Breaking Barriers: Advancing Drug Delivery Through Polymer-Based Nanoparticles

What biological barriers might polymer-based nanoparticles overcome to enhance drug delivery to particular organs or tissues?

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ABSTRACT

Polymer-based nanoparticles demonstrate promising results in increasing the delivery of tailored drugs to organs and tissues. In this study, we investigated the ability of polymer-based nanoparticles to bypass various biological barriers. Our research explores the roles of protein adsorption, immune clearance in the liver and spleen, permeation across the endothelium, penetration through the tissue interstitium, and endocytosis in the target cell. Strategies to prevent and overcome these barriers are thoroughly discussed, especially focusing on nanoparticle combination therapy. The paper highlights the advantages of nanoparticle-based drug delivery, including increased biocompatibility, specificity, and drug stability. Understanding and improving these tactics will lead to more efficient and individualized treatments, presenting a brighter outlook for nanomedicine. Various techniques for monitoring the course and development of medication delivery using nanoparticles have also been discussed.

INTRODUCTION

The development of effective drug delivery systems has allowed nanoparticles to emerge as a promising solution, providing a platform for targeted drug delivery to specific organs and tissues. However, biological barriers pose formidable challenges to the successful application of nanoparticles in drug delivery. While methods of overcoming them have been vastly explored in the pharmaceutical industry, the threat still exists. This research paper explores an up-and-coming procedure called nanoparticle combination therapy, and how it revolutionises drug delivery systems. We delve into its methodology and various improvements that might be made in the future.

1. NANOPARTICLES AND THEIR USES

1.1 Structure and Features of Nanoparticles

A nanoparticle (NP) is a small particle that is measured in nanometers and generally ranges from 1 to 100 nanometers in size. There are two approaches that are used in the formation of nanoparticles, including top-down and bottom-up methods. The top-down method is when large particles break down into smaller ones to generate the nanostructure that is required. The second technique is known as the bottom-up method, which incorporates an arrangement of single atoms with molecules to form larger nanostructures. Nanoparticles are used in

many diverse fields such as medicine, environmental preservation, cosmetics, etc. due to their ability to recreate materials in order to complete a specific role. The structure of nanoparticles and drug carriers is based on Paul Ehrlich's "magic bullet". Today, modern nanoparticles are usually constructed from multiple components, including a drug carrier, targeting ligands, and receptors. Drugs are distributed through ligand-receptor recognition, which not only helps in targeted drug delivery but also prevents healthy cells from being damaged in treatments such as cancer, which include drugs harmful to the body's cells. Other than this, nanoparticles also have two main parts, which are hydrophobic and hydrophilic, respectively.

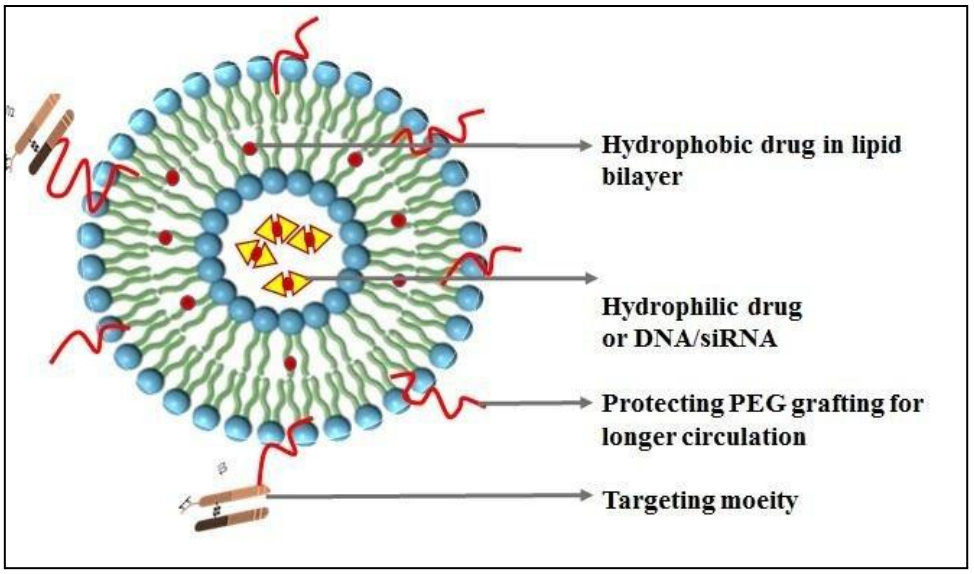

Fig. 1.1 shows a cross-section of the parts of a nanoparticle

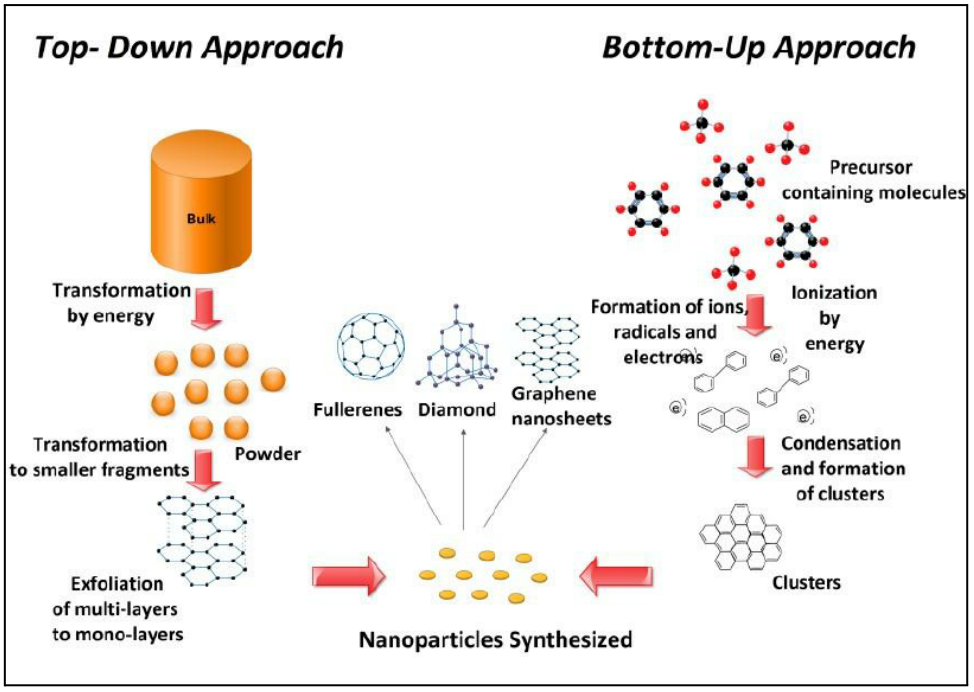

Fig. 1.11 is a visual representation of how both methods work to form nanoparticle structures

1.2 Polymeric Nanoparticles

Polymeric nanoparticles are composed of synthetic or natural polymers. They are often preferred for fields such as medicine and drug delivery for their suitable size, modifiable surface properties, biocompatibility, and improved stability during storage/biological interactions. Polymer-based nanoparticles are also beneficial as they are biodegradable and less/non-toxic, while also increasing the stability of volatile pharmaceutical agents, having targeted drug delivery and non immunogenicity.

Experiments have proved that such surface-modified nanoparticles with targeting ligands had a longer circulation time than others. Additionally, they demonstrated improved bioavailability and RES clearance, which is largely responsible for the clearance of nanoparticles from biological systems. This shows that polymer-based nanoparticles are capable of effectively overcoming biological barriers. Optimising these strategies is essential for the development of effective nanomedicine for targeted drug delivery. Moreover, they can prevent already present enzymes (endogenous) from degrading the quality of the drug.

1.3 Advantages of Nanoparticle Use in Drug Delivery

Nanoparticle delivery systems are more reliable than other delivery methods due to their increased strength, durability, and improved electrical conductivity throughout the body, including enhanced catalytic conductivity. Moreover, they have excellent biocompatibility and enhanced specificity. They can also produce a controlled release of medication from just one dose.

2. DRUG DELIVERY SYSTEMS

2.1 Drug Delivery Systems vs Regular Administration

Drug designing is one of the most advanced topics of research in the realm of nanoparticles. This is largely because it provides the ability to have greater control over factors such as diffusivity, solubility and drug release profiles. This leads to many further advantages, including an enhanced drug life and other side effects. Drug delivery via nanoparticles is done in 2 ways inside the human body: passive or self-delivery. In passive delivery, the drug is stored at the centre of the nanoparticle as a result of the hydrophobic effect. These nanoparticles are then sent to the targeted site where the drug is released due to it being present in a lower amount at the site in the hydrophobic surroundings. In self-delivery, the drug is reversibly combined with the nanoparticle itself and it releases at the target site upon reaching it. Time is of the essence in this method as the drug can not be combined with the nanoparticle for long periods of time. Research/experiments done recently support the claim that drug delivery systems using nanoparticles are the most viable method of administering useful drugs inside the body due to numerous reasons, including improved efficiency, amplified solubility, and the protection of the drug from other sources.

2.2 How to Track the Path & Progress of Drug Delivery

There are many methods used to administer the distribution and behaviour of the nanoparticles inside the human body. Fluorescent imaging is a method that uses fluorescent dyes to allocate nanoparticles. These emit rays of specific wavelengths when excited by an external light source which permits visualisation of the drug. Moreover, in Magnetic Resonance Imaging, superparamagnetic nanoparticles alter the local magnetic field, allowing the distribution of the nanoparticle to be clearly pictured. In Computer Tomography, nanoparticles with high atomic levels elevate the X-ray absorption, resulting in improved images showcasing the nanoparticles' distribution. Furthermore, Scintigraphy allows radiolabeled nanoparticles to be tracked using gamma cameras, enabling imaging of the distribution and accumulation of nanoparticles at specific target sites. Lastly, electron microscopy is used to view each nanoparticle at high resolution so its distribution and morphology can be tracked.

3. BIOLOGICAL BARRIERS IN DRUG DELIVERY

3.1 What are biological barriers?

Biological barriers are a means designed by nature to keep foreign/potentially harmful materials out of the body. Enhancing drugs to pass through these barriers is one of the major requirements of the pharmaceutical industry. As a result, various techniques are employed. Larger molecules can be transported by tissue-specific transporters, or weak points can be targeted. These depend on the specific target site and selected drug.

3.2 Protein Adsorption

When molecules—often small proteins—are adsorbed onto nanoparticles, a protein corona is formed. This protein corona can significantly impact the nanoparticles' properties, such as their size, charge, and hydrophobicity, subsequently influencing their biodistribution, cellular uptake, and toxicity. Some proteins present in the bloodstream are serum albumin, Immunoglobulins, such as IgM and IgG, and Fibrinogen, all of which play a similar role in mediating the process of opsonization.

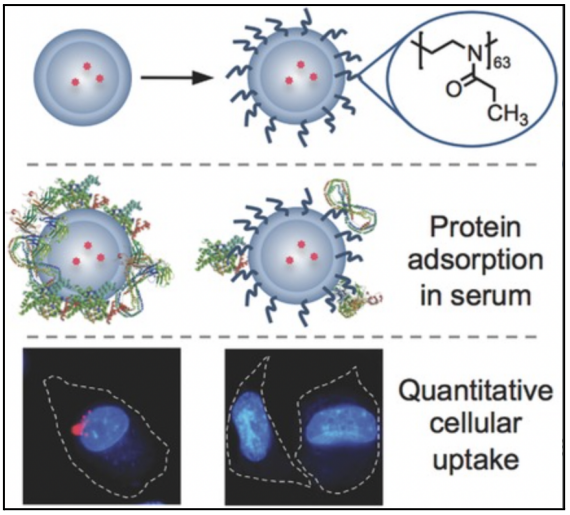

Fig. 3.1 shows a comparison of protein adsorption between poly (2-oxazolines) and Polyethylene glycol

To avoid unwanted protein adsorption, nanoparticles are coated with poly(2-oxazolines), which results in a stealth coating comparable or superior to Polyethylene glycol, a polymeric material with unique hydrophilicity and electrical neutrality. Both have hydrophilic properties, allowing them to create protective, hydrated layers. This layer is able to repel the proteins, preventing them from adsorbing onto the nanoparticle. However, the chemical structure of poly(2-oxazolines) allows for more precise control of the polymer's molecular weight and composition, enhancing protein adsorption properties.

3.3 Other Biological Barriers in Intravascular Delivery

First is the immune clearance in the liver and spleen. It is the reticuloendothelial system, which is composed of cells that are able to perform phagocytosis of foreign materials and particles. The liver and spleen are meant to filter toxins from the bloodstream. However, by doing this, nanoparticles are unable to reach their target and are removed through circulation. Due to the high concentration of phagocytic cells in the liver and spleen, most particles are cleared by a receptor-mediated mechanism in only a few minutes. Surface modifications such as PEGylation can be utilised to minimise immune detection and increase the duration nanoparticles spend in the bloodstream. PEGylation has a covert effect, lowering opsonin adsorption and subsequent absorption by macrophages, including those in the liver and spleen. According to one study, PEGylation of nanoparticles reduces uptake by phagocytic cells in the liver and spleen, leading to increased circulation time and lower immune clearance. Non-PEGylated nanoparticles, on the other hand, are taken up and cleared more quickly by the mononuclear phagocyte system.

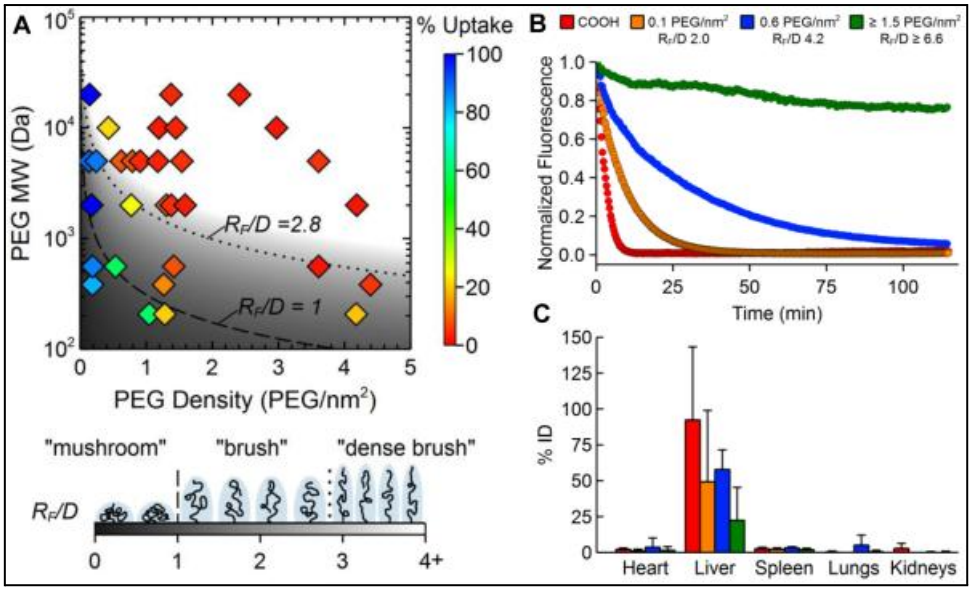

Fig. 3.2 shows the results of an experiment conducted to evaluate the influence of surface PEG surface density on macrophage absorption of polystyrene NPs in vitro and blood circulation time in mice in vivo.

Fig. 3.2 suggests that the densest brush, or highest levels of PED surface density, leads to lower absorption of NPs by macrophages and a slow decrease in blood circulation time. Hence, it can be concluded that PEGylation effectively reduces the immune clearance of nanoparticles in the liver and spleen, providing a promising approach for improving nanoparticle circulation and enhancing drug delivery to target tissues.

Next is permeation across the endothelium into target tissues. Under normal healthy conditions, NPs are not able to cross the endothelium of blood capillaries; however, in certain conditions like inflammation or cancer, endothelial cells lose cellular integrity due to the activation of proinflammatory cytokines, and the gap between endothelial cells is increased. Through this, the NP is able to reach the diseased site through abnormal endothelial gaps.

After that, penetration through the tissue interstitium takes place. NPs also face another barrier after escaping from blood capillaries. This is during their transport through dense interstitial space and extracellular matrix (ECM) to reach target cells. This interstitial space is composed of collagen and an elastic fiber network of proteins and glycosaminoglycans that form the ECM. In certain diseases like tumors, the collagen content is higher than that of normal tissue, and the excessive rigidity of the ESM poses a barrier to NPs to transport from the capillaries to target cells. (in normal conditions, the interstitial spaces and ECM provide structural integrity to the tissue.)

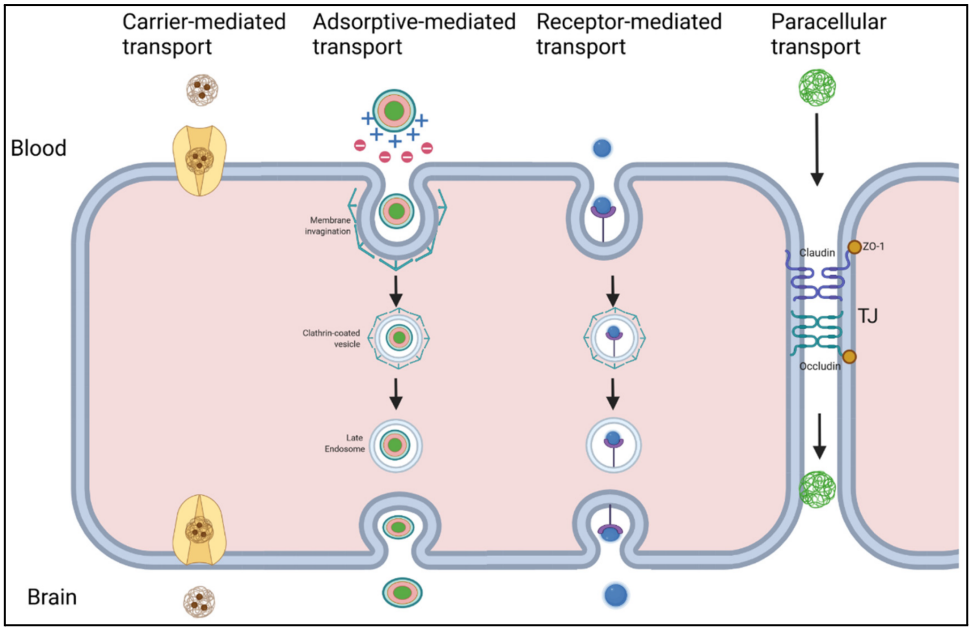

Fig 3.2 A clear representation of how nanoparticles help overcome the permeation of endothelial cells

Endocytosis in the target cell also takes place after that. Plasma membrane and intracellular localization in the target cell. Nanoparticles are not able to enter through diffusion; therefore, they use endocytic processes like pinocytosis, phagocytosis, or endocytosis. NPs are transported in vesicles from early endosomes or lysosomes using internalisation mechanisms. If NPs are able to escape the endosome or lysosome, they diffuse into the cytoplasm and theoretically enter the nucleus. No NPs larger than 9 nm are able to pass through the nuclear membrane pore. If delivery is intended across the skin and mucosal membrane, they possess barrier properties that prevent and restrain the transport of foreign materials, including NPs. Studies demonstrate the enhanced endocytosis of nanoparticles by cancer cells and how this behaviour could be exploited for targeted drug delivery to cancerous tissues.

Overcoming biological barriers presents a significant challenge for nanoparticles in drug delivery. To maximise the potential of nanoparticle-based drug delivery, new and improved methods must emerge. Researchers are exploring innovative strategies to enhance nanoparticle functionality, and one upcoming strategy that may be utilised in the future is Nanoparticle Combination Therapy.

3.4 Nanoparticle Combination Therapy

Nanoparticle combination therapy takes advantage of the unique properties of different nanoparticles and their ability to recreate specific materials to overcome specific challenges encountered during drug delivery. It involves the use of multiple types of nanoparticles or therapeutic agents within a single drug delivery system in order to overcome various biological barriers and improve treatment outcomes. There are multiple ways that this is done.

One such way is targeted drug delivery, which allows different types of nanoparticles to be functionalized with specific ligands or targeting moieties and enables precise delivery to the intended target site. For instance, one type of nanoparticle could be designed to target tumour cells, while another targets immune cells to enhance the overall effectiveness of cancer therapy. This could help tackle multiple diseases at the same time and speed up the recovery process. Creating a synergistic effect by combining different therapeutic agents in nanoparticles could also help overcome drug resistance and improve treatment efficacy as the combined action is more potent than the individual components alone, enabling the drug to act more efficiently and quickly.

Nanoparticle combinations can also improve tissue penetration, especially in cases where the target tissue has a dense extracellular matrix or is shielded by a biological barrier. For example, one nanoparticle type may facilitate penetration through the blood-brain barrier, while another can deliver the therapeutic payload once inside the brain tissue. This provides the particles with the freedom to carry out even more effective targeted drug delivery as some particles are able to cross biological barriers that others aren't, giving them entry into regions that other particles would not be able to access.

It's important to note that while nanoparticle combination therapy shows great potential, the design, optimization, and translation of such approaches to clinical practice are complex tasks that require extensive research and testing. Moreover, potential interactions between different nanoparticles and therapeutic agents must be thoroughly evaluated to ensure safety and efficacy.

CONCLUSION

In conclusion, this study highlights the promising possibilities of polymer-based nanoparticles in drug delivery systems, demonstrating their ability to overcome different biological barriers. We discuss the roles of protein adsorption, immune clearance in the liver and spleen, permeation across the endothelium, penetration through the tissue interstitium, and endocytosis in the target cells. The beneficial effects of enhanced biocompatibility, specificity, and drug stability are highlighted. Furthermore, in-depth discussions of ways to overcome these barriers are discussed with a particular emphasis on nanoparticle combination therapy. This research highlights the advantages of nanoparticle-based drug delivery, providing nanomedicine with greater prospects for the future and more effective customised therapies. Moreover, multiple techniques for monitoring distribution have been investigated, advancing the creation of efficient and precise drug delivery devices. Although nanoparticle combination therapy exhibits a lot of potential, more investigation and testing are required to ensure its security and success in clinical settings. Overall, this research conveys multiple possibilities for improving drug delivery methods and redefining nanomedicine.

CITATIONS

1. *What are nanoparticles? definition, size, uses and properties TWI*. Available at: https://www.twi-global.com/technical-knowledge/faqs/what-are-nanoparticles#:~:text=A%20nanoparticle%20is%20a%20small,to%20their%20larger%20material%20counterparts. (Accessed: 06 August 2023).
2. Cagliani, R., Gatto, F. and Bardi, G. (2019) *Protein adsorption: A feasible method for nanoparticle functionalization?*, *Materials (Basel, Switzerland)*. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6632036/
3. Shevchenko, V.Ya. and Madison, A.E. *Structure of nanoparticles: I. Generalized Crystallography of nanoparticles and magic numbers - glass physics and Chemistry*, *SpringerLink*. Available at: https://link.springer.com/article/10.1023/A:1014201530029#citeas (Accessed: 06 August 2023).
4. Patra, J.K. *et al.* (2018) *Nano based drug delivery systems: Recent developments and future prospects - journal of nanobiotechnology*, *BioMed Central*. Available at: https://jnanobiotechnology.biomedcentral.com/articles/10.1186/s12951-018-0392-8 (Accessed: 06 August 2023).
5. Barua, S. and Mitragotri, S. (2014) *Challenges associated with penetration of nanoparticles across cell and tissue barriers: A review of current status and future prospects*, *Nano today*. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4129396/ (Accessed: 06 August 2023).
6. H;, B.J.N. *[the reticuloendothelial system. an overview of function, pathology and recent methods of measurement]*, *Zeitschrift fur Gastroenterologie*. Available at: https://pubmed.ncbi.nlm.nih.gov/8165827/#:~:text=The%20Reticuloendothelial%20System%20(RES)%20consists,are%20located%20in%20the%20liver. (Accessed: 06 August 2023).
7. Rosales, C. and Uribe-Querol, E. (2017) *Phagocytosis: A fundamental process in immunity*, *BioMed research international*. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5485277/#:~:text=Phagocytosis%20is%20an%20important%20process,derived%20vesicle%2C%20known%20as%20phagosome (Accessed: 06 August 2023).
8. Zeiger, H. (2016) *Study investigates mechanism of nanomaterial clearance by liver*, *Phys.org*. Available at: https://phys.org/news/2016-08-mechanism-nanomaterial-clearance-liver.html (Accessed: 06 August 2023).
9. *Factors affecting the clearance and biodistribution of polymeric ...* Available at: https://pubs.acs.org/doi/10.1021/mp800051m (Accessed: 06 August 2023).
10. Monopoli, M.P. *et al.* (2012) *Biomolecular Coronas provide the biological identity of nanosized materials*, *Nature News*. Available at: https://www.nature.com/articles/nnano.2012.207 (Accessed: 06 August 2023).
11. *Understanding the nanoparticle–protein corona using methods to ... - PNAS*. Available at: https://www.pnas.org/doi/10.1073/pnas.0608582104 (Accessed: 06 August 2023).

12. Tenzer, S. *et al.* (2013) *Rapid formation of plasma protein corona critically affects nanoparticle pathophysiology*, *Nature News*. Available at: https://www.nature.com/articles/nnano.2013.181 (Accessed: 06 August 2023).
13. *The evolution of the protein corona around ... - ACS publications*. Available at: https://pubs.acs.org/doi/10.1021/nn202458g (Accessed: 06 August 2023).
14. Tenzer, S. *et al.* (2013) "Rapid formation of plasma protein corona critically affects nanoparticle pathophysiology," *Nature Nanotechnology*, 8(10), pp. 772–781. Available at: https://doi.org/10.1038/nnano.2013.181.
15. Huesmann, D. (2016) "Reducing adsorption of proteins on nanoparticles," *Advanced Science News* [Preprint]. Available at: https://www.advancedsciencenews.com/reducing-adsorption-proteins-nanoparticles/#:~:text=To%20avoid%20an%20undesired%20protein,especially%20for%20targeted%20drug%20delivery.
16. Bernhard, C. *et al.* (2021) "*In Situ* Label-Free Study of Protein Adsorption on Nanoparticles," *Journal of Physical Chemistry B*, 125(31), pp. 9019–9026. Available at: https://doi.org/10.1021/acs.jpcb.1c04775.
17. Koshkina, O. *et al.* (2016) "Tuning the surface of nanoparticles: Impact of poly(2-ethyl-2-oxazoline) on protein adsorption in serum and cellular uptake," *Macromolecular Bioscience*, 16(9), pp. 1287–1300. Available at: https://doi.org/10.1002/mabi.201600074.
18. Harris, J.M. and Chess, R.B. (2003) "Effect of pegylation on pharmaceuticals," *Nature Reviews Drug Discovery*, 2(3), pp. 214–221. Available at: https://doi.org/10.1038/nrd1033.
19. Veronese, F.M. and Pasut, G. (2005) "PEGylation, successful approach to drug delivery," *Drug Discovery Today*, 10(21), pp. 1451–1458. Available at: https://doi.org/10.1016/s1359-6446(05)03575-0.
20. Gadade, D.D. and Pekamwar, S.S. (2020) "Cyclodextrin based nanoparticles for drug delivery and theranostics," *Advanced Pharmaceutical Bulletin*, 10(2), pp. 166–183. Available at: https://doi.org/10.34172/apb.2020.022.
21. Hoogenboom, R. (2009) "Poly(2-oxazoline)s: A Polymer Class with Numerous Potential Applications," *Angewandte Chemie*, 48(43), pp. 7978–7994. Available at: https://doi.org/10.1002/anie.200901607.
22. Hersh, A., Alomari, S. and Tyler, B. (2022) "Crossing the Blood-Brain Barrier: Advances in nanoparticle technology for drug delivery in Neuro-Oncology," *International Journal of Molecular Sciences*, 23(8), p. 4153. Available at: https://doi.org/10.3390/ijms23084153.
23. Moghimi, S. M., Hunter, A. C., & Murray, J. C. (2001). Nanomedicine: current status and future prospects. The FASEB Journal, 19(3), 311-330.
24. Owens III, D. E., & Peppas, N. A. (2006). Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. International Journal of Pharmaceutics, 307(1), 93-102.
25. Wilhelm, S., Tavares, A. J., Dai, Q., Ohta, S., Audet, J., Dvorak, H. F., & Chan, W. C. (2016). Analysis of nanoparticle delivery to tumours. Nature Reviews Materials, 1(5), 16014.
26. Yu, M., Zheng, J. (2018). Clearance Pathways and Tumour Targeting of Imaging Nanoparticles. ACS Nano, 12(10), 9836-9846.

27. Glossary: Bottom up vs Top-down (in the context of nanoparticle formation). Available at: https://ec.europa.eu/health/scientific_committees/opinions_layman/glossary/abc/bottom-up-top-down.htm#:~:text=The%20%E2%80%9Ctop%2Ddown%E2%80%9D%20approach,and%20molecules%20into%20larger%20nanostructures
28. FIGURE 10.1 Bottom-up and the top-down approaches in synthesis of... (no date). Available at: https://www.researchgate.net/figure/Bottom-up-and-the-top-down-approaches-in-synthesis-of-carbon-based-nanomaterials_fig1_270583669
29. Liwang Shi et al. 2021. Effects of polyethylene glycol on the surface of nanoparticles for targeted drug delivery - Nanoscale (RSC Publishing) DOI:10.1039/D1NR02065J. Available at: https://pubs.rsc.org/en/content/articlehtml/2021/nr/d1nr02065j