REVIEW ARTICLE

A Review of the Efficacy of Nanodrug Delivery Systems: Is It Worth the Hype?

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Abstract

Nanodrug delivery systems are gradually becoming the current "talk of the town" due to their efficiency in treating different diseases in a more advanced manner when compared to conventional drug-delivery systems. It is well known that drugs can be given through various routes of administration, such as the popular oral, subcutaneous, and intravenous routes. It is quite surprising that formulating these same drugs as nanoparticles (NPs) and administering them to the patient could produce better results. Different studies have shown the effects of nanodrug delivery systems in targeting cancer cells, ameliorating pulmonary arterial hypertension, and providing improved treatments for ophthalmic conditions such as glaucoma. In most studies, nanodrug delivery systems have been shown to exhibit targeted action at the desired site or organ, low toxicity, and fewer systemic side effects. These new insights can provide an enhanced understanding of the benefits of NP formulations of drugs, as well as open up new pathways for future creative techniques in addressing emerging medical conditions. Furthermore, these formulations generally consist of polymer- or liposome-based or coated NPs, as they are easily biodegradable, meaning they have a higher ability to disintegrate and, at the same time, are not harmful to living tissues, thereby displaying greater compatibility. New connections can be established through the utilization of NPs in the treatment of emerging diseases worldwide. Data from these studies could provide a foundation for groundbreaking and innovative strategies in coping with or fighting even the recent COVID-19 pandemic.

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Introduction

Whenever a patient is admitted to a hospital and diagnosed with any sort of disease or disorder, familiar or unfamiliar, the physician tends to start the patient on a regimen consisting of different medications. The patient is expected to follow unique schedules for each of the prescribed drugs, some taken *quaque die* or *bis in die*, meaning once or twice daily, respectively. Generally, these drugs can also be differentiated according to their route of administration, with a few injected intravenously and the majority given orally in the form of tablets. Pharmacokinetically, the pathway of any drug can be explained by the four critical processes of absorption, distribution, metabolism, and excretion.

The active components of the drug reach the systemic circulation and are distributed to various tissues of the body, including the specific dysfunctional tissues or organs. This conventional method of drug delivery has many drawbacks, however, such as causing severe adverse effects, allowing only a small dose of the drug to reach the proper site of action, and the fact that some drugs can easily be degraded by gastrointestinal (GI) secretions. Hence, researchers have already taken up the challenge of creating or modifying existing drugs in a new form that can be more beneficial to patients, such as the emergence of nanodrug delivery systems.

Nanoparticles (NPs) are tiny substances not visible to the human eye and are sized at the nanoscale, that is, under 100 nm.[1] NPs are not simple in their composition and consist of three distinct layers: (1) the surface layer, operationalized with a range of small molecules, metal ions, surfactants, and polymers; (2) the shell layer, chemically different from the core, permitting absorbance of the drug onto its surface; and (3) the core, constituting the inner material and representing the central portion of the NP.[2] Thus, these NPs possess significant physical and chemical properties that enable them to participate in the innovative combination of nanotechnology and medicine. Due to their ultrafine size, NPs are easily taken up by the target organ, helping them to permeate and retain inside the tissues while producing minimal side effects.[3] In addition, the use of nanodrug delivery systems can improve the safety and effectiveness of therapeutic agents, lowering toxicity and preventing possible difficulties such as low water solubility and poor bioavailability.[3]

Potential Therapeutic Applications of Nanoparticles

Targeting Cancer Cells

Cancer is one of the leading causes of death worldwide, and more people are being affected by carcinogenic substances as the years pass. Cancer is a condition in which cells act abnormally and start proliferating at a rate beyond the usual borders, forming masses of cancer cells called tumors that can eventually spread to different parts of the body. Chemotherapy and radiation are currently the treatments available to slow down the progression of cancer in a patient. Although chemotherapy destroys the rapidly dividing cells in an attempt to eliminate cancer and prolong a person's life, it also kills the surrounding healthy cells, weakening the person's immune system and exhibiting serious side effects such as hair loss, GI disturbances, and others. On that account, it is crucial to specifically target the cancer cells or tumors without affecting the normal function of healthy tissues. This is the point where nanodrug delivery systems/nanocarriers come into play, as they are highly selective in releasing the loaded anticancer agent at a high concentration along with a reduced systemic distribution.[4] pH-responsive nanocarriers, especially, react to the acidic environment of the tumor, exposing a larger surface area to the drug.[5]

The design of the nanocarriers helps researchers achieve these optimal characteristics. In a recent study,

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nanocomposites containing iron oxide (Fe_3O_4) NPs embedded in chitosan (CS) polymer and coated with reduced graphene oxide (rGO) were invented.[4] In this design, graphene oxide (GO) acts as a surfactant to stabilize hydrophobic molecules, but due to its low solubility, it has been coated with the polymer CS.[6] The use of CS NPs has favored the development of nanodrug delivery systems since it is a natural, biodegradable polymer with enhanced bioavailability properties. Likewise, CS has an excellent ability to inhibit tumor cells, with an improved drug-loading capacity, and in the acidic environment of a tumor site can distribute the drug molecule to a larger extent.[4] In addition to CS, other polymers can form a spherical structure with a hydrophilic shell and a hydrophobic inner layer, enabling the storage of compounds with low water solubility in the heart of the mice.[6] The anticancer drug primarily used in this fabrication was doxorubicin (DOX), and Fe_3O_4 acted as a magnetic agent. While investigating the field emission-scanning electron microscopy (FE-SEM) images, it was found that the interactions between the rGO and Fe_3O_4 allowed for systematic drug loading, with a maximum of 95% of DOX molecules loaded onto the nanocomposite and released on the active surface.[4] A nanocarrier of nanoscale graphene oxide (NGO) and polyethylene glycol (PEG) helped release DOX in a parallel fashion due to the feeble hydrogen bonding.[7] In another study conducted to investigate the effects of anticancer auraptene (AUR)-NPs, the AUR-loaded penta-block and tri-block NP also displayed a sustained and controlled release of the drug, inhibiting the HT-29 colon cancer cells' growth rate.[6]

This proves that a high amount and concentration of a drug can be loaded onto the nanocarrier or NP, ensuring that more of it can reach the targeted site of action. The multidrug resistance effect that cells tend to exhibit can be prevented when cancer cells are treated with polymeric NPs containing drugs, since DOX-loaded rGO/Fe_3O_4/CS/folic acid (FA) nanocomposite was transported *via* the receptor-mediated endocytosis mechanism, being more easily absorbed.[4] Furthermore, the magnetic aspects involved in nanocarriers open the door for the active transport of drug molecules, concentrating on the tumor region.[8] Toxicity studies of the zebrafish suggested no toxic effects or abnormalities of the nanocomposite.[4]

Nanoeye Drop Formulations

Administration of eye drops may look like a simple task—the person tilts their head back and pulls their lower eyelid to form a pouch, then squeezes the bottle so that one or two drops fall into the pouch. But does that guarantee that those eye drops will be absorbed properly into the eye? Well, the answer is no, because even when applied correctly and completely, most of the liquid is drained by the nasolacrimal duct, having very poor bioavailability. Also, the compounds in eye drops lose their penetrating power due to the presence of the cornea, a structure at the surface of the eye, which prevents hydrophilic or bigger-sized materials from entering the eye.[9] NP drug delivery systems show promising results in this aspect as well, providing new applications for future ophthalmic treatments.

Dynamic light scattering (DLS) measurements of the trimethyl-lock (TML) prodrug NPs in aqueous media showed a maximum transmittance of 20% at an 800 nm wavelength. When compared to Azopt (glaucoma eye drops available commercially), the transmittance of TML prodrug NPs was higher by a hundredfold, since the maximum transmittance of Azopt was only 0.2%.[9]

When examining the hydrolysis rate of the nanoeye drops in the harvested aqueous humor of rats, the TML prodrug NPs were spontaneously hydrolyzed and released some of the brinzolamide, and upon further testing with the eyes of Sprague Dawley (SD) rats, produced the expected ocular hypotensive effects.[9] Again, NPs in eye drops penetrate the cornea with ease due to their minute size and "water-fearing" nature, leading to a decrease in intraocular pressure (IOP).[10] Additionally, the histological sections of the rat cornea were assessed for any toxicity after the administration of TML prodrug nanoeye drops, and no damage occurred in the tissues.[9] According to the evidence established in this study, it can be inferred that if Azopt and TML prodrug nanoeye drops were placed on a balance, TML prodrug nanoeye drops would weigh more because of their superior merits and high efficiency in treating glaucoma.

Attenuation of Pulmonary Artery Hypertension

Pulmonary artery hypertension (PAH) is a progressive condition identified by high blood pressure in the pulmonary artery along with increased pulmonary vascular resistance. If left untreated, it can lead to right ventricular failure and eventually death.[3] Even in improving lung disorders like PAH, NPs and nanodrug delivery systems have initiated a massive impact since their manipulation can aid in targeting a specific drug to the lungs. Intravenous prostacyclin or epoprostenol are generally the pharmacological treatments to improve the PAH condition, but it is inconvenient and, as previously mentioned, causes serious adverse effects.[3] ONO1301, a synthetic molecule, exhibits prostacyclin activity for a long duration and is also an inhibitor of thromboxane synthase, so if created in the form of nanospheres—ONONS—it can provide benefits in treating patients with PAH.[3] Results of the conducted experiment depicted that treatment with ONO1301/ONONS increased hepatocyte growth factor (HGF) levels in the supernatant, suppressing the proliferation of pulmonary smooth muscle cells (PASMCs) and decreasing the levels of inflammatory markers like transforming growth factor-beta (TGF-β), interleukin-1 beta (IL-1β), and IL-6.[3] HGF levels have also been correlated with the inhibition of inflammation in the lungs of PAH rats, alleviating the intensity of PAH.[11] Particularly focusing on the tissue distribution of these nanospheres, it is clear that there was a significant accumulation of ONONS in the lungs of the PAH rat, without any drastic changes in the other organs between the normal and PAH rats.[3]

In a similar study on PAH, a different nanoformulation containing an iron-based metal-organic framework (MOF), nano MIL-89, loaded with sildenafil, was tested to check the way it improves the condition.[12] The nano MIL-89 readily absorbed >90% of the sildenafil during loading, and within the first 60 minutes, sildenafil began to work on the mouse aorta, causing vasodilation and relaxing the vessels.[12] Once again, NPs have demonstrated their efficiency in affecting only the necessary organ, not any of the surrounding tissues or organs. Subsequently, a greater quantity of the drug can be loaded onto the NP, making it easier to release the drug over longer periods.

Bridging Connections to the Recent Pandemic

The world is still suffering from the deadly coronavirus, or COVID-19, which all of a sudden froze day-to-day lives and forced everyone to adapt to new ways of living, like wearing face masks, maintaining social distancing, quarantining, implementing lockdowns, and, not to forget, conducting online classes. The innovative strategies in formulating drug-loaded NPs can help in some way in recovering from this pandemic. COVID-19 is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which infects different parts of the respiratory system, mainly the lungs, and spreads from the mucous membranes of the upper and lower respiratory tract to other cells of the body, generating a sequence of immune responses.[13] Drugs that could

treat COVID-19 have to be able to target the main protease, M^{pro}, which plays an important role in mediating viral replication and transcription.[14] The ideology is that if it's possible to alter any of these drugs that could be potentially used in the treatment of COVID-19 in the future in the form of NPs, then the drugs will specifically concentrate and focus on the lungs and the respiratory tract. Thus, when a patient appears to have early symptoms of COVID-19 and is dealing with the initial stage of infection, these NP formulations will have the ability to improve their condition and prevent the worsening of their symptoms. Nevertheless, the process will be time-consuming and expensive, with several preclinical (*in vitro* and *in vivo* studies) and clinical trials before confirming its use in treating the disease.

Potential Drawbacks of Nanodrug Delivery Systems

Although the minute size of NPs allows them to enter the cells and tissues to provide targeted action easily, the same size can become a problem if the necessary precautions are not taken when formulating them. NPs are so small, and, due to this reason, they can lead to difficulties in inhalation and can irritate or even damage the lungs.[15] Therefore, the researchers should be careful while preparing the drug–NP combinations. Moreover, the steps involved in producing nanodrug delivery systems can be costly and require a lot of time to formulate unique compositions.

Conclusion

Utilizing NPs in the medical field as carriers for different drugs has contributed new knowledge to build future opportunities in treating emerging diseases. Therefore, nanodrug delivery systems are indeed worth the hype. The therapeutic goals that nanodrug delivery systems could achieve sound optimistic but still have some room for improvement. Reassuring, through multiple studies, that these NPs do not cause any toxicity and systemic side effects is a key element to progress any step further. Nanotechnology in medicine and pharmacy has an excellent scope, and its prospects seem to be high in the upcoming years.

Statement of Originality

We hereby declare that this submission is entirely our own work, in our own words, and that all sources used in researching it are fully acknowledged, and all quotations properly identified. The work has not been published or submitted elsewhere and is completely original.

Author Contributions

Daisy P Pugazhenthi came up with the idea and topic of interest and wrote the first draft. Ramya A and Dheenadhayalan Murugavel revised the draft and made the necessary corrections. Karthickeyan Krishnan and Shanmugasundaram Palani made further suggestions and approved the final draft of the article.

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