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Polymers in Drug Delivery: Analyzing β-Carotene Aggregation in Response to PEG-b-PLA

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ABSTRACT

Synthetic polymers have quickly become ubiquitous in all aspects of modern society, from single-use plastics to medical treatment. This study focuses on the behavior of polymers in the medical context of drug delivery, which requires a highly controlled and targeted release of the therapeutic agent. However, current medical treatments such as anticancer drugs lack precision and lose effectiveness after entering the body. PEG-b-PLA is uniquely structured to have both hydrophilic and hydrophobic ends, which makes it capable of forming polymeric micelles. β-carotene, a lipophilic compound, was employed as a surrogate molecule to represent an anticancer drug. This study's purpose was to study PEG-b-PLA in aqueous solutions with varying concentrations of β-carotene and sodium chloride to mimic a human drug delivery procedure. It was hypothesized that PEG-b-PLA would limit the aggregation of β-carotene to a constant size, regardless of the outside environment. For that purpose, this study created four mixtures, each with varying concentrations of DI water, β-carotene, sodium chloride, and PEG-b-PLA. Qualitative data was collected by using a laser beam to observe the aggregation of β-carotene in each mixture, and each mixture was analyzed in a dynamic light scattering (DLS) instrument to determine exact micelle sizes. It was determined that the addition of PEG-b-PLA significantly reduced the aggregation of β-carotene in an electrolyte solution, demonstrating the stabilizing role PEG-b-PLA plays in drug delivery. Recent innovations like smart polymers consist of molecules like PEG-b-PLA and have been shown to successfully transport medical drugs, potentially making highly targeted anticancer treatment a reality.

Introduction

Though synthetic polymers were only discovered in the early 20th century, they have quickly become an indispensable and ubiquitous feature of modern society. The advent of synthetic polymers has furthered the boundaries of what is possible, ranging from industrial strength adhesives to medical applications. From non-stick cookware to nylon to styrofoam, these polymers have made modern convenience possible and have formed the backbone of modern society. This study aims to observe the behavior of polymers in the specific medical context of drug delivery.

In the realm of modern pharmaceuticals, the development of effective drug delivery systems has become paramount in ensuring the safe and efficient transport of therapeutic agents to their intended targets within the human body. The fundamental challenge in drug delivery lies in optimizing the pharmacokinetics of the therapeutic agent—balancing the need for controlled, sustained release with minimized adverse effects and increased bioavailability. Medical drugs can be both hydrophobic and hydrophilic, but regardless of this polarity, both require transport and dosage control. PEG-b-PLA, a copolymer composed of poly(ethylene glycol) (PEG) and poly(lactic acid) (PLA) blocks, has emerged as a promising candidate for enhancing the delivery of a diverse range of bioactive compounds, including life-saving drugs. This is due in part to the unique structure of PEG-b-PLA, as seen in Figure 1. The poly(ethylene glycol) end of the molecule is hydrophilic, enabling

interactions with water and aqueous substances such as blood, while the poly(lactic acid) end of the molecule is hydrophobic and will only interact with non-polar molecules such as hexane (Cho et al., 2015).

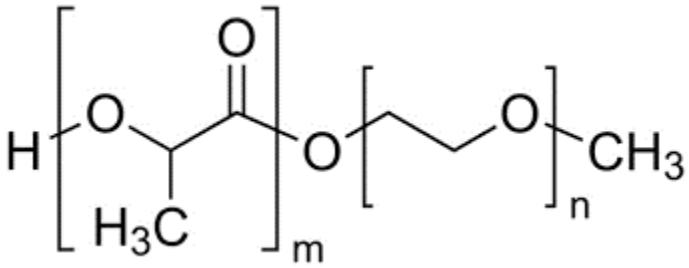

Figure 1. Chemical structure of PEG-b-PLA. The left end is the PLA end, which is hydrophobic. The right end is the hydrophilic PEG end.

PEG-b-PLA copolymers have garnered significant attention in the field due to their biocompatibility, versatility, and precise ability to facilitate controlled drug release. Prior research has shown the propensity of PEG-b-PLA to form polymeric micelles with a hydrophobic interior in an aqueous environment, which has been attributed to PEG-b-PLA's unique structure with both hydrophilic and hydrophobic ends. When placed in an aqueous solution, water will solvate the hydrophilic PEG chains particular well and the PLA poorly, causing the former to spread out to increase contact with water molecules and the latter to scrunch up and restrict inter-molecular interactions to other PLA chains (Wang et al., 2018). By exploring the behavior of PEG-b-PLA in drug delivery by utilizing β-carotene, this study aims to shed light on its potential for improving the absorption and effectiveness of life-saving drugs in the human body.

β-carotene, a naturally occurring compound that serves as a precursor to vitamin A, is employed as a surrogate in this investigation. Its selection as a model therapeutic agent is predicated on its hydrophobic and highly lipophilic nature, due to its structure as a hydrocarbon lacking functional groups (Mercadante et al., 1999). Additionally, β-carotene is highly conjugated, which makes it a deeply colored compound and makes it suitable for experimental procedures such as dynamic light scattering (DLS). β-carotene's characteristics of poor water solubility and low bioavailability make it comparable to certain life-saving and anticancer drugs, such as Pt(CH3)2I2{bipy} (Arabi et al. 2023). Consequently, β-carotene is a pertinent candidate for understanding the behavior of PEG-b-PLA as a drug delivery vehicle.

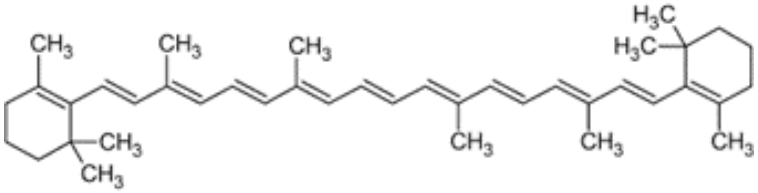

Figure 2. The chemical structure of β-carotene. Note the long hydrocarbon chain and conjugated structure.

This research study endeavors to provide insights into how PEG-b-PLA copolymers can be employed to improve the delivery of life-saving drugs in situations where optimizing drug solubility and bioavailability are critical. Through a comprehensive exploration of the interactions between PEG-b-PLA and β-carotene, this study seeks to inform the development of innovative drug delivery systems capable of enhancing the therapeutic outcomes of critical medications, potentially saving lives and improving the overall well-being of patients.

Drug Delivery: An Overview

The delivery of therapeutic agents to target sites within the human body is a foundational challenge in modern medicine. From the earliest herbal remedies to contemporary pharmaceuticals, the quest for effective drug delivery has been a driving force in the evolution of medical practices. Over time, the integration of advanced materials and innovative technologies has paved the way for transformative developments in the field of drug delivery. Among these materials, polymers have emerged as versatile and indispensable components, revolutionizing the precision, safety, and efficacy of therapeutic interventions (Hubbell & Chilkoti, 2012).

The historical roots of polymer utilization in drug delivery can be traced back to ancient civilizations, where natural polymers such as starch, gelatin, and cellulose were employed as excipients in herbal remedies and early drug formulations. However, the formal recognition and systematic incorporation of synthetic polymers into drug delivery systems gained prominence in the mid-20th century. The advent of biodegradable and biocompatible polymers, such as poly(lactic acid) (PLA) and poly(glycolic acid) (PGA), marked a significant turning point in the quest for safer and more efficient drug delivery methods. These innovations have allowed for a more targeted approach to drug delivery. In short, while drug delivery is by no mean a modern development, this modern field of drug delivery that involves synthetic polymers will be the core focus of the study.

Drug delivery, at its very core, entails the transport of drugs into the body. However, beneath that deceptively simple definition is a complex support system of polymers and technologies designed to support the drug through the human body. Polymers are carefully designed to ensure the drug can be maximally effective and precise, thus ensuring the drug only impacts the specific organ system or area that necessitates the drug (Allen & Cullis, 2004). Drugs are usually absorbed in the small intestine, meaning that they must pass through the acidic environment of the stomach. Preventing the premature digestion of polymers by acidic stomach acid is a medical priority.

Benefits of Polymers in Drug Delivery

The late 20th century witnessed an exponential growth in the application of polymers in drug delivery, driven by their ability to address several critical challenges. Polymers are able to perform many functions that were not possible with medical technologies available two centuries ago.

Specifically, prior research has concluded that polymers have allowed for a far more controlled process of drug delivery. With polymers, medical professions now have the ability to encapsulate drugs within polymer matrices and tailor the release kinetics, which has enabled sustained, controlled drug release, minimizing fluctuations in drug concentration and enhancing patient outcomes. Polymeric micelles can protect sensitive drugs from degradation, preventing them from being prematurely released into the bloodstream. This additional stability provided by polymers has also improved the precision by which drugs can now be transported and delivered. Polymers can be engineered to deliver drugs specifically to the intended site of action, reducing off-target effects and enhancing therapeutic outcomes (Tibbitt et al., 2015).

Shortcomings in Current Medical Treatments

Current research only further underscores the need for alternative methods of drug delivery and medical treatment. Bhavya Khullar and Sarah Iqbal, research managers at the Center for Science and Environment and the George Institute for Global Health, respectively, observed anticancer drugs and their effectiveness. They find that although the drugs currently on trial and in therapy can kill cancerous cells in petri plates, their effectiveness and strength is greatly reduced *in vivo*, or when administered to patients. The researchers claim that this is due to how the human body is innately designed to “neutralize foreign and toxic materials which enter our body.” Adding to the issue, the vast majority of current cancer drugs are “non-specific” and can often end up “damaging

healthy tissue" (Kullar & Iqbal, 2016, p. 1583). This is highly significant, as it underscores how imprecise and broad current medical treatments are. Adding to the concerns of Kullar and Iqbal, current medical drugs can excessively aggregate within the bloodstream, which has been correlated with drug overdoses and blockages in arteries, which result in strokes and heart attacks (Wei et al., 2015). Given these current shortcomings in drug delivery methods, it is imperative to better understand the behavior of polymers under these aqueous environments, and if they offer clear benefits over current medical treatments.

In particular, though there is ample research on the ability and potential of polymers in medical contexts, PEG-b-PLA has not been as thoroughly studied in the medical context of drug delivery. The purpose of this research study was to explore the behavior of the polymer PEG-b-PLA in this medical context. Specifically, PEG-b-PLA was studied in different aqueous solutions with varying concentrations of β-carotene and sodium chloride to mimic a human drug delivery procedure. Given that PEG-b-PLA is capable of forming micelles, it was hypothesized that PEG-b-PLA would limit the aggregation of β-carotene to a certain size by enveloping the β-carotene. Additionally, it was hypothesized that the polymer would result in a β-carotene particle size smaller than what it would be if the polymer was not present.

In the sections that follow, the context, methodology, results, and discussion of the study will be explained, offering a comprehensive understanding of the behavior of PEG-b-PLA in human drug delivery and its potential implications for future medical interventions.

Materials

PEG-*b*-PLA copolymer with different molecular weights were purchased from Sigma-Aldrich (St. Louis, MO). β-carotene was also obtained from Sigma-Aldrich (St. Louis, MO). DI water and sodium chloride were also utilized.

Additionally, four clear glass bottles, one laser pointer, one mortar and pestle, one weigh glass, and two 50 mL graduated cylinders from the chemistry laboratory at Carnegie Mellon University were used. Finally, A DynaPro NanoStar II DLS instrument produced by Wyatt Technology (Santa Barbara, CA) was utilized as a tool to collect quantitative data for micelle sizes.

Figure 3. PEG-b-PLA, purchased from Sigma-Aldrich. This was the polymer researched and observed in this study.

Figure 4. β-carotene, purchased from Sigma-Aldrich. This was the surrogate molecule utilized in this study to mimic an anticancer therapeutic agent.

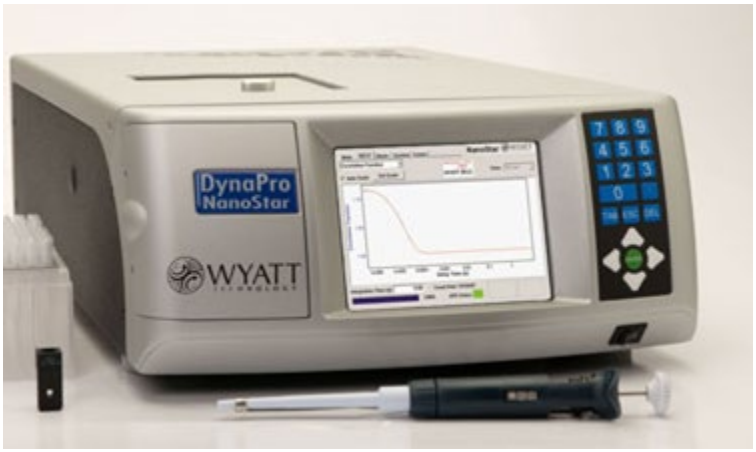

Figure 5. DynaPro NanoStar II Dynamic Light Scattering (DLS) Instrument, produced by Wyatt Technology. This was the instrument used to collect exact, quantitative data regarding micelle sizes in each of the four mixtures.

Methods

This study's aim was to determine how PEG-b-PLA behaves in different aqueous solutions to mimic different scenarios within the human body for drug delivery. Specifically, this meant observing and documenting changes in the aggregation of β-carotene particles in different environments.

For that propose, this study used four different mixture samples with varying concentrations of DI water, β-carotene, sodium chloride, and PEG-b-PLA. β-carotene was utilized as a surrogate molecule to model an anticancer drug that needs to be delivered into the body. Laser pointers were used to observe mixtures for any particle aggregation using qualitative dynamic light scattering (DLS) analysis.

To create the first mixture, 200 mg of β-carotene was ground into a fine powder using the mortar and pestle before being added to the bottle. 400 mL of DI water was added to dilute the mixture and create "mixture 1." To create the second mixture, 1 g of sodium chloride was added to a separate bottle. Next, 200 mL of

mixture 1 was added to that bottle to create "mixture 2." These solutions were shaken and thoroughly mixed for 2 minutes before using a laser pointer to observe any light scattering in the samples.

After 30 minutes, 100 mL from mixture 1 was transferred to a separate bottle, labeled "mixture 3." 100 mg of PEG-b-PLA and 5 mL of DI water were then added to create the third mixture. Separately, 100 mL from mixture 2 was transferred to the last remaining bottle, labeled "mixture 4." 100 mg of PEG-b-PLA and 5 mL of DI water were then added to create the fourth and final mixture. Both samples were shaken and thoroughly mixed for 2 minutes before using a laser pointer to observe any light scattering in the samples.

Observations of any light aggregation were recorded to observe any differences in laser beam visibility, clarity, and penetration. Using DLS, the behavior of the laser beam indicates the size and distribution of particles in a suspended solution. A laser that cannot penetrate the entire solution has a high amount of its photons scattered by the particles (thus indicating a solution with a high aggregation of particles).

In addition to the qualitative data recorded using a laser pointer, samples of all four mixtures were analyzed using a DynaPro NanoStar II DLS instrument to determine the average particle size (in nanometers) of each mixture.

This procedure was repeated multiple times to address any extraneous factors and reduce experimental uncertainty.

Results

The following figures illustrate the behavior and specific degree of aggregation of β-carotene in each mixture.

Figure 6. Photo of mixture 1, with laser beam present. Note how the laser reaches the end of the bottle.

Figure 7. Photo of mixture 2, which laser beam present. Notice how the laser is more unclear compared to mixture 1 and fails to penetrate the entire bottle.

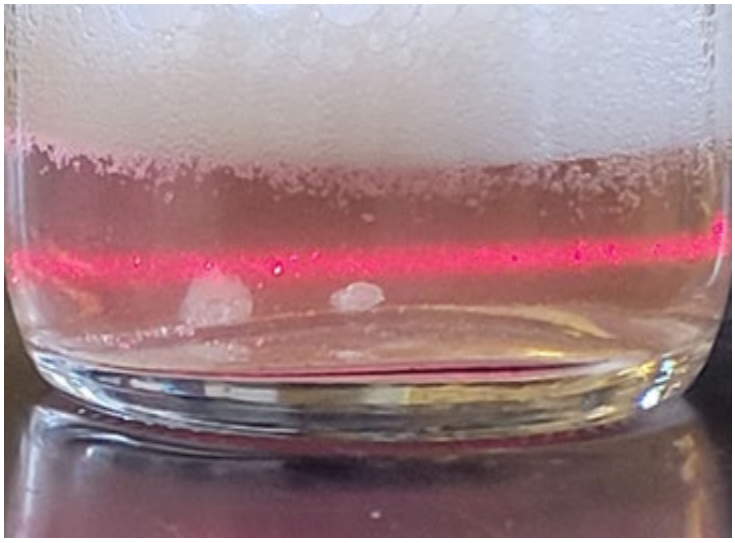

Figure 8. Photo of mixture 3, the mixture with PEG-b-PLA and β-carotene but no sodium chloride. Note how the laser passes completely through the bottle.

Figure 9. Photo of Mixture 4, the mixture with β-carotene, PEG-b-PLA, and sodium chloride. Notice how the laser passes completely through the bottle.

Table 1. Particle/micelle size in each mixture. Using a DynaPro NanoStar II dynamic light scattering (DLS) instrument, the size of the largest particles in each suspension was approximated using size analysis from DLS picture images.

	Largest Particle Size/Particle (approximation, in nm)
Mixture 1	89 nm
Mixture 2	>250 nm
Mixture 3	100 nm
Mixture 4	100 nm

Discussion and Analysis

DLS principles will now be used to analyze the four mixtures in regard to the behavior of the laser beam photons and how much aggregation is present in each mixture. In mixture 1, the laser is able to pass through the entire bottle, which indicates an insignificant amount of light scattering. However, some scattering is occurring, since the laser beam is noticeably clearer at the point closer to the laser pointer itself, which correlates with some particle aggregation in the solution.

This particle aggregation is due to β-carotene's nonpolar structure, as seen in Figure 2. As mentioned earlier, β-carotene is a highly hydrophobic molecule with a long hydrocarbon chain. When placed into a polar medium like water, β-carotene aggregates together, because it has strong intermolecular interactions with other β-carotene molecules, but weak intermolecular interactions with water. Essentially, mixture 1 models the behavior of a nonpolar drug in an aqueous, sodium chloride-lacking environment without the presence of polymers. Though there is not significant aggregation within the mixture, that is a product of the weakly polar nature of the medium, not an outside factor like a polymer.

In mixture 2, the laser fails to penetrate the entire bottle, indicating a significantly larger amount of light scattering. This greater amount of light scattering is a result of a greater aggregation of the β-carotene

molecules. This larger aggregation is due to the addition of sodium chloride, a highly polar compound. Because sodium chloride dissociates into charged ions in aqueous solutions, the medium is significantly more polar than it was in mixture 1. As a result, β-carotene aggregates into far larger masses. According to data from the electron microscopes, particles in this mixture are around three times larger than the particles in mixture 1, with a diameter of approximately 250 nm, as seen in Table 1. This addition of sodium is key, as it mimics all biological systems, since biological fluid is electrolytic and contains ions. Consequently, the large aggregation of β-carotene in this mixture is particularly concerning, as it underscores how β-carotene could block vital arteries within the body if its aggregation is not restricted in such aqueous environments.

In mixture 3, the laser passes through the entire bottle clearly, indicating minimal light scattering and smaller particle sizes. Similarly, mixture 4 allows the laser to completely pass through the bottle, suggesting that the particle sizes in mixture 3 and mixture 4 may be roughly equal.

Mixture 3 and 4 illustrate the significant, stabilizing impact polymers such as PEG-b-PLA have on life-saving drugs. As mentioned earlier, PEG-b-PLA is uniquely structured so that one end (the PEG end) of the molecule is hydrophilic, while the other end (the PLA end) is hydrophobic. These two contrasting ends make PEG-b-PLA ideal for forming polymeric micelles, which create a hydrophobic interior but hydrophilic interior, which can interact with mediums such as blood. In the study, β-carotene, a highly non-polar molecule, was able to be sheltered in the interior of the polymeric micelle formed by PEG-b-PLA. Additionally, due to the presence of the polymers, the micelle is structurally stable. As seen in the data in Table 1, despite changes in sodium chloride concentration in the medium (thus impacting the polarity of the outside environment), the aggregation of the β-carotene remained constant. In a drug delivery, PEG-b-PLA would ensure that regardless of external environment, it could still deliver the correct dosage of life saving drugs. Too much aggregation of the nonpolar drug would likely result in a clotting of arteries or an overdose, but through the interactions of polymers like PEG-b-PLA, those harmful outcomes are avoided. The qualitative observations of Figures 3 through 6 are supported by the quantitative data in Table 1, which detail the specific sizes of particles in each mixture using size analysis of the images taken using an DLS instrument.

The results of this study do suggest micellization of the β-carotene in the polymer. Through these results, it was observed that the addition of sodium chloride changed the aggregation of β-carotene without the polymer, but aggregation of β-carotene remained constant with the addition of PEG-b-PLA. These results are similar to those of Kataoka et al. (2011) who show that polymeric micelles are less resistant to environmental fluctuations.

The observations supported the proposed hypothesis that the aggregation of β-carotene would remain constant regardless of the outside environment when PEG-b-PLA was added. However, the proposed hypothesis incorrectly predicted the difference in β-carotene aggregation between mixtures 1 and 3 by assuming the addition of PEG-b-PLA would reduce β-carotene aggregation in all mixtures. To the contrary, in the absence of both sodium chloride and PEG-b-PLA, the β-carotene would in fact aggregate to a smaller size (89 nm) than when PEG-b-PLA was added (100 nm). Regardless, the results highlighted the stabilizing role PEG-b-PLA plays in drug delivery.

Applications

Given that PEG-b-PLA prevents excessive drug aggregation, it is useful in a variety of medical contexts. In recent years, smart polymers, polymer capsules that are responsive and adaptable to a wide variety of environmental conditions, have been experimentally proven to help in targeted drug delivery (Leichty, 2012). Therefore, smart polymers can ensure that drugs are only delivered to the parts of the body that necessitate them and are not prematurely digested. Most significantly, these smart polymers often consist of polymeric micelles to shelter nonpolar drugs through the body. Those micelles rely on polymers similar in structure to PEG-b-PLA,

such as poly(N-vinyl-2-pyrrolidone), poly(ethylene imine), and poly[N-(2-hydroxypropyl) methacrylamide], which contain both the shell-forming and core-forming parts of a polymeric micelle (Cabral et al., 2018).

This targeted drug delivery is especially useful for cancer treatments. Polymer-transported drugs "preferentially accumulate in the tumor sites unlike conventional chemotherapy," which cannot discriminate between healthy and cancerous cells (Parveen et al., 2019, p. 1). Importantly, prior studies state that while current anticancer treatments like chemotherapy can kill mutated cells, they also inadvertently kill many healthy cells. Targeted drug delivery can help remedy that issue to help improve the precision of anticancer drugs within the body. As a sign of the growing popularity of utilizing targeted drug delivery in anti-cancer treatments, polymer drug conjugates such as Zoladex, Lupron Depot, On Caspar PEG intron are becoming more commonly used in treatment of prostate cancer and lymphoblastic leukemia (Bowen et al., 2015).

Additionally, because of the targeted treatment polymers facilitate, polymeric nanocarriers effectively mitigate many of the cytotoxicity concerns and "severe side effects" of other cancer treatments (Parveen et al., 2019, p. 2). The effectiveness of anticancer therapeutics has even been experimentally proven to be improved "17-70 fold" through targeted polymer delivery (Parveen et al., 2019, p. 17).

However, while polymeric nanocarriers have been proven to be more precise than conventional anticancer treatments, their long-term health effects and cytotoxicity are not yet well understood. Additionally, many polymers are purposefully designed to be non-biodegradable, meaning that they can remain in the human body or the environment for long periods of time. Future directions for research could involve more specifically evaluating the cytotoxicity of polymers and determining if polymers can be designed to be both medically precise yet environmentally sustainable.

Conclusion

DLS analysis in this study has reinforced the crucial impact polymers play in drug delivery. Rather than having highly variable aggregations of particles that could change in response to external stimuli, PEG-b-PLA stabilizes the aggregations of β-carotene so that they can stay in masses of a fixed size regardless of the medium they are in. In the context of drug delivery, PEG-b-PLA ensures that the correct dosage of a crucial drug is delivered to the targeted part of the body.

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References

Allen, T. M., & Cullis, P. R. (2004). Drug Delivery Systems: Entering the Mainstream. Science, 303(5665), 1818–1822. http://www.jstor.org/stable/3836507

Arabi, A., Cogley, M. O., Fabrizio, D., Stitz, S., Howard, W. A., & Wheeler, K. A. (2023). Anticancer Activity of Nonpolar Pt(CH3)2I2{bipy} is Found to be Superior among Four Similar Organoplatinum(IV) Complexes. Journal of molecular structure, 1274(Pt 1), 134551. https://doi.org/10.1016/j.molstruc.2022.134551

Ashley, G. W., Henise, J., Reid, R., & Santi, D. V. (2013). Hydrogel drug delivery system with predictable and tunable drug release and degradation rates. Proceedings of the National Academy of Sciences of the United States of America, 110(6), 2318–2323. http://www.jstor.org/stable/41992223

Bowen, R. L., Perry, G., Xiong, C., Smith, M. A., & Atwood, C. S. (2015). A clinical study of lupron depot in the treatment of women with Alzheimer's disease: preservation of cognitive function in patients taking an acetylcholinesterase inhibitor and treated with high dose lupron over 48 weeks. Journal of Alzheimer's disease : JAD, 44(2), 549–560. https://doi.org/10.3233/JAD-141626

Cabral, H., Miyata, K., Osada, K., & Kataoka, K. (2018). Block copolymer micelles in Nanomedicine Applications. *Chemical Reviews*, *118*(14), 6844–6892. https://doi.org/10.1021/acs.chemrev.8b00199

Cho, H., Gao, J., & Kwon, G. S. (2015). Peg- B -pla micelles and PLGA- B -peg- b -plga sol–gels for drug delivery. Journal of Controlled Release, 240, 191–201. https://doi.org/10.1016/j.jconrel.2015.12.015

Gingell, J. C., Gillatt, D. A., & Beeley, L. (1988). Any Questions. BMJ: British Medical Journal, 297(6656), 1110–1110. http://www.jstor.org/stable/29701344

Hubbell, J. A., & Chilkoti, A. (2012). Nanomaterials for Drug Delivery. Science, 337(6092), 303–305. http://www.jstor.org/stable/23271837

Ting, J. M., Ricarte, R. G., Schneiderman, D. K., Saba, S. A., Jiang, Y., Hillmyer, M. A., Bates, F. S., Reineke, T. M., Macosko, C. W., & Lodge, T. P. (2017). Polymer Day: Outreach experiments for high school students. *Journal of Chemical Education*, *94*(11), 1629–1638. https://doi.org/10.1021/acs.jchemed.6b00767

Kataoka, K., Harada, A., & Nagasaki, Y. (2011). Block copolymer micelles for drug delivery: design, characterization and biological significance. Advanced Drug Delivery Reviews, 47(1), 113–131. https://doi.org/https://doi.org/10.1016/S0169-409X(00)00124-1.

Khullar, B., & Iqbal, S. (2016). Size matters: nanoparticles in cancer therapy. Current Science, 111(10), 1583–1584. http://www.jstor.org/stable/24909392

Langer, R. (1990). New Methods of Drug Delivery. Science, 249(4976), 1527–1533. http://www.jstor.org/stable/2877809

Liechty, W. B., Kryscio, D. R., Slaughter, B. V., & Peppas, N. A. (2010). Polymers for drug delivery systems. Annual review of chemical and biomolecular engineering, 1, 149–173. https://doi.org/10.1146/annurev-chembioeng-073009-100847

Liso, P. A., Rebuelta, M., San Román, J., Gallardo, A., & Villar, A. M. (1996). Polymeric drugs derived from ibuprofen with improved antiinflammatory profile. Journal of biomedical materials research, 32(4), 553–560. https://doi.org/10.1002/(SICI)1097-4636(199612)32:4<553::AID-JBM8>3.0.CO;2-Q

Mercadante, A. Z., Steck, A., & Pfander, H. (1998). Carotenoids from guava (Psidium guajava L.): Isolation and Structure Elucidation. Journal of Agricultural and Food Chemistry, 47(1), 145–151. https://doi.org/10.1021/jf980405r

Parveen, S., Arjmand, F., & Tabassum, S. (2019). Clinical developments of antitumor polymer therapeutics. RSC advances, 9(43), 24699–24721. https://doi.org/10.1039/c9ra04358f
Patel, V., Papineni, R. V. L., Gupta, S., Stoyanova, R., & Ahmed, M. M. (2012). A Realistic Utilization of Nanotechnology in Molecular Imaging and Targeted Radiotherapy of Solid Tumors. Radiation Research, 177(4), 483–495. http://www.jstor.org/stable/41433212

Sharma, S., Parveen, R., & Chatterji, B. P. (2021). Toxicology of Nanoparticles in Drug Delivery. Current pathobiology reports, 9(4), 133–144. https://doi.org/10.1007/s40139-021-00227-z

Śliwa A, Góralska J, Czech U, Gruca A, Polus A, Zapała B, Dembińska-Kieć A (2012)
Modulation of the human preadipocyte mitochondrial activity by beta-carotene.
Acta biochimica Polonica 59, 39-41 [PubMed:22428124]

Tibbitt, M. W., Rodell, C. B., Burdick, J. A., & Anseth, K. S. (2015). Progress in material design for biomedical applications. Proceedings of the National Academy of Sciences of the United States of America, 112(47), 14444–14451. https://www.jstor.org/stable/26465838

Wang, J., Li, S., Han, Y., Guan, J., Chung, S., Wang, C., & Li, D. (2018). Poly(Ethylene Glycol)-Polylactide Micelles for Cancer Therapy. Frontiers in pharmacology, 9, 202. https://doi.org/10.3389/fphar.2018.00202

Wei, T., Chen, C., Liu, J., Liu, C., Posocco, P., Liu, X., Cheng, Q., Huo, S., Liang, Z., Fermeglia, M., Pricl, S., Liang, X.-J., Rocchi, P., & Peng, L. (2015). Anticancer drug nanomicelles formed by self-assembling amphiphilic dendrimer to combat cancer drug resistance. Proceedings of the National Academy of Sciences of the United States of America, 112(10), 2978–2983. https://www.jstor.org/stable/26461752