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Should Pharmaceutical Scientists Use Liposomes or Micelles as A Means of Drug Delivery?

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ABSTRACT

Nanotechnology is the manipulation of matter on a near-atomic scale to produce structures, machines, and devices. Nanotechnology is being used as a method to deliver drugs to combat cancer due to current, artificial systems producing harmful side effects. In this, two main systems stand out: liposomes and micelles. This paper compares the two systems to decide whether one system is more capable and should currently be used in drug deliveries. This paper will look at the structure of liposomes and micelles, clinical studies, and issues that have been noted. It was found that liposomes have a higher carrying capacity and can carry multiple types of drugs. In clinical trials, liposomes were found to be just as effective as current systems. However, they are known to have premature drug releases as well as being difficult to load. Micelles were found to be smaller, making them easier to enter the body. They are also easier to manufacture. In clinical studies, they were found to be just as effective as current systems. However, micelles are not as flexible, have a smaller volume, and much less stable than liposomes. Through compiling the advantages and disadvantages of both of these systems, it was found that overall, liposomes were a better system for drug delivery.

Introduction

Drug delivery is one of the most important aspects of combating cancer. Without it, drugs necessary to fight off cancer would be lost inside the body. But current systems of drug delivery have limitations. Most current systems result in harmful side effects. Due to this, new solutions are being proposed, with Nanotechnology being at the forefront. Nanotechnology is the manipulation of matter on a near-atomic scale to produce structures, machines, and devices. With its rise, nanotechnology has been seen as a potential solution for drug delivery. Two main systems stand out: liposomes and polymeric micelles. Micelles are composed of a single layer of phospholipids that create a bubble in which a drug can be stored. This bubble is composed of a hydrophilic shell with a hydrophobic solution in the core. Liposomes on the other hand are composed of a phospholipid bilayer. This bilayer creates a bubble in which an aqueous drug can be stored. With these two systems, one question remains: which system should pharmaceutical scientists use to deliver anticancer drugs. This is important because each system has its own advantages and disadvantages, and although a concrete conclusion is reached, understanding each system's advantages and disadvantages may decide what delivery method is best. Also, understanding the disadvantages of each system may help scientists create solutions to these issues. To determine which system is more capable, multiple factors were taken into consideration. These factors include, but are not limited to, capacity, stability, and usability. Looking at these factors, it was determined that liposomes are the better choice for drug delivery.

Liposomes

Structure

Liposomes were first described in 1964 by Alec D. Bangham. Essentially, they are spherical vesicles made up of a phospholipid bilayer. Inside this bilayer is a soluble drug inside of an aqueous solution. Between each of the lipid layers, an insoluble drug can be inserted(Hoffenberth et al., 2016). Due to this, liposomes can fulfill many different functions at the same time since each drug can perform its own task. Liposomes are usually synthesized via the disruption of biological membranes, such as the use of sonication. The size of a liposome is 100-500nm(Almeida et al., 2020). This makes liposomes better for carrying larger quantities of drugs as they have more space to store their drugs, though much of its space is composed of a hydrophilic drug.

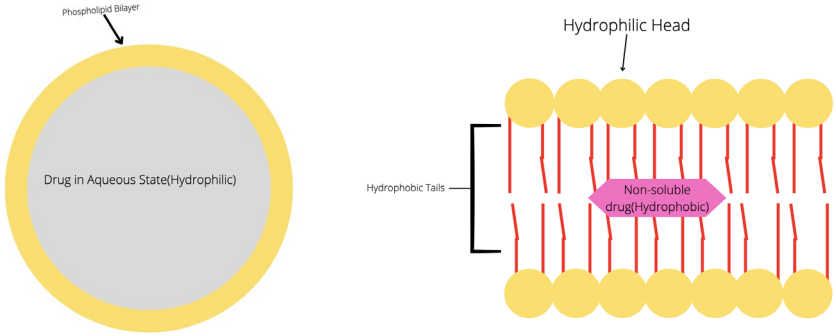

Figure 1. Model of Liposome

Loading

When it comes to liposomes, drugs have to manually be inserted. Conventionally, there are two main strategies to do this: active and passive methods. In the passive method, a drug is dissolved in an organic phase with the phospholipid mixture, followed by solvent evaporation and thin film formation, which results in the encapsulation of a hydrophilic drug in an aqueous core and or a hydrophobic drug in between the phospholipid bilayer. This method allows easy incorporation of various drug molecules without further chemical modifications. However, this method also results in limited control over the selective loading of drugs into specific parts of the liposome(Almeida et al., 2020). In active loading, the drug is loaded into as-synthesized liposomes by the establishment of a pH gradient. This allows the drug to exist in a stable amphipathic system, enabling migration across the lipid bilayer into the aqueous core. This is followed by forming a complex between the drug and a ‘trapping’ agent in the liposome's buffer (Almeida et al., 2020).

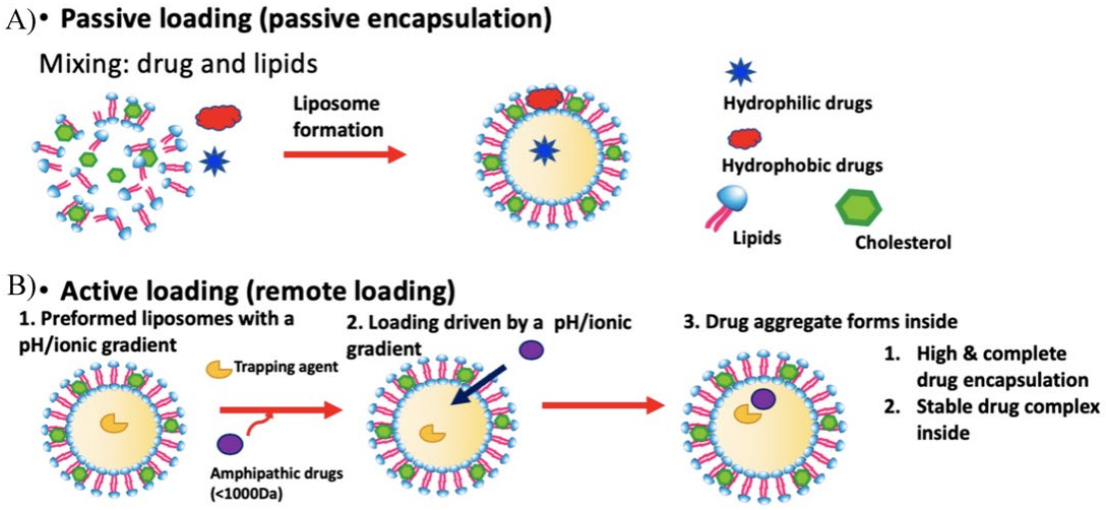

Figure 2. The two methods for loading liposomes: **(A)** passive loading and **(B)** active loading. (Pauli et al., 2019)

Clinical Trial

Liposomes have been used to store drugs to combat cancer, including the drug paclitaxel(PTX), sold under the brand name Taxol. PTX is a natural anti-cancer drug derived from the bark of Pacific Yew(Taxus Brevifolia). Due to the fact that it is inherently hydrophobic, it is stored in Cremophor El(CrEL). This is a non-ionic solubilizer and emulsifier that is made by reacting ethylene oxide with castor oil(Aronson, 2016). This artificial solution has resulted in setbacks. CrEL is known to induce acute systemic side effects within 10 min of initiation of drug infusion, including anaphylactic hypersensitivity reactions (HSRs), hypotension, neutropenia, cardiotoxicity, neuropathy, and hyperlipidemia(Huang et al., 2018). This danger has made it so other drugs have to be administered. With Taxol, other drugs such as corticosteroids and antihistamines are sometimes used as premedications as well as inserting Taxol with a slower infusion rate. Even so, ~40% of patients still suffer from HSRs(Huang et al., 2018). This results in deficient performance as the drug presents a danger to its users. This is also made worse when using PTX to combat lung cancer as drug distribution within lung parenchyma is often suboptimal as systemically administered chemotherapeutics are generally cleared quickly, leaving only a small percentage of the total dose locally available in the lung(Hoffenberth et al., 2016). This prevents PTX from being capable as a very little amount of what is administered actually ends up being used to combat lung cancer and is wasteful. These setbacks have made liposomes a particularly viable solution. In one experiment, PTX was passively loaded into liposomes(known as lipo-PTX). This along with Taxol and Abraxane, PTX bound to the protein albumin, was compared to a PBS (control) liposome by injecting them into mice.

It was found that At pH 7.4, only 16% of PTX was released from lipo-PTX within 24 h, whereas 45% of PTX was released from Taxol in the same time period. Taxol achieved 50% PTX release at 34 h; conversely, the amount of PTX released from lipo-PTX was only 47% after 168 h incubation in PBS at pH 7.4. These results suggested that lipo-PTX is significantly more stable than the Taxol formulation and that collateral toxicity to normal tissue might be alleviated due to reduced premature release of PTX(Huang et al., 2018). This stability ensures that PTX isn't wasted and can reach a tumor to combat cancer. In the actual combatting of cancer, the capability of lipo-PTX was comparable to Taxol, with The half maximal inhibitory concentration (IC50) values of lipo-PTX ranged between 4. and 13.2 nM(Huang et al., 2018). Lipo-PTX also showed no signs of HSRs. Whereas Taxol often has the side effect of myelosuppression, lipo-PTX administered into the bloodstream showed no signs of this. Lipo-PTX administered mice had a lower amount of ECG abnormalities, with only

22% of all mice showing these. For reference, ECG abnormalities were present in 100% of all Taxol administered mice and 66% of all Abraxane administered mice(Huang et al., 2018). These findings indicate liposomes were much better at drug delivery for paclitaxel than both Abraxane and Taxol as lipo-PTX had the same therapeutic efficacy as the other systems but with much fewer dangerous side effects.

Downsides

While liposomes have seen much success in their ability to transport anticancer drugs successfully, they have some issues. Since they have to be made manually, they can be difficult to synthesize. The manual loading of liposomes is also difficult, preventing them from being as readily available as other systems of drug delivery. The size of liposomes can also be a problem. When liposomes flow through capillaries in the RHS, the small size of the pores may cause extravasation(Sercombe et al., 2015). This can disrupt stability and cause the drug to not reach cancer cells. Also, while liposomes have been relatively non-toxic, anti-cancer liposomes that contain cytotoxic drugs have shown indirect signs of macrophage destruction. For example, administration of pegylated liposomal doxorubicin (PLD) (Doxil®) in mice showed a dose-dependent clearance saturation effect due to partial blockade of the RES in the liver. This effect was not present after administration of a similar free doxorubicin dose or phospholipid dose in drug-free liposomes(Sercombe et al., 2015). This means that liposomes that get stuck in small capillaries can cause damage to cells within the body, though this damage is from the anti-cancer cells themselves. Also, plasma proteins in the blood have the potential to cause vesicular destabilization. This is dependent on many factors like size, surface charge and stability(Sercombe et al., 2015). Even still, this does prevent liposomes from being as effective as they could be. Even after that, liposomes have been seen being subject to the EPR effect. The EPR effect refers to the increased permeability of the vasculature that supplies pathological tissues (e.g., tumors and conditions involving inflammation). At these sites, deregulations in angiogenesis and/or the increased expression and activation of vascular permeability factors predominate which leads to fenestrations that can range from 300 to 4700 nm. This may result in liposome extravasation(Sercombe et al., 2015) decreasing its stability even further. These issues with stability hinder liposome capability as some of the drugs may be lost in the bloodstream. Also, some liposomal systems are able to trigger an acute hypersensitivity syndrome known as complement activation–related pseudoallergy (CARPA). This has the effects of anaphylaxis, facial flushing, facial swelling, headache, chills, and cardiopulmonary distress, with 2-45% of those administered with these drugs reporting these systems(Secrcombe et al., 2015). This can be fixed with standard allergy medications but still have the potential to make these drug deliveries uncomfortable.

Micelles

Structure

Micelles are made up of ionized phospholipid monolayers shaped into a circular vesicle. While they are similar in shape to liposomes, they are much smaller (10-100nm)(Hoffenberth et al., 2016). In micelles, the hydrophilic heads form the outer end with the hydrophobic tails enclosed. While micelles are much smaller than liposomes, and thus cannot carry as much as liposomes, the smaller size allows them to enter cells much easier than liposomes.

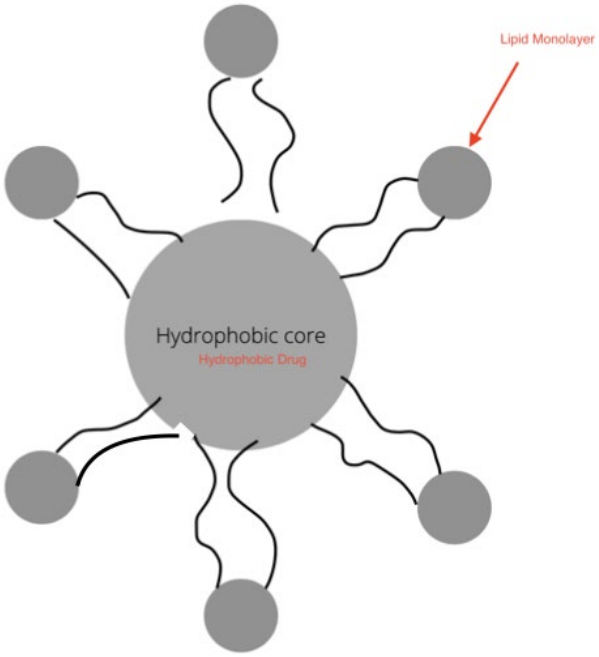

Figure 3. Model of Micelle

Loading

Micelles can self-load themselves due to the amphipathic abilities of ionized fatty acids. These ionized fatty acids have a nonpolar tail and a polar head. Because the head is polar, it can interact with water through hydrogen bonds. However, the tails cannot sustain hydrogen bonds. This causes multiple ionized fatty acids to create globular structures(micelles). Add an insoluble(nonpolar and hydrophobic) drug, and these micelles will form around the drug. This simplicity makes micelles much easier to create and much cheaper to manufacture as compared to liposomes.

Clinical Trial

Micelles have also been used as tools to deliver PTX. Genexol-PM is a CrEL free micelle that was used to combat ovarian cancer. These micelles along with carboplatin were given to randomly assigned women along with a control group that was given standard Genexol (uses CrEL) and carboplatin.

The experimental group showed a CA-125 and RECIST composite overall response rate (ORR) of 88.0%, with a 95% confidence interval (CI) of 80.4-95.6. The control group showed a CA-125 and RECIST composite ORR of 77.1% (95% CI, 67.1 to 87.1). The between-groups difference in ORR was −10.9%, which was not statistically significant (p=0.701), and was lower than the non-inferiority threshold (16.3%), indicating that the Genexol-PM was not inferior to Genexol(Lee et al., 2018). This means that these micelles were just as capable in this setting as regular CrEL systems. The potential for use is existent. During the study period, 441 adverse events occurred in 50 subjects (100.0%) in the Genexol-PM group, including 49 serious events (11.1%, 49/441). In the Genexol group, 376 adverse events occurred in 44 subjects (91.7%), including 40 serious events

(10.6%, 40/376). Except for alopecia, the rates of hematologic and non hematologic adverse events did not significantly differ between the two groups. Neutropenia occurred in 43 patients (86.0%) in the Genexol-PM group and 37 patients (77.1%) in the Genexol group (p=0.120), even though a higher paclitaxel dose was administered in the Genexol-PM group. In the Genexol-PM group, there were 104 confirmed instances of hematologic toxicities (23.6%, 104/441) compared to 77 instances in the Genexol group (20.5%, 77/376). Hypersensitivity reactions occurred in seven patients (14.0%) in the Genexol-PM group, and three patients (6.3%) in the Genexol group (p > 0.99). Incidences of peripheral neuropathy and myalgia did not significantly differ according to study treatment. Peripheral neuropathy occurred in 42 patients (84.0%) in the Genexol-PM group with no serious cases, and in 31 patients (64.6%) in the Genexol group with one case (2.1%) considered serious (p=0.148)(Lee et al., 2018). While Genexol-PM did have many adverse effects, including a greater number of cases of hematologic toxicities, many of the side effects were not as damaging as regular Genexol, meaning that Genexol-PM is a much safer alternative than CrEL based systems.

Disadvantages

Micelles still have disadvantages that make them less capable than they can be. Micelles are much smaller than liposomes, meaning they cannot hold an equivalent amount of a drug as liposomes. Also, micelles lack the ability to carry both hydrophobic and hydrophilic drugs as they can only store simple hydrophobic drugs. While the cheap and easy construction makes them a solid choice for these hydrophobic drugs, they lack the ability to transfer other types of drugs. This makes them less flexible than liposomes as liposomes can carry both hydrophobic and hydrophilic drugs. However, one of the biggest roadblocks for the use of micelles is their instability. Micelle stability can be compromised very easily. Proteins may absorb onto these micelles which results in particle clearance. Along with protein interactions, lipid rich particles such as lipoproteins can also hinder stability Incubation of mPEG-CL micelles in whole plasma disrupts micelles, with radioactively labeled carrier and drug distributing among several LDL, HDL, and lipoprotein fractions(Langridge & Gemeinhart, 2020). These stability issues hinder the ability of micelles to successfully deliver drugs as the drug itself may get lost in the bloodstream.

Discussion

Both systems have their own advantages and disadvantages. Both systems were found to be just as effective as CrEL based systems of drug delivery. Liposomes were found to have the ability to carry a larger volume of drugs as they can be made a lot larger than micelles. However, this size has the issue of creating a blood clot if the liposome enters a capillary that has a diameter smaller than the liposome itself. Liposomes were also found to be more flexible as they can carry both hydrophobic and hydrophilic drugs. However, liposomes do have an issue with premature drug delivery as plasma proteins can cause destabilization. Also Liposomes subject to the EPR effect may have their stability compromised. Liposomes also are less easy to produce as they have to be made manually, either with passive or active loading. This makes them more expensive to produce. Micelles on the other hand are much smaller than liposomes. This makes it much easier for them to enter cells as compared to liposomes but also makes them lack the same carrying capacity as liposomes. Micelles can also be self-assembled. This makes it so micelles are easier to synthesize. The smaller size and easier synthesis also makes them much cheaper than liposomes. However, micelles have the disadvantage of being less flexible that liposomes as they cannot carry both hydrophobic and hydrophilic drugs. Micelle stability also leaves much to be desired as micelles can break apart really easily when they come into contact with lipid rich particles and proteins.

Due to the issues of stability and lack of flexibility seen with micelles, liposomes are seen to be the better system of drug delivery. Their larger size also contributes to this as they can carry a higher volume of drugs to combat cancer.

Conclusion

With current systems of drug delivery systems having harmful side effects, nanotechnology has been seen as a potential solution for the hurdles of drug delivery. In this, two main systems stand out: liposomes and micelles. But which system should be pursued? Liposomes have a much larger carrying capacity, being able to carry 5 times as much as the largest micelles. They also can carry multiple drugs, making them much more flexible than micelles. In clinical trials, liposomes carrying PTX had the same efficacy as CrEL based systems with much less harmful side effects. However, liposomes must be loaded manually, which is difficult. Their size can create blood clots and they are known to have premature drug releases. Micelles are smaller, meaning they can carry less but have the ability to enter cells more easily. They are also easily manufactured to store hydrophobic drugs. In clinical trials, they had the same efficacy as CrEL based systems with less serious cases of side effects, although side effects were present. However, they cannot store both hydrophobic and hydrophilic drugs, and they are overall much less stable. It is because of these disadvantages that make liposomes much better as a system as they can store more drugs, are more flexible, more safer, and more stable. Even still, micelles have the potential to be improved. Their simplicity makes them a great system that, when successfully made stable, have the potential to become just as capable as liposomes. While liposomes are currently better, researchers should push for innovations that make micelles more stable and safe, hopefully making them just as capable as other systems.

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