Encapsulation and Release of Small Molecules From Polymeric Micelles

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Abstract
The overall objective of this research is to create a new drug delivery system using polymeric micelles. The overall research is split up into four parts:
(1) Synthesis of amphiphilic polymers
(2) Finding and purifying the appropriate small molecule drug
(3) Encapsulation of the small drug in the polymeric micelle
(4) Release of the small drug from the polymeric micelle

Background
Drug Delivery System
Drug delivery systems are created to deliver a pharmacological compound while modifying its release profile, absorption, distribution, and elimination. An appropriate drug delivery system improves the efficiency and safety of the drug, while providing the patient with comfort and convenience. Examples of common drug delivery routes include non-invasive peroral (by the mouth), topical (skin), transmucosal (nasal, buccal, and rectal), and inhalation. Recent research into alternate drug delivery systems is necessary because many drugs degrade due to enzymes or fail to be adequately absorbed into the body’s circulatory system due to the drug’s molecular size and/or charge. Injection and nanomalle therapy have already been developed, while current efforts include targeted delivery, where the drug is only activated in a specific area of the body, and sustained release formulations, where the time-release of the drug is controlled. This research deals with the sustained release formulation by way of polymeric micelles.

Encapsulation
Formation of Polymeric Micelle

Normal phase micelles (Figure 1) are surfactant molecules dispersed in an aqueous solution. Since the aqueous solution is polar, it can dissolve the hydrophilic (polar) heads of the surfactant molecule, while simultaneously failing to dissolve the hydrophobic (non-polar) tails of the surfactant molecule. This causes the molecule to form a hydrophobic core around the hydrophilic tails’ center. Inverse phase micelles have the hydrophilic heads at the centre with the hydrophobic tails extending outward. This research is concerned with synthesizing amphiphilic polymers that form normal phase micelles. Normal phase polymeric micelles encapsulate drugs that usually fail to be adequately absorbed and act as carriers within the body’s water-based circulatory system. Advantages of polymeric micelles as a drug carrier are that they can deliver these types of drugs to their desired site of action at concentrations that exceed the normal amount, thus increasing their bioavailability.

Dialysis
Dialysis is “the separation of small solute particles from colloidal particles by means of a semi-permeable membrane.” Dialysis was determined to be the best known encapsulation method for this research. Since PEG-Glu100-Leu100 and indomethacin are soluble in THF, a solution can be made and placed into the semi-permeable membrane bag. The idea is that when this bag is stirred in water, the THF will flow out of the bag and the water will flow in. As the concentration of water increases inside of the bag, PEG-Glu100-Leu100 starts to form micelles around the indomethacin molecules.

Release of Indomethacin from PEG-Glu100-Leu100

To create an environment like the human body, the encapsulated indomethacin was put in a buffer of pH 7.4 and stirred over an interval of time. At each interval, a small amount was removed from the solution and analyzed using UV Spectroscopy. A calibration curve of the concentration of indomethacin in the buffer vs. absorption at 408 nm was used to calibrate the data gathered for the time interval release analysis, providing a graph of time vs. concentration. The time release was analyzed to show the progression of indomethacin release from the PEG-Glu100-Leu100 encapsulation. The time release graph shows what is called a “burst release,” which means the drug is rapidly released from the encapsulation.

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Results & Future Research
As shown in the NMR after dialysis, the indomethacin was successfully encapsulated by the PEG-Glu100-Leu100 and a time release profile was gathered, thus providing preliminary information that this polymer has potential in a new drug delivery system. Since this experiment did not physically prove that an actual micelle was formed, further research will have to be performed to provide this information. Also, more data can be gathered using different types of polymers with the same methods. This could lead to different time release profiles, as well as a better vehicle polymer for the small molecule drug to be carried to a specific area. Once more research has been performed on the polymeric micelle drug delivery system, the next step would be to focus on specific small molecule drugs and how to deliver them to a particular site in the body.

NMR Purified Indomethacin

Figure 1: Normal Phase Polymeric Micelle

Figure 2: The molecular structure of PEG-Glu100-Leu100 polymer. Labelled in red is the hydrophilic head of the polymer. Labelled in blue is the hydrophobic tail of the polymer.

Figure 3: Mylan 147 capsule

Figure 4: Chemical structure of indomethacin. The hydrophobic components are boxed in blue. The hydrophilic components of indomethacin make this small molecule similar to the polarity of the hydrophobic tail of the polymers being synthesized. Indomethacin was found to dissolve in THF, chloroform, and partially in water.

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