Evaluating the effectiveness of smart nanomaterials in Nanodrug Delivery Systems

Ahmed Hussein – STEM High School For Boys – 6

Eshaan Niraj Rajesh Kumar – Fitzalan High School

Hana Urukalovic – American International School Of Zagreb

Mentor: Ahmed Moussa, STEM High School for boys – 6th October

Abstract

Nanodrug delivery systems (NDDSs) are drug delivery systems made of materials on the nanoscale which encapsulate active compounds which aim to treat certain conditions. They can be made of many different materials; however, hydrogels, polymeric nanoparticles, and carbon nanotubes have become one of the more prominent NDDSs in recent years. Each NDDS has properties specific to its material. This literature review will seek to establish which NDDS has the best abilities in terms of some specific general properties which can be observed in all DDSs, with the focus on hydrogels, polymeric nanoparticles, and carbon nanotubes. After analyzing the data and properties of each of the three materials, we found each one surpasses the others in one property that makes it unique. Thus, determining which of these specific NDDSs is the most effective in general is difficult, and they should be chosen based on what they would be utilized for in a specific circumstance.

Keywords: nano-drug delivery systems, hydrogels, polymeric nanoparticles, carbon nanotubes, biomedicine, toxicity, bioavailability, retention, biodistribution, biocompatibility, solubility, sustained release, administration routes, mechanical strength

I. Introduction

Nano drug delivery systems have recently become increasingly more studied for their potential. Their main advantage is their improved bioavailability and specific drug delivery, which makes them better suited for the treatment of some conditions than traditional drugs. Because of this, drug delivery systems have become more sophisticated as they focus on a more controlled and targeted release. This helps avoid the systemic release of the therapeutic substance. Bioavailability implies the part of the drug in question which enters the circulation and is, therefore, able to be absorbed and have an effect. The bioavailability of nanoparticles is generally improved due to increased solubility or the mechanisms which allow for their passage through cell membranes. [1] Because of this potential of nanoparticles, it is important to understand the general mechanisms of certain types of NDDSs (nano-drug delivery systems), and the materials used in their production, such as carbon nanotubes, polymeric nanoparticles, and hydrogels.

II. Methodology

This paper is designed to critically evaluate the overall efficacy of 3 smart nanomaterials when used in Nanodrug Delivery Systems. Scientific information was carefully selected by the authors from numerous reliable sources. To facilitate this, Zotero was used to bookmark every source and its respective citation, which was then added to an extensive Bibliography. All citations and the Bibliography follow the IEEE citation styles due to its widespread usage in highly scientific research papers. By analytically assessing each of the 3 materials before rigorously comparing all of them together, the authors were able to fully describe each material in its own context before formulating further comparisons. The criteria for finding sources was restricted so that only primary sources are used – this action demonstrates that scientific information is not unaltered in phrasing nor the style of writing, as only the sources are located and used.

III. Materials

iii. Hydrogels

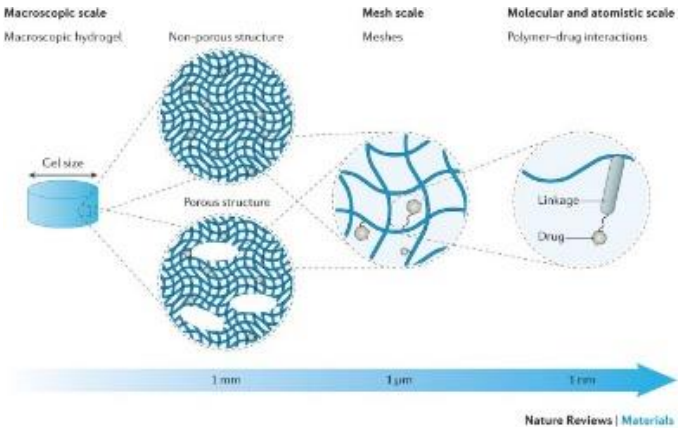

Figure 1: Hydrogels

A hydrogel is a three-dimensional (3D) network of hydrophilic polymers that can expand in water and store a significant quantity of water while preserving structure owing to chemical or physical cross-linking of individual polymer chains, as seen in figure 1. Biopolymers and/or polyelectrolytes are used to make hydrogels. [2] For a substance to be classified as a hydrogel, it must contain at least 10% water by weight (or volume). Because of their high water content, hydrogels have a similar degree of elasticity to real tissue. The network's hydrophilicity is owing to the presence of hydrophilic groups.

Hydrogels may be classified into two categories, according to the source: those made of natural polymers and those made of synthetic polymers [3]. Physical, chemical, and biological hydrogels are all possible. A change in environmental circumstances such as temperature, ionic concentration, pH, or other factors such as the mixing of two components can cause physical gels to transition from liquid to gel. When compared to other weak materials, chemical gels employ covalent bonding to provide mechanical integrity and degradation resistance. The gelation process in biochemical hydrogels is aided by biological agents such as enzymes and amino acids. [2]

Hydrogels are utilized in a variety of applications. This is owing to their unique architectures and compatibility with a variety of operating situations. Hydrogels' flexibility, which is due to their water content, allows them to be used in a variety of environments ranging from industrial to biological, and the biocompatibility of the materials used to make them, as well as their chemical behavior in biological environments, which can be nontoxic, broadens their applications to the medical sciences. [2] pH-sensitive hydrogels, temperature-sensitive hydrogels, electro-sensitive hydrogels, and light-responsive hydrogels are among the numerous kinds available for various purposes. The range of kinds makes it easier to use them in several applications.

Strengths

To avoid fast clearance by phagocytic cells, particle size and surface characteristics can be tweaked, allowing for both passive and active drug targeting. [4] Hydrogels are an excellent alternative for

medication delivery because of their characteristics. Controlling two parameters, the degree of cross-linking in the matrix and the affinity of the hydrogel to the aqueous environment in which swelling occurs can result in high porosity hydrogel structures. Because of their porous architecture, hydrogels are extremely permeable to a variety of medicines, allowing them to be loaded and released under controlled settings [5]. The ability to release medicines for extended periods of time (sustained-release) is the major benefit derived from hydrogels in drug delivery studies, resulting in the administration of a high concentration of an active pharmaceutical material to a specific site for an extended length of time. [2] Improved treatment effectiveness and reduced adverse effects by controlled and prolonged medication release at the target location. Drug loading is quite high and may be accomplished without the use of chemicals; this is an essential aspect of maintaining drug activity. [4] Oral, pulmonary, nasal, parenteral, intra-ocular, and other modes of delivery are also possible. [4] Because of their high water content, hydrogels have a similar degree of elasticity to real tissue. They're biodegradable, biocompatible, and injectable. [6] Due to their small size, capillary veins can reach the tiniest capillaries and penetrate tissues through paracellular or transcellular routes. [4]

Weaknesses

The primary drawback of hydrogel is that it is non-adherent and may require a secondary dressing to keep it in place. [6] Traditional medication delivery has certain disadvantages, such as higher circulating drug level volatility, more frequent dosage administration, increased gastrointestinal discomfort, and dose-related adverse effects. [6] Causes the maggots to move, causing the feeling. [6] Hydrogels are difficult to handle, have limited mechanical strength, and are costly. [6]

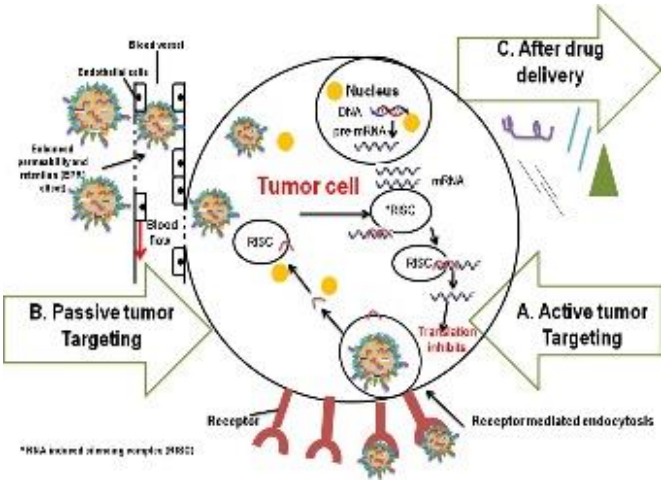

Figure 2: Polymeric nanoparticles for targeted drug delivery system for cancer therapy

iv. Polymeric Nanoparticles

Polymeric nanoparticles are made of polymers - macromolecules made up of different monomers which form a branched linear chain. In terms of their function and properties, selecting specific monomers results in specific and varying properties of the polymer overall. The customization of polymers could be achieved through chemical derivatization or directly on biopolymers. The process of creating polymers may also require surfactants - amphiphilic self-assembling organic molecules. Most of the surfactants used for this purpose are made up of a hydrocarbon chain that is bonded with an ionic functional group. Alternatively, polymers that have a low molecular weight could also be used as surfactants and are often found in the nanocarrier formulation as stabilizers in order to stabilize dispersion during nano-emulsion. One advantage of stabilizers is that they reduce the surface tension of nanoparticles, as well as increasing their ability to bond with lipid structures. Some surfactants have also contributed to the reduction of the diameter of nanoparticles. [7]

Strengths

Some studies have shown that there is increased retention of polymeric nanoparticles in the body and bloodstream, lower cardiovascular effects, and lower nephrotoxicity and hepatotoxicity. Another great potential of polymeric nanoparticles is that they

hinder multidrug resistance moderated by the human ATP-binding cassette transporter superfamily. Some proteins such as P-gp/ABCB1, BCRP/ABCG2, and MRP2/ABCC2 are associated with the decreased efficacy of chemotherapeutic treatment, and nanoparticle drugs have shown potential to inhibit multidrug resistance in this case, which leads to more effective treatment. Gold-based nanoparticles have been used in cancer diagnosis for X-ray imaging since they have been shown to take up X-rays more effectively while maintaining low to no toxicity. Gadolinium polymeric particles are used as contrast agents in MRI imaging, also for diagnosing cancer. Many nanoparticle drug delivery systems are being researched today, and the ones approved for medical use at the moment include albumin-based nanoparticles, polymeric nanoparticles, liposomes, and inorganic nanoparticles, all of which have great potential. [7]

Weaknesses

The main weaknesses of polymeric nanoparticles arise from their limited shape, electromagnetic properties, chemistry, and their wide size distribution agglomeration state. These factors could potentially lead to poor oral bioavailability, poor tissue distribution, and instability during circulation. The way polymeric nanoparticles interact with living cells may also lead to some unwanted effects. Another issue is their uneven size during the production process. Even though they are mostly all spherical, the diameter of the nanoparticles produced could vary. However, this issue could be resolved by the use of particle replication in non-wetting templates (PRINT), which would ensure that all nanoparticles produced are the same size, and would permit their further customization. Other limitations of using polymeric nanoparticles come from their high production cost. There are not many materials available for their production despite them being extensively researched. The high costs of clinical trials for nanoparticle drugs are an obstacle to their research since this means that the pharmaceutical companies behind it suffered economic losses in many cases. This issue could be resolved by focusing more closely on specific conditions for which some nanoparticle drugs could be used, therefore limiting the scope of the research and potentially the cost of it as well. The manufacturing process of nanoparticle drugs also poses a complication that prevents their mass use, but there are some potential solutions to this such as using some already existing methods for their mass production. Meanwhile, new methods of production are still needed for some new nanoparticles such as polymersomes. Additionally, producing multifunctional nanoparticles requires more steps of production, which is another challenge that is yet to be overcome. [7]

v. Carbon Nanotubes

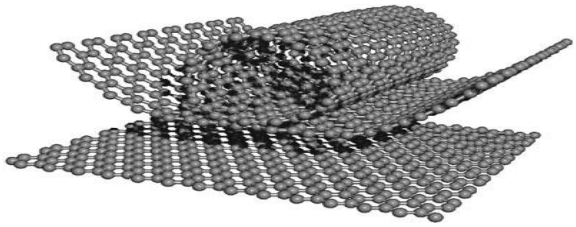

Figure 3: Carbon nanotubes' structure.

Carbon has different allotropes (nanotubes, buckyballs, graphite, diamond, and more), due to its 4 valence electrons enabling it to form superstructures. Carbon Nanotubes (CNTs) are hollow, cylindrical tubes of a hexagonally tessellated lattice of covalent bonds between carbon atoms, as shown in figure 3 [8]. Covalent bonds are very strong because they need a lot of energy to break up. In this hexagonal lattice, more than 347 kJ of energy is required to break up every mole of C-C bond [9].

Strengths

Given that one requires more than 347 to break up a single C-C covalent bond, this ID superstructure of C-C covalent bonds is equipped with a high strength-to-weight ratio (high tensile strength whilst being lightweight). This high tensile strength statistically will lead to higher levels of durability, and this is shown in the application of CNTs to manufacture durable products such as bicycle frames. Applying

the same level of durability will lead to more long-lasting NDDSs. Lightweight properties will make it easier for mass manufacturing, increasing the availability of NDDSs made with CNTs to potential patients who may benefit from it the most. Their nanoscale enables easier cellular transportation due to their atomic size. They can be biosynthesized at the molecular level to make them more adaptable for a variety of biological applications such as acting as a viable material for NDDSs. In traditional high school biology classes, it is taught that a red blood cell is adapted to lose its nucleus to have a larger surface area to carry more hemoglobin, as it takes up the shape of a biconcave disk in doing so. This biological optimization in cellular transportation is akin to that of NDDSs that are made out of CNTs. This is actively demonstrated in the fact that their high surface are-to-volume ratio maximizes their capacity to store chemicals, allowing for optimized and efficient transportation of larger quantities of drugs per journey. Specific applications of CNTs to NDDSs include the simplicity of cellular acceptance, elevated drug insertions. These applications allow them to be particularly valuable for cancer therapy [10].

Weaknesses

CNTs encompass poor solubility in aqueous solutions. Given that water is an exceedingly prevalent and necessary compound in all living organisms, CNTs' biocompatibility with water molecules will pose a risk on the grounds of toxicity. Moreover, its nanoscale means that less than 100 nm can make it easier for CNTs to easily escape from phagocytic defenses, as well as an act beyond its purpose to unnecessarily edit proteins by altering the DNA/ RNA base pairs. As a result, an inflammatory response is likely to be triggered. [10].

IV. Analysis

Hydrogels, polymeric nanoparticles, and carbon nanotubes all have characteristics that may be utilized to determine which nano-drug delivery method is optimal based on these properties. Sustained-release, administration methods, mechanical strength, customizability, retention, toxicity, biocompatibility, drug-carrying capabilities, and production cost are all factors to consider.

i. Hydrogels

Because of their properties, hydrogels are an ideal choice for drug administration. High porosity hydrogel structures may be achieved by controlling two parameters: the degree of cross-linking in the matrix and the affinity of the hydrogel for the aqueous environment in which swelling occurs. Hydrogels are very permeable to a range of medications due to their porous design, allowing them to be loaded and discharged under regulated conditions []. The capacity of hydrogels in drug delivery studies to release medicines for extended periods (sustained-release) is the most significant benefit, resulting in the administration of a high concentration of an active pharmaceutical substance to a specific location for an extended period of time. [2] Because of their small size, they can penetrate tissues via paracellular or transcellular pathways and reach the smallest capillary capillaries. [4] They can be given in several ways, such as oral, pulmonary, nasal, parenteral, intra-ocular, and so on. [4] Hydrogels have a similar degree of flexibility to actual tissue due to their high water content. Last but not least, they're biodegradable, injectable, and biocompatible. [6] There are, however, certain drawbacks to using hydrogels to treat NDDS. The main disadvantage of hydrogel is that it is non-adherent, thus it may be necessary to use a secondary dressing to hold it in place. [6] Hydrogels are also difficult to handle, have little mechanical strength, and are expensive. [6] Overall, the benefits of hydrogels outweigh the drawbacks, making them a suitable material for the creation of NDDS.

ii. Polymeric Nanoparticles

Polymeric nanoparticles are macromolecules whose properties will vary depending on which monomers they consist of. This allows for their great versatility and customization. An important advantage of polymeric nanoparticles is their increased retention, lower nephrotoxicity, and hepatotoxicity as well as fewer cardiovascular effects. They also have the potential to inhibit multidrug resistance inhibited by the human ATP binding Cassette, which has allowed for more efficient execution of chemotherapeutic treatment when combined with polymeric nanoparticle drugs, and they have been found useful in cancer diagnosis during MRI and X-ray imaging. However, they can have a limited shape, size, chemical, and electromagnetic properties which can lead to poor oral bioavailability and tissue distribution, alongside instability in circulation. The issue of their uneven size during production could be solved by the use of PRINT. Despite this, the production cost of polymeric nanoparticles remains too high for their wider use, which is arguably why they have not been researched to a greater extent [7].

iii. Carbon Nanotubes

Carbon nanotubes are a feasible option if they are biosynthesized to assure full biocompatibility with the human body and its defense mechanisms. Nonetheless, due to its high tensile strength for added durability, lightweight properties for easier transportation and manufacturing, and high surface area for highly optimized drug-carrying capacities, it may prove to be the most effective material for NDDSs (assuming it achieves a high level of biocompatibility on average). Carbon Nanotubes are possibly the most effective material for Nanodrug Delivery Systems based on these criteria alone.

iv. Overall Properties

Certain properties common to hydrogels, polymeric nanoparticles, and carbon nanotubes can be used to estimate which nano-drug delivery system is best based on these properties. They can be evaluated on their properties in terms of sustained release, administration routes, mechanical strength, customizability, retention, toxicity, biocompatibility, drug-carrying capacities, and production cost. All three of the nano-drug delivery systems discussed in this paper outperform traditional pharmaceuticals in terms of their biocompatibility and customizability. Hydrogels are proven to be the drug delivery system with the best-sustained release properties and the most versatility in terms of administration routes, which are for example a limitation of polymeric nanoparticles. However, polymeric nanoparticles have increased retention and lower toxicity when compared to hydrogels and carbon nanotubes. On the other hand, carbon nanotubes have a very high mechanical strength (which is an important limitation of hydrogels), are lightweight, and have very good drug-carrying capacities. In terms of cost, all of the nano-drug delivery systems above have very high manufacturing costs. Therefore, it is hard to determine which of these specific NDDSs is overall the most suitable one, and this should be determined based on what they would be used for in a specific situation.

V. Conclusion

We have analyzed the properties of the three nano-drug delivery systems' materials and evaluated them to find the best material in terms of sustained release, administration routes, mechanical strength, customizability, retention, toxicity, biocompatibility, drug-carrying capacities, and production cost. In terms of biocompatibility and customizability, the three nano-drug delivery technologies addressed in this study surpass conventional medicines. Hydrogels have been shown to have the best-sustained release properties and the most versatility in terms of administration routes, which is a limitation of polymeric nanoparticles, for example. When compared to hydrogels and carbon nanotubes, polymeric nanoparticles exhibit higher retention and lower toxicity. Carbon nanotubes, on the other hand, have a high mechanical strength (which is a major drawback of hydrogels), are lightweight, and have an

excellent drug-carrying capacity. All of the nano-drug delivery methods mentioned above have extremely high production costs. As a result, determining which of these specific NDDSs is the most suitable in general is difficult, and this should be chosen based on what they would be utilized for in a specific circumstance.

As noticed from the analysis, every NDDS material is unique for a specific use. It will ultimately depend on the circumstance it will be used for and in. Therefore, determining which one is the "ultimate" material is, almost, an impossible task.

VI. References

[1] Arayne MS, Sultana N, Qureshi F. nanoparticles in delivery of cardiovascular drugs. Pak J Pharm Sci. 2007;20:340–8.

[2] Morteza Bahram, Naimeh Mohseni and Mehdi Moghtader (August 24th 2016). An Introduction to Hydrogels and Some Recent Applications, Emerging Concepts in Analysis and Applications of Hydrogels, Sutapa Biswas Majee, IntechOpen, DOI: 10.5772/64301. Available from: https://www.intechopen.com/chapters/51535

[3] A.K.A. Silva, C. Richard, M. Bessodes, D. Scherman, O.W. Merten, Growth Factor Delivery Approaches in Hydrogels, Biomacromolecules. 2009; 10(1): 9-18, DOI: 10.1021/bm801103c

[4] Gonçalves, C., Pereira, P., & Gama, M. (2010). Self-Assembled Hydrogel Nanoparticles for Drug Delivery Applications. Materials, 3(2), 1420–1460. https://doi.org/10.3390/ma3021420

[5] M. Bahram, N. Nurallahzadeh, N. Mohseni, pH-sensitive Hydrogel for Coacervative Cloud Point Extraction and Spectrophotometric Determination of Cu(II): Optimization by Central Composite Design, J. Iran. Chem. Soc. 2015; 12(10): 1781-1787, DOI: 10.1007/s13738-015-0653-5

[6] Ruchi Singh*, Surya Goel, Pankaj Kumar Sharma and Abhinav Agarwal, "Hydrogel as a Novel Drug Delivery System: Recent Advancements and Patents", Current Nanoscience 2021; 17(1) . https://doi.org/10.2174/1573413716999200626211915

[7] B. Begines *et al.*, "Polymeric Nanoparticles for Drug Delivery: Recent Developments and Future Prospects," *Nanomaterials*, vol. 10, no. 7, p. 1403, Jul. 2020, doi: 10.3390/nano10071403.

[8] Britannica, "carbon nanotube | Properties & Uses," *Encyclopedia Britannica*. https://www.britannica.com/science/carbon-nanotube.

[9] "Bond Energies," *Chemistry LibreTexts*, Oct. 02, 2013. https://chem.libretexts.org/Bookshelves/Physical_and_Theoretical_Chemistry_Textbook_Maps/Supplemental_Modules_(Physical_and_Theoretical_Chemistry)/Chemical_Bonding/Fundamentals_of_Chemical_Bonding/Bond_Energies#:~:text=Atoms%20bond%20together%20to%20form.

[10] A. Eatemadi *et al.*, "Carbon nanotubes: properties, synthesis, purification, and medical applications," *Nanoscale Research Letters*, vol. 9, no. 1, p. 393, 2014, doi: 10.1186/1556-276x-9-393.