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Liposomal Drug Delivery: Comparative Kinetics, Efficacy, and Applications in Targeted Therapeutics

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Abstract: During the Second World War, in order to reduce infections in soldiers' wounds, nurses had to inject the injured with multiple shots of penicillin per day because one single shot of penicillin only lasts a short period of time, but the lack of human resources prevented some of the wounded soldiers from receiving the dose of penicillin that they needed[1]. To reduce the need for human labor in penicillin intake, Romansky discovered that mixing penicillin with lipids would prolong the time in which penicillin has effect. This innovation saved a lot of people from infection at the time. Lipid-based drug carriers have been developed and innovated even more throughout the years.A few years ago, the COVID-19 pandemic has facilitated advancements in vaccination technologies, including the use authorization of mRNA vaccines encapsulated in lipid nanoparticles. Traditional drug delivery methods, such as oral intake, injection, and transdermal applications, usually face challenges like low accuracy, toxicity, and variable effectiveness. However, liposomes, discovered in the 1960s, emerged as a drug carrier that, due to their specific structure, allowed for prolonged and site-specific drug release. Liposomes can encapsulate drugs of different molecular qualities, allowing lipid-based drug carriers to have excellent performance in carrying both hydrophobic and hydrophilic drugs. This paper examines the composition of liposomes, the different factors of the lipid bilayers, and the release kinetics in drug delivery. Using a hybrid modeling approach of first-order kinetics and the Higuchi model, the study simulates drug release profiles. The liposomal formulation of drugs demonstrates the potential of lipid-based delivery systems in enhancing the efficacy while minimizing side effects of treatments.

Keywords: Liposome, Lipid based drug delivery, drug delivery.

1. Introduction

COVID-19 was first reported in 2019, the outbreak of it has caused a severe public health crisis across the world. Two vaccines consisting of mRNA encapsulated by lipid nanoparticles have been given emergency use authorization (EUA) by the US-FDA for COVID-19 treatment by 2022. (Wilson 2022)

Traditionally, drugs were delivered through inhalation, swallowing, by absorption through the skin, or by injection (NIH2022). Determined by the specific property of the drug itself and the condition of the patient, the drug delivery method would be chosen. However, there are many drawbacks of these methods of drug deliveries including but not limited to the uncontrolled drug's movement pathway, loss of drug to untargeted areas, and toxicity to healthy tissues that absorbed the drug

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(Hassan2019). The ideal drug delivery method would promote high efficiency, low toxicity, and accurate targeting.

In the early 1960s Bangham and his Colleagues observed that egg lecithin reacted with water, forming lipid vesicles. These intricate figures were first named smectic mesophases, then termed liposomes(Wagner2011). In the following years, liposomes have been studied and developed as drug carriers. Due to phospholipids' property of having a hydrophilic head and a hydrophilic tail, it is easy for them to self-assemble spontaneously into vesicles of phospholipid bilayers when mixed with aqueous solutions.

Liposomes come in a variety of sizes and shapes depending on the purpose of the liposome. Liposomes could be classified as either unilamellar vesicles or multilamellar vesicles depending on the number of layers the liposome has. Liposomes with only one layer can also be further classified into small unilamellar vesicles(SUV) with a diameter between 20-100nm, Large unilamellar vesicles (LUV) with a diameter greater than 100 nm, medium unilamellar vesicles (MUV), and Giant unilamellar vesicles (GUV) with a diameter larger than 1000 nm. Multilamellar vesicles, liposomes with multiple concentric layers, typically have a diameter greater than 400 nm (Smirnova 2015), and multivesicular vesicles, with multiple bilayers that are not concentric. (Mardešić 2023)Lipid nanoparticles are also carriers of drugs that are made of phospholipid. However, lipid nanoparticles may not have a complete phospholipid bilayer and instead may only have one layer. This allows lipid nanoparticles to be smaller in size compared to other liposomes.

Liposomes, as they were made of phospholipids, do not pose any threat to the human body as phospholipid is a critical component of cell membranes. Liposomes can carry drugs accurately to targeted areas by either fusing with the targeted cell membrane,(Ou 2022) or provide a stable drug release at the targeted area. Liposomes, by carrying drugs either within its aqueous core or in between its phospholipid bilayers, can release the carried drugs slowly by allowing the drugs to slowly leak through the liposomes' phospholipid bilayer. Unlike free drugs injected into one place, drugs carried in liposomes can be held in one place better, as the phospholipid bilayer fixes the drugs inside and prohibits it from flowing away from the targeted site. The slow and stable release of drugs has provided a possibility for long time local anesthesia and a solution for chronic pain. (Innocan Pharma Corporation 2024)

The FDA has approved a variety of liposomes for medical uses. Notable examples including liposomal Bupivacaine(FDA), Paclitaxel(FDA), and Irinotecan(FDA) . These approvals underscore the significant advancements that have been made in this area. Liposomes are continuously being studied and tested with different fabrication materials and drug loadings in order for liposomes to become useful in a wider range of healthcare treatments.

2. Overview

A major component of liposomes is the polar lipid. Lipids are composed of a "head" and a "tail". Lipids' tails are made of a chain of hydrocarbon single and, sometimes, double bonds. Due to this tail's property of being nonpolar, this side of the molecule is hydrophobic. The lipid "heads", however, could either be charged or not charged. A charged "head" structure would make a lipid polar and have a hydrophilic side in addition to a hydrophobic one[2]. Having such a structure allows polar lipids to self-assemble into spheres of lipid bilayers when placed into water or aqueous solutions. Sometimes, liposome membranes will contain a proportion of cholesterol to harden the membrane and making it more stable, as seen in Figure 1A.

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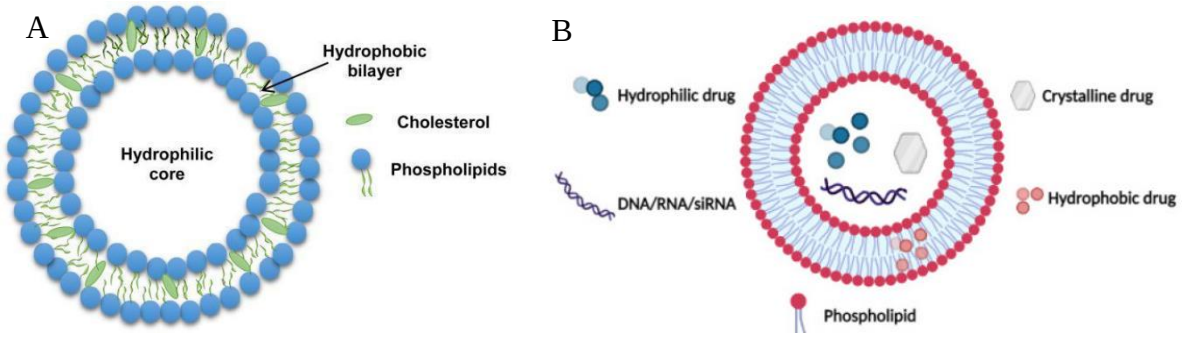

Figure 1: (A) Schematic representation of a liposome showing its phospholipid bilayer and cholesterol components [3]. The bilayer structure allows the liposome to encapsulate therapeutic agents effectively. (B) Liposomes can encapsulate both hydrophobic/lipophilic and hydrophilic/lipophobic drugs, making them versatile drug delivery systems [4]. Cholesterol and polar lipids are typically incorporated into the bilayer to enhance stability and maintain membrane integrity [5].

2.1. Saturated and Unsaturated

The hydrophobic “tails” of lipids are made of chains of hydrocarbon bonds. Due to the property of hydrocarbon bonds, the chain could consist of all single bonds, or a combination of single and double bonds. A lipid is saturated when the “tail” is made of single hydrocarbon bonds only and unsaturated when there is one or more double bonds present in the “tail”. Whether the polar lipid is saturated or not, it does not change the property of polar lipids of having a hydrophobic “tail” and a hydrophilic “head”, but the property of the lipid “tail” could demonstrate its impact in other places.

2.1.1. Saturated

Saturated lipids are lipids with only single bonds on their “tail” of hydrocarbon bonds. This allows the “tails” of saturated lipids to appear straight in molecular view. The different structure allows saturated lipids to obtain a higher phase change temperature and a more rigid layer that lowers the release rates as it forms lipid bilayers[6]. This could be beneficial when fabricating liposomes, as using saturated lipids in the liposome fabrication process could allow the liposomes produced to have a stable and slow release rate of drugs. However, this could also mean trouble as sometimes liposomes produced with only saturated lipids could have a layer so rigid that the drugs were barely released from the vesicles and delivered to targeted sites.

2.1.2. Unsaturated

Unsaturated lipids are lipids with one or more double bonds on their “tail” of hydrocarbon bonds. Unsaturated lipids, inturn have a bent “tail” in molecular view. Compared to saturated lipids, unsaturated lipids tend to have lower phase change temperature and a softer bilayer that offers fast release of drugs. (Nsairat 2022)Unsaturated lipids, therefore, could be very useful when trying to produce lipids with fast release rates. However, unsaturated lipids could also mean lower stability of liposomes fabricated with it and higher burst rates.

2.2. Charged lipids: Cationic and Anionic

Lipids could be categorized by their different “tails" , but they could also be categorized by their hydrophilic “heads". The hydrophilic head could be neutral, positively charged, or negatively charged. The property of the “head” would impact the performance of the liposome fabricated in various ways.

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2.2.1. Neutral

Neutral means that the lipid's hydrophilic "head" has little or no charge. Neutral liposomes have a longer circulation time along with lower cytotoxicity compared to cationic liposomes as the lack of charge prohibits neutral liposomes from interacting with negatively charged proteins in serum and blood. Neutral liposomes are also found more advantageous in applying active targeting strategies since neutral liposomes have nonspecific electrostatic interactions present. The lack of charge in neutral liposomes prevents it from initiating interactions between other unwanted materials, therefore making it a relatively stable liposome.

2.2.2. Cationic

Cationic means that the lipid has a positive charge on the hydrophilic end. Cationic liposomes are advantaged in delivering nucleic acid. As nucleic acids can only be effective if it was delivered completely into the cytoplasm. This forces the liposomes that carry the nucleic acid to be able to perform endocytosis with the cell membrane. The positive charges on liposomes fabricated with positive lipids help the liposome with cell binding, endocytosis, and the fusion of anionic endosomal membranes, since opposite charges attract and cell membranes are negatively charged. Moreover, cationic liposomes have higher DNA entrapment efficiency and higher efficiency in protecting DNA in the cytoplasm during nuclear entry. However, Cationic lipids have the potential to disrupt the anionic cellular membrane, which could result in cytotoxicity, an unfavorable result[7].

2.2.3. Anionic

Anionic means that the lipid has a negative charge on its hydrophilic "head". Unlike Cationic liposomes, anionic liposomes are rarely used in gene therapies since the negative charge of the liposomes would likely repel the negative charge of cell membrane, causing a failure to deliver nucleic acid into the cell. Anionic liposomes, compared to neutral and anionic liposomes, are more stable in suspension and plasma media as they cause fewer aggregations. Compared to cationic liposomes, anionic lipids also showed lower cytotoxicity, which is mainly due to anionic lipids' similar quality to natural cell membranes. (Tseu2023)

2.3. Drug properties

Liposomes are made for carrying drugs, and depending on the property of the drugs, the release rate, the encapsulation efficiency, and a lot of other properties may change about the delivery.

2.3.1. Hydrophobic/Lipophilic

Hydrophobic drugs, like Doxorubicin, paclitaxel, vitamin D, and others, can be difficult to deliver due to its chemical nature of avoiding aqueous environments, making them poorly soluble in water. This means that the drug cannot be carried within the aqueous core of liposomes. Lipophilic means that the drug can be dissolved within lipids. Many drugs are hydrophobic and lipophilic at the same time, including Doxorubicin, paclitaxel, and vitamin D. Both hydrophobic and lipophilic drugs have a higher affinity for lipids than they have water. Therefore, hydrophobic drugs and lipophilic drugs can be loaded with the lipid that makes the liposome.

For drugs that are hydrophobic or lipophilic, they could be loaded in between the membranes of the liposomes. Since these drugs cannot be dissolved in water and form aqueous solutions, these drugs would typically be added into the lipid with organic solutions during the forming of lipid thin films. Due to this way of loading the drugs. The encapsulation efficiency of the drug is controlled by the drug's solubility with the polar lipids. In this way, an encapsulation efficiency of 100% can sometimes

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be achieved. (Zheng 2022)The high encapsulation efficiency ensures that a maximum amount of the drug is incorporated into the liposomes.

2.3.1.1. Steroid

Steroids are effective drugs used to treat a variety of diseases and illnesses. However, steroids could result in severe side effects in chronic use when the drug starts interacting with non targeted tissues[8]. By loading steroids in liposomes, however, the targeting of drugs can be much more accurate. The semipermeable nature of lipid bilayers will slow the diffusion of Steroids while the structure of lipids allows the liposomes to be held on to the specific target site with the steroids, providing an accurate and slow release of steroids. Steroids are lipids, and they also have similar properties as the polar lipids used to fabricate liposomes. Lipids can load hydrophobic molecules in their lipid bilayers while loading hydrophilic drugs in their aqueous core. Considering the property of steroids, this means that steroids are hydrophobic but lipophilic, making steroids easily loaded in liposome bilayers.

2.3.2. Hydrophilic/Lipophobic

Drugs that are hydrophilic are able to dissolve in water and form aqueous solutions.

Lipophobic drugs are drugs that do not dissolve in lipids, and therefore, are not able to dissolve in the lipid bilayers. Both hydrophilic drugs and lipophobic drugs can be loaded aqueously.

Drugs that are hydrophilic or lipophobic can be loaded within the aqueous cores of liposomes. This kind of drug would typically be dissolved in aqueous solutions, then added into the polar lipid film. As the lipids self-assemble into bilayer structures, they encapsulate a portion of the aqueous solution. The drug will be encapsulated along with the aqueous solution as the polar lipids form vesicles. However, the encapsulation efficiency of the drugs would be limited to the volume of solutions trapped within the liposomes. Since the liposomal structure cannot capture all of the added solution, the encapsulation efficiency of hydrophilic and lipophobic drugs usually ranges from 10% to 30%[9]. This limitation means that a significant portion of the drug may remain unencapsulated, necessitating further steps to remove or recycle the free drug such as dialysis.

2.3.3. Protein

Compared to drugs that are not organic macromolecules, proteins are much more susceptible to losing function to changes in the environment. For example, Proteins can undergo denaturation, or the unfolding of the protein structure causing the protein to lose its function, due to changes in pH values, high temperature, electricity, enzymes and proteases, or others. Denaturation by enzymes would be the most likely reason why a protein experiences denaturation after being delivered into the body. When delivered into a body, It is very possible that some of the proteins would be lost on their way to the targeted site due to undesired interactions with enzymes that may denature the protein. By loading proteins in either the aqueous core or the lipid bilayer of the liposomes based on the property of the protein, the undesired interactions can be minimized. Using a permeability layer of liposomes would also help minimize undesired enzymes trapped within the liposome[10].

2.3.4. Nucleic Acid

Nucleic acid is a category of macromolecules made of nucleotides that is used to treat various diseases due to their ability to carry protein-making signals and templates. For example, the COVID-19 vaccine is mainly composed of mRNA, a nucleic acid, delivered with lipid. However, there are also quite a few shortcomings of nucleic acids. Nucleic acids, though effective, have low stability, low bioavailability, and poor targeting, preventing nucleic acids from performing the best effect in vivo.

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However, by carrying nucleic acids in lipid coverings, nucleic acids can get better stability by avoiding hydrolysis, thereby having a better chance of showing a great performance[11]. Wrapping nucleic acid with lipids also helps deliver the nucleic acids through cell membranes and into the cells. Most cell membranes carry a negative charge in nature, which repels nucleic acids, who also carry a negative charge. This makes delivering nucleic acids into cells especially challenging, but by wrapping the nucleic acids with positively charged lipids, the cationic lipid surfaces can actively interact with cell membranes, delivering nucleic acids through the cell membrane.

2.4. Methods

2.4.1. Hypothetical Release Profile Modeling

To simulate the release profiles of various drug formulations encapsulated within liposomes, a combination of first-order kinetics and the Higuchi model was employed. This hybrid approach allowed for the accurate modeling of both the initial burst release and the slower, sustained release phase, capturing the complex dynamics of drug diffusion from liposomal carriers.

The initial burst release phase was modeled using the *first-order kinetics equation***,** which is typically employed to represent the rapid release of the drug shortly after administration, as a result of diffusion from the liposome's outer layers. The equation used is:

$$Q(t) = Q_{\{\infty\}}\left(1 - e^{\{-k_1 \cdot t\}}\right)$$

In this equation, Q(t) represents the cumulative drug release at time t, while $Q_{\{\infty\}}$is the total drug amount that will eventually be released. The term k_1 is the first-order rate constant, and it dictates the speed of the burst release. This portion of the model is particularly useful for describing systems where the drug is quickly released due to the high initial concentration gradient between the liposome and its environment.

Following the burst release, a slower, diffusion-controlled release phase was modeled using the *Higuchi model*, which has been widely used to describe drug release from matrix-based systems. This is represented by the equation:

$$Q(t) = k_H \cdot \sqrt{t}$$

Here, kHk_HkH is the Higuchi rate constant, which is related to the diffusion properties of the drug from the liposome, while $\sqrt{t}$ accounts for the time dependence of the diffusion process. This model accurately captures the steady release phase commonly seen after the initial burst, where the drug slowly diffuses out of the liposome over an extended period.

The two models were combined to form a hybrid equation that encapsulates both the initial burst release and the sustained release:

$$Q(t) = Q_\infty \cdot \left(1 - e^{\{-k_1 \cdot t\}}\right) + k_H \cdot \sqrt{t}$$

In this combined equation, $Q_{\{\infty\}}$approaches 100%, representing the total drug release over time. The parameters k_1 , k_H, and $Q_{\{\infty\}}$were adjusted to fit experimental release data from the various liposomal formulations, providing a comprehensive model for drug release behavior. This combination of models allows for the detailed simulation of the biphasic release patterns commonly observed in liposomal drug delivery systems.

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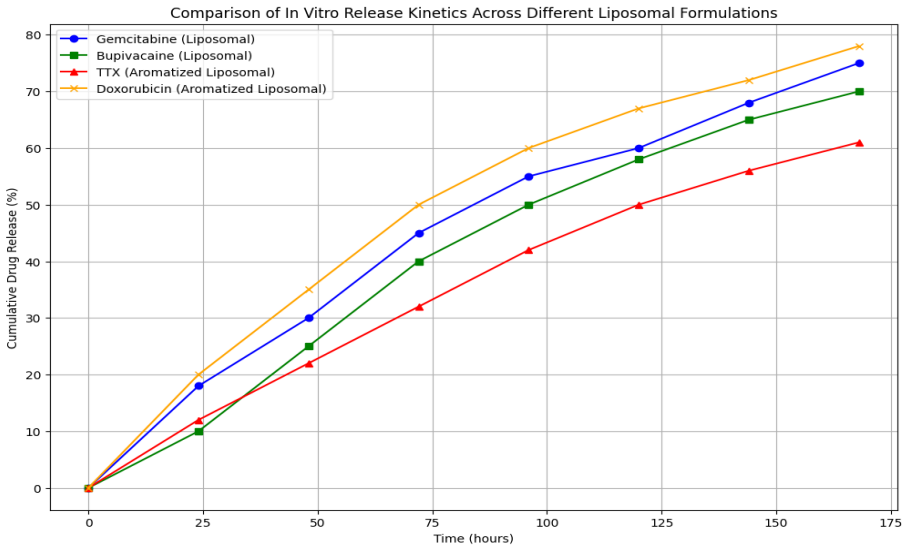

Figure 2: Comparison of cumulative drug release (%) over time for various liposomal formulations, including Gemcitabine, Bupivacaine, TTX (Aromatized Liposomal), and Doxorubicin (Aromatized Liposomal). The data demonstrates the differing release kinetics, with Doxorubicin showing the highest cumulative release, followed by Gemcitabine, Bupivacaine, and TTX.

3. Current Use

Sometimes, drugs that require to be used for a specific location or to be used for a long time cannot be directly injected into peoples bodies because of the potential harm of cytotoxicity and reduced time for which the drug is effective. As seen in Figure 3, the rate of release of drugs is much slower in liposomes than without. The location specificity and the slow release of drugs in lipid-based drug carriers solves this problem perfectly. Although still being studied and developed, there are some lipid-based drug carriers that have already been put into use.

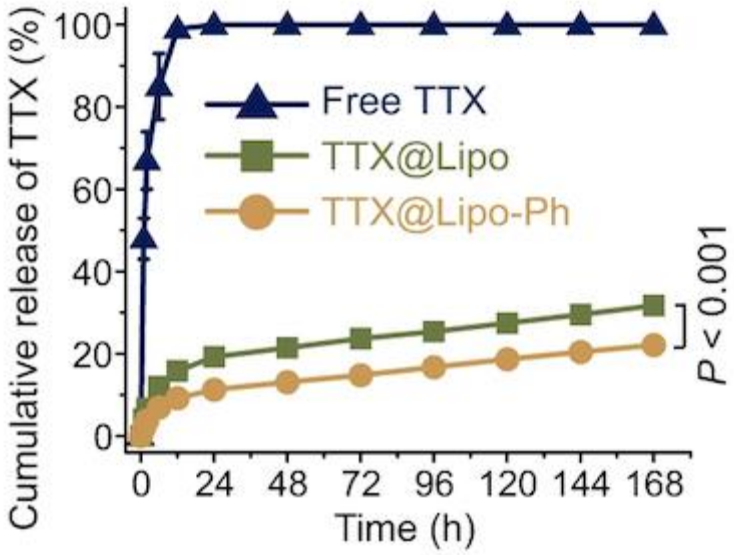

Figure 3: Cumulative release of TTX when the drug is carried in different liposomes compared to when the drug is not carried in any liposomes. The sharp increase of the dark blue line compared both the yellow and green line implied that the drug release is more slow and controlled when carried in liposomes than when it is not [12].

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3.1. COVID Vaccine

The COVID-19 pandemic has caused a large-scale panic including deaths worldwide. The development and distribution of mRNA vaccines have been pivotal in combating the COVID-19 pandemic. These vaccines work by delivering a piece of the virus's mRNA into the body cells. The cells, in turn, produce a protein that triggers an immune response. This allows the body to develop antibodies for the virus without having to come in contact with the actual virus. The mRNA, however, as a nucleic acid, is very fragile and degrades before it actually gives an effect if directly injected into the human body. Moreover, the mRNA generally has a negative charge, which repels the natural cell membrane which also has a negative charge. A crucial yet often overlooked aspect of mRNA vaccine is the use of lipid carriers to deliver the mRNA into the cells. Lipid carriers may be made with positively charged lipids that can protect the mRNA from degrading while escorting mRNA through the cell membrane as the positive charges enhance attractions with the cell membrane.

Other than mRNA delivery, liposomes, a kind of lipid carrier, is also talented in targeted drug delivery. Liposomes are capable of targeting an accurate and steady release of drugs that initiates immune responses. As Anti-tumor cells often contain cytotoxicity, this targeted delivery greatly facilitates tumor treatments while not harming healthy cells[13].

3.2. Crossing Blood Brain Barrier

In addition to already put-into-use treatments involving lipid carriers, lipid carriers are also capable of crossing cell membranes. The ability of lipid carriers to pass a selective permeable membrane implies that lipid carriers may also be potent of crossing the blood-brain barrier(BBB), a highly selective barrier that protects the brain from harmful substances in the bloodstream. This protection mechanism of the body also restricts drug delivery into the brain. However, lipid-carriers may overcome this barrier and improve treatments for Central Nervous System illness. Liposomes, a kind of lipid based drug carrier, cannot diffuse through the BBB due to its big size, instead, liposomes may cross the BBB through the transportation systems. Currently liposomes are known to be engineered to cross the BBB through Adsorptive-mediated transcytosis, receptor-mediated transcytosis, and carrier-mediated transcytosis[14].

3.3. Chronic pain

Lipid carriers are also being explored for the potential in providing a steady and long lasting pain-management. By encapsulating drugs within liposomes, it is possible to achieve a slow and sustained release of the drug as they pass through the lipid bilayers slowly. Furthermore, liposomes are capable of maintaining the release in a set position, meaning that the drug delivery can be accurately targeted. The controlled local release of pain-killing medicines like bupivacaine could be a solution to chronic pain as it minimizes the side effects by targeting only the paint areas and could last a long time[15].

4. Discussion

The continuous study and development of lipid-based drug delivery systems represent a significant improvement in modern pharmacology. The unique properties including biocompatibility and ability to encapsulate a variety of drugs allowed lipid based drug delivery systems to address many of the challenges faced by the traditional drug delivery methods.

The targeted slow release of drugs is particularly useful in medical treatments that require such a prolonged effect. The property of liposomes allows for an initial burst release of drugs, which enables for an immediate drug availability. Moreover, the ability to alter the release kinetics of the drug by changing the composition of liposomes, such as adjusting the cholesterol content, integrating specific

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proteins, or using different polar lipids, offers the potential for personalized drug delivery. This customization can help increase treatment efficacy, reduce cytotoxicity, and improve patient outcomes, especially in conditions requiring precise drug delivery, such as chronic pain management and cancer treatments.

5. Conclusion

Lipid-based drug delivery systems present a versatile and potent tool for medicine delivery. This offers the ability to overcome a lot of limitations related to traditional drug delivery systems. The release profile as modeled in this study provides a framework for understanding the release kinetics of drugs from lipid carriers. In the future, it might even be possible to design drug delivery systems targeting the specific needs of specific patients, increasing the efficacy and minimizing the side effects. Continued research and development in this area will be crucial for unlocking the full potential of lipid-based drug deliveries in future applications.

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