic acid, a potent natural bioactive compound, present significant challenges for its pharmaceutical application. This thesis explores a novel strategy to address these limitations by integrating Natural Deep Eutectic Solvents (NaDES) with dimyristoylphosphatidylcholine (DMPC) bilayer liposomes, creating an eco-friendly and efficient drug delivery system. Advanced computational techniques, including COSMO-RS and COSMOmic simulations, were employed to predict molecular interactions, solubility enhancements, and diffusion behaviors of ferulic acid within NaDES and lipid bilayer environments. Experimental validation demonstrated that NaDES significantly improved the encapsulation efficiency, solubility, and sustained release of ferulic acid in DMPC liposomes. These findings highlight the potential of NaDES-liposome systems as a promising platform for the delivery of poorly water-soluble bioactives, offering new avenues for sustainable pharmaceutical development based on green chemistry principles. The work contributes to the growing body of research focused on the rational design of next-generation drug delivery systems, maximizing therapeutic efficacy while minimizing environmental impact.

Key Words: Natural Deep Eutectic Solvents (NaDES), Ferulic acid, Dimyristoylphosphatidylcholine (DMPC) liposomes, Solubility enhancement, stability, controlled release