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REVIEW ARTICLE

An Assessment of *In-vitro* and *In-vivo* Evaluation Methods for Theranostic Nanomaterials

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Abstract: Nanoparticles (NPs) as nanocarriers have emerged as novel and promising theranostic agents. The term theranostics revealed the properties of NPs capable of diagnosing the disease at an early stage and/or treating the disease. Such NPs are usually developed employing a surface engineering approach. The theranostic agents comprise NPs loaded with a drug/diagnostic agent that delivers it precisely to the target site. Theranostics is a field with promising results in enhancing therapeutic efficacy facilitated through higher payload at the targeted tissue, reduced dose, and dose-dependent side effects. However, controversies in terms of toxicity and size-dependent properties have often surfaced for NPs. Thus, a stringent *in-vitro* and *in-vivo* evaluation is required to develop safe and non-toxic NPs as theranostic agents. The review also focuses on the various entry points of NPs in the human system and their outcomes, including toxicity. It elaborates the evaluation criteria to ensure the safe use of NPs for diagnostic and therapeutic purposes.

Keywords: Theranostics, nanoparticles, toxicity, pharmacokinetic, proteins molecules, blood-brain barrier.

1. INTRODUCTION

Nanotheranostics is a rapidly growing pharmaceutical technology for tracking the release and delivery of drugs simultaneously and determining real-time therapeutic effectiveness *via* a bifunctional nanoscale carrier. It has been shown over the past decade that imaging (diagnosis) and therapy (drug delivery) can be integrated into one "theranostic nanoparticle" [1]. The nanocarriers include polymeric nanoparticles (NPs) encasing radionuclides, ultrasound-triggered polymeric NPs, superparamagnetic polymer-based NPs, and nano-sized fluorescent polymer formulations. Although John Funkhouser first coined the term 'theranostic' as early as 1988, he successfully illustrated theranostics as substances that incorporate the modalities of therapy as well as their use in diagnostic imaging. This fundamental concept was extended to disease imaging and treatment [2-4]. All these findings suggest that nanocarriers can be efficiently employed for identification, diagnosis, and treatment breakthroughs. There are several advantages to the ideal theranostic nanomaterial: (a) the ability to accumulate selectively in the targeted tissue, (b) the ability to selectively provide successful therapeutic action, (c) the ability to aid in biochemical and morphological characteristics of the disease, and (d) the ability to biodegrade into non-toxic by-products [1, 5]. NPs range in size from 1-100 nm and are significantly smaller (100,000 times) than regular human cells. They have demonstrated significantly stronger surface interactions with biomolecules and better cell uptake through receptors, antibodies, and enzyme-mediated interactions when compared to conventional formulations [2, 6]. For selective detection and treatment, NPs can be coated, functionalized, and incorporated with various bioconjugate moieties employing a surface modification approach [7]. The tumor-targeted theranostic NPs are developed by conjugating variable targeting ligands that hold specificity to bind with overexpressed receptors. Recently, tumor angiogenesis showed promising targets for functionalized organic and inorganic nanomaterials and has demonstrated wide application in cancer theranostics [8]. A variety of targeting ligands such as antibodies, protein fragments, small peptides, proteins molecules, lectin, aptamer, *etc*., have been employed as theranostic NPs [5, 9].

Among the most efficient diagnostic agents, quantum dots (QDs) have shown promising results in theranostic applications. Their therapeutic and diagnostic efficiency is ascribed to their photoluminescence properties [1, 3]. The next generation of targeted NPs allows early diagnosis of disease, concurrent monitoring, and care with minimal toxicity, higher payload, and low off-target accumulation [3]. These systems are competently referred to as theranostic nanocarriers that can simultaneously diagnose and treat the disease and integrate diagnostic imaging and therapeutic modalities. The desired qualities include a biodegradable nature, high surface area, facile surface modifying properties, and practical scale-up for commercialization [3, 4, 10]. For cure and early diagnosis of disease, the theranostics approach has shown favorable results and application in terms of precise accuracy in detecting altered pathological tissue conditions and, at the same time, the ability to offer control drug delivery and biodistribution. These characteristics make QDs promising for therapy, precise doses, and minimized adverse side effects [11, 12].

Literature review suggests that NPs have attained a good standing in therapy and diagnostic usage [13]. NPs are bestowed with numerous properties, namely nanosize, biocompatibility, biodegradability, targeting potential, facile fabrication, surface modification, stability, high encapsulation efficacy, and many more [14]. NPs display enhanced therapeutic activity of the loaded drug leading to an overall improvement in therapeutics and diagnostics. However, the toxicity of NPs is controversial and is under investigation [15]. Along with drug/nanoformulation administration, NPs also enter into our body through various other means, such as from the environment. The multiple portals of entry utilized are depicted

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