Identification and Analysis of TiO_2 Nanoparticles Coated with Polyethylene Glycol for Use in A Drug Delivery System

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Abstract

The present study aims to analyze and discuss the synthesis, modification, and biocompatibility of Polyethylene Glycol (PEG)-coated Titanium Dioxide (TiO_2) nanoparticles, highlighting their potential applications in drug delivery systems. It focuses on improving the solubility, stability, and bioavailability of titanium dioxide nanoparticles when coated with PEG. The article assesses the size, surface charge, and modification of PEGylated TiO_2 nanoparticles through the use of Fourier-transform infrared spectroscopy (FTIR), dynamic light scattering (DLS), and zeta potential analysis. Accordingly, successful PEG coating of the TiO_2 nanoparticles was presented to result in stable colloidal suspensions, characterized by uniform particle size and narrow size distribution. With the use of targeting ligands, PEG-TiO_2 nanocarriers may both target cancer cells and avoid the reticuloendothelial system. Studies on the drug loading and release kinetics of PEG-coated TiO_2 nanoparticles in vitro have shown some promising results over an extended period when it comes to the sustained and regulated release of the loaded model anticancer agent. This would promise improved stability, a better therapeutic index and lower side effects in contrast to traditional drug delivery systems. This review also explains the effectiveness of these altered nanoparticles in transporting drugs like chemotherapy, antibiotics, and anti-inflammatory medications The challenges and future possibilities of using PEGylated TiO_2 nanoparticles in clinical settings are also discussed.

keywords: TiO_2 nanoparticles, Polyethylene Glycol, drug delivery system, biocompatibility, nanotechnology.

1. Introduction

Nanometer-sized materials have recently gained a considerable amount of attention because of their unique physical and chemical properties and their importance in technological applications [1]. Nanoparticles are a specific type of particles with sizes ranging from 1 to 100 nm, together with the surrounding interfacial layer [2]. Because of their diverse size-related features, including as their enormous surface area to volume ratio and high quantum yield, nanoparticles have shown promise for developing applications in biology, electronics, and medicine [3]. Beneficial drug release requires the improvement of a few elements, such as the drug's physicochemical characteristics, focus tissue microenvironment, drug carrier type, thickness, composition, and delivery vehicle [4]. A major obstacle to effective cancer treatment remains as the targeted medication accumulation at tumor locations. Modifying the carrier with targeting ligands, including peptides, antibodies, and small molecules, is a potential approach to creating a tumor-targeted nanocarrier. These ligands can specifically identify and bind to the surface receptors that are overexpressed on cancer cells, promoting their uptake by cancer cells. So, a combination of stimuli-triggered medication release and cancer cell targeting would provide for an excellent anti-cancer drug delivery system [5]. To further lessen systemic toxicity and undesirable side effects, it is also crucial to make sure that loaded medications are kept sealed during bloodstream circulation and are rapidly released upon reaching and collecting in tumor tissues. Conventional drug delivery methods have certain drawbacks, such as low therapeutic index and low drug bioavailability. However, with titanium dioxide (TiO_2) nanoparticles mediated drug delivery, we can accomplish regulated and sustained drug release, high delivery efficiency, and reduced adverse effects. Subsequent to a rapid release rate, the pharmaceuticals are released gradually over an extended period of time [6][7]. Titanium Dioxide (TiO_2) nanoparticles are widely used because of its high refractive index, chemical stability and non- toxicity. Normal-sized (>100 nm) titanium dioxide (TiO_2) is classified as being biologically inert in both humans and animals. It has been demonstrated that TiO_2 is both inexpensive and non-toxic compared to majority of the majority of metal-oxide nanoparticles for drug delivery systems [8].

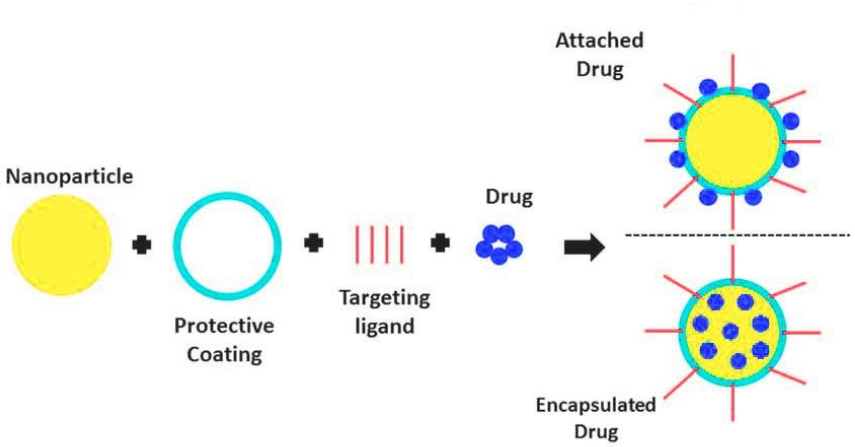


Fig. 1. Targeted drug delivery with drug loading options [22]

Titanium dioxide (TiO_2) nanoparticles exhibit photo-catalytic antibacterial activity and good biocompatibility. Although TiO_2 nanoparticles have been employed for drug delivery, stable colloidal suspensions with repeatable particle size and charge still represent obstacles. When uncoated, their small size and corresponding high surface area lead the nanoparticles to cluster in aqueous conditions and trigger gene activation [9]. Under UV light, the photocatalytic activity of titanium dioxide (TiO_2) aggregates in disinfection characteristics, primarily linked to the production of reactive oxygen species [10]. Large-TiO_2 NP aggregates have a more significant impact on cell viability and molecular gene expression, as suggested by cytotoxicity and mRNA expression studies. The limitations can be overcome by coating the TiO_2 nanoparticles with Polyethylene Glycol (PEG). Polyethylene glycol (PEG), a non-toxic and non-immunogenic coiled polymer of repeating ethylene ether units, when conjugated with TiO_2 nanoparticles, reduces their cytotoxicity by physically blocking the nanoparticles from producing potentially toxic reactive oxygen species (ROS) [9]. PEG is generally considered a safe polymer and is therefore widely utilized in medicine and biotechnology due to its unique properties, such as biocompatibility, ready excretion from living organisms, and resistance to protein adsorption. PEGylated nanoparticles are more biocompatible and have a longer half-life in the bloodstream, while uncoated NPs are rapidly eliminated by reticuloendothelial system (RES) macrophages [11]. Nanoparticles with a PEG coating on them are able to withstand blood and protein components adhering to their surfaces [12]. In this work, a brief overview of the synthesis and characterization of PEG coated-TiO_2 nanoparticles has been provided with respect to their application as drug carriers. This paper aims to critically assess the existing synthesis methods, characterization techniques, and use of TiO_2-PEG nanoparticles in improving drug delivery systems. This review also highlights the key challenges and future possibilities for research in this field.

2. Materials and Methods

2.1. Synthesis of TiO_2 Nanoparticles

TiO_2 nanoparticles can be synthesized using sol-gel method, through hydrolysis of Titanium tetra isopropoxide (TTIP). The regulated size, shape, and high surface reactivity of nanoparticles produced via the sol-gel process make them especially well-suited for further surface modification [13]. Initially, titanium isopropoxide undergoes hydrolysis under acidic conditions leading to the formation of a gel-like material; this is then dried before calcination at 450°C yielding crystalline TiO_2 nanoparticles. The calcination process, depending on the temperature and reaction time, turns the matrix from gel into crystalline anatase or rutile. By altering factors within this reaction such as precursor concentration or solution pH, one may regulate both dimensions and morphology of these tiny particles [14].

2.2. Modification of TiO_2 NPs by PEG

Polyethylene glycol (PEG) is used as a coating agent to modify the surface of TiO_2 nanoparticles. Polyethylene glycol is a biocompatible polymer that, when attached to the surface of NPs, improves colloidal stability and enhances their biocompatibility while preventing agglomeration [9]. TiO_2 NPs must be modified to avoid aggregation and sedimentation. At first, TiO_2 nanoparticles are suspended in deionized water and sonicated, and after sonification, PEG is added in a low concentration to prevent encapsulation of nanoparticles in the suspension. The blend is ultrasonicated and eventually stirred at room temperature for 24 hours to make the hydrophilic

polymer to wrap around the TiO_2 nanoparticles. After stirring, the suspension is centrifuged to precipitate the unreacted reagents, and with that, the TiO_2 nanoparticles are successfully modified with PEG while the supernatants are dialyzed and collected [15].

2.3. Characterization Techniques

Characterization describes the extensive procedures needed to determine a material's structure or to learn more about its functional, chemical, and physical attributes [16]. Precise characterization of PEGylated TiO_2 nanoparticles allows accurate analysis of their physiochemical properties, such as their size and distribution, morphology and structure, surface composition, and surface charge [17]. This analysis can offer valuable insights into the stability, interaction, and prospective applications of the nanoparticles. Through characterization, it is possible to assess the consistency of nanoparticle synthesis, PEG coating efficiency, and therapeutic effectiveness of PEGylated TiO_2 nanoparticles as drug carriers for prospective drug delivery applications. Table 1 outlines key characterization techniques used for analyzing TiO_2 nanoparticles, focusing on their respectable findings and outcomes.

Table 1. Experimental Techniques used for nanoparticles

Techniques	Analyzed Property	Findings/Outcome	References
Fourier-Transform Infrared Spectroscopy (FTIR)	Surface composition, Ligand binding	Detection of PEG functional groups (C-H, O-H) on the surface, confirming PEG's conjugation with TiO_2 nanoparticles by hydrogen bonding.	[18]
Dynamic Light Scattering (DLS	Particle size distribution	Analyzing narrow size distribution in TiO_2 nanoparticles, indicating uniformity in size.	[12]
Zeta Potential Analysis	Surface charge, stability	Reduced zeta potential for synthesized TiO_2 nanoparticles, indicating increased stability and lack of agglomeration.	[15][19]

2.4. Drug Loading and Release

Drugs are incorporated into PEGylated nanoparticles through physical adsorption, with stirring facilitating the drug loading process. Drug loading capacity and encapsulation efficiency are influenced by variables such as the drug-to-carrier weight ratio, incubation period, and material order [15]. The effectiveness of the treatment is marginally increased when nanoparticles that increase drug permeability in the cellular environment are present, suggesting that even with a slow-release rate, the drug's effectiveness is maintained. In vitro investigations are usually used to examine the drug release profile, wherein the nanoparticles are cultured in buffer solutions that replicate physiological circumstances. A quick release phase is followed by a prolonged release phase in the pH-responsive release profile of the PEGylated NPs [12].

3. Applications in Drug Delivery

Nanomaterials have gathered significant interest in the contemporary medical sector owing to their recent uses in drug delivery systems and cancer diagnostics [16].Nanostructure based drug delivery, with enhanced drug bioavailability, better release time of therapeutic molecules and large surface area has emerged as one promising method of targeting anticancer drugs to optimize the chemotherapeutic efficacy while minimizing the unfavorable effects on healthy tissues. The enhanced ability of nanoparticles to adhere to cell surface signals and diffuse into cells has resulted in advanced drug pharmacokinetics and biodistribution [12][19]. Titanium oxide nanocarriers, with their excellent adsorption capacity, photocatalytic characteristics, and high surface area, provide an ideal matrix for drug loading [15]. However, these nanoparticles may cause cytotoxicity, inflammation, and heat shock resistance as side effects. With PEG as a hydrophilic barrier, potential adverse effects are reduced, and nanoparticles have improved biocompatibility and in vivo circulation duration, allowing for robust delivery and controlled drug release mechanisms to cancer cells [9][18]. Titanium oxide nanoparticles can be further modified with targeting ligands such as peptides, antibodies, or small molecules, for active drug targeting, with the folate receptor (FR) on cancer cells identified as a possible target for ligand directed cancer therapeutics [5][12]. This targeted delivery approach minimizes non-specific uptake of toxic agents and enhances drug accumulation at the target site. Stimuli-triggered drug release, where the nanocarriers release drugs in response to specific stimuli like

pH, temperature, and redox potential, creates an excellent drug delivery system when combined with cancer cell targeting [5]. Table 2 provides an overview of recently reported drugs and how PEGylated TiO_2 nanoparticles contribute to their delivery and release mechanism.

Table 2. Overview of Drugs Delivered via PEG-Coated TiO_2 Nanoparticles

Drug Name	Targeted Disease/Condition	Function of PEG-Coated TiO_2 Nanoparticles	References
2-Methoxyestradiol (2ME)	Anti-cancer (Angiogenesis Inhibitor)	Enhances suspension stability and prevents early degradation, resulting in improved anticancer efficacy.	[18]
Doxorubicin	Breast cancer, Bladder cancer	Enables controlled drug release, improving therapeutic efficacy while reducing systemic toxicity.	[15]
Paclitaxel	Lung cancer, Ovarian cancer	Enhanced drug loading capacity, controlled drug release profile and higher anticancer activity.	[12]
Imatinib	Chronic Myeloid Leukemia (CML)	Provides magnetically guided delivery, improving bioavailability and effectively targeting cancer cells.	[20]

4. Challenges and Future Aspects

Despite remarkable advancements in PEGylated TiO_2 nanoparticle-based drug delivery systems, challenges remain that need to be addressed or handled for their widespread application. TiO_2 nanoparticles are considered to be biocompatible, but long-term effects, especially when PEGylated, are still unknown. Detailed in vivo studies are necessary since extended accumulation of these nanoparticles inside the body may result in unanticipated toxicity [15][21]. Nanoparticles can still be identified by immune cells when PEGylated, despite reduction in opsonization which may eventually lead to the rapid clearance of these nanoparticles from bloodstream [12]. Besides, characterization techniques like DLS and Zeta potential analysis don't provide much about the degree or consistency of PEG attachment, limiting the knowledge of successful PEG modification. PEGylation raises the loading capacity for certain drugs, although not all therapeutic medications respond to it in the same way. Complicating matters further is the high cost of PEG and other materials involved in manufacturing, along with the challenge of accommodating drugs with varying solubility or binding affinities, which often require different loading strategies. Looking ahead, future research should be focused on addressing current challenges and advancing the traditional drug delivery system with targeted drug delivery, controlled release mechanisms, and more advanced characterization methods. Functionalizing the PEG-coated TiO_2 nanoparticles with ligands or antibodies can further enhance the targeted drug delivery and minimize the side effects while maximizing the treatment outcomes. Stimuli-responsive PEGylated TiO_2 nanoparticles release their drug components in response to external stimuli – pH, temperature, etc., this might increase localized drug release to the intended sites and prevent healthy tissues from unnecessary exposure to the drug. Understanding the nanoparticles behavioral patterns in various conditions within the body could assist in making improved designs for the nanocarriers. Moreover, advanced characterization techniques like atomic force microscopy (AFM), cryo-TEM, and Raman spectroscopy may serve as alternatives to DLS and Zeta potential analysis to assess the structure, thickness, and interactions of the PEG layer with biological surroundings. Thus, even though PEG encapsulated TiO_2 nanoparticles can be very effective in improving drug delivery systems, major strategies will be towards achieving less costly and less complex process of making these nanocarriers whilst maintaining consistency to facilitate their transition from laboratory to clinical setting.

5. Conclusion

In this study, we reviewed the synthesis, surface modification, and characterization of TiO_2 nanoparticles for drug delivery systems, focusing on cancer therapy. Attaching Polyethylene Glycol (PEG) to the surface of TiO_2 nanoparticles enhances the nanoparticles' stability and degree of dispersibility, reflecting a reduction in zeta potential. Drug loading and in vitro drug release investigations have shown that PEG-modified nanoparticles may effectively carry therapeutic drugs and control their release, particularly in an acidic environment similar to cancerous tissue. This prolongs the duration of action while minimizing the side effects of the drug and eases the frequency through which the drugs are administered for maximum therapeutic effect. Despite these promising results, challenges remain, including toxicity and other risks, interaction with the immune system and further

clearance, and inconsistent drug loading efficiency. Future research should be directed toward refining the synthesis methods, improving targeting mechanisms, and assessing the feasibility of multifunctional nanoparticles.

6. References

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