



Theranostics Nanomedicine: Recent Advancement, Applications and Challenges

**Shailesh Ghaywat ^a, Payal Dhande ^a, Sneha Gaurkar ^a, Samiksha Upadhyay ^a,
Vaishnavi Raut ^a, Neha Binjhade ^a, Kamlesh Wadher ^{a*} and Milind Umekar ^a**

^a Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Many advancements have been made in treatment and diagnosis tools with the progress in modern medicine and technology. Theronostics are multifunctional nanomaterials that combine therapeutic as well as imaging functions. Theranostic nanomedicines are used for checking drug release and efficacy. The amalgamation of diagnostic and therapeutic agents within a single system provides the target site localization and accumulation of nanomedicines in organs. It provides a transition from conventional medicine to personalized medicine. Many different types of nanomedicines have been evaluated over the years. Theragnostics approach includes pharmacogenomics, personalized medicine and imaging to develop efficient new targeted therapies which will help in better and optimize drug selection along with monitoring the therapy response to increase drug safety and efficacy. This review summarizes the recent development and various nanocarriers developed for nanotheranostics, includes inorganic Nanoparticles, Polymeric, dendrimers, micelles, liposomes, metallic, and carbon nanotubes.

Keywords: *Theranostics; nanomedicine; nanoparticles; personalized therapy; liposomes; targeting.*

1. INTRODUCTION

The past decade witnessed a tremendous progress in the field of diagnostics and treatments due to the advancement in medicinal and pharmaceutical area. Theranostic is an emerging therapeutic system which combines therapy and diagnostic strategy in a nanostructure entity for developing targeted personalized therapy [1]. Theranostic obtained when a single particle (nanoparticle), is fabricated which contain a combination of therapeutic element (drug) and diagnostic/imaging element. In the scientist community, there is increase in the interest for theranostic drug delivery systems for the management of diseases such as, inflammatory and cancer [2]. Recent Innovations in nano delivery system have led to the escalating research work and advancement on nanotheranostics due to various advantages of nanoparticles such as site-specific targeting, thermo stimulation, phototherapy and delivery of combination of drugs [1]. There are various diagnostic/imaging agents utilized in Theranostic nano carriers such as quantum dots, fluorescent dyes and superparamagnetic iron oxides for optical imaging, magnetic resonance imaging (MRI), nuclear imaging and computed tomography [3]. For theranostic applications, various combinations of therapeutic and imaging combinations are possible.

Several drug delivery systems reported to use clinically such as, liposomes, micelles and nanoparticles etc. [4,5]. Therapeutics along with the Imaging agents generally added in to into nanocarrier system, with the aim to provide diagnostic information and thus utilize as

theranostic agents which help to observe drug release as well as drug efficacy [1]. In the present Review article, we discussed the possible use of nanocarrier system for drug delivery and imaging purposes, along with the recent applications and challenges of Theronostics in Pharmaceutical drug delivery development.

2. THERANOSTIC NANOMEDICINE

Due to multifunctional and intrinsic molecular characteristics, nanomaterials have emerged as one of the promising tool in theranostics and biomedical science [6-8]. The variety of Theronostic platforms are explored such as in therapy, formulation design, diagnostics, imaging, drug delivery. Also, utilization for the diagnosis and treatment of many diseases including Inflammations, cardiovascular diseases, diabetes and cancer are shown in Fig. 1.

With the advancement of technology, Nanotheranostics have been developed for checking release, distribution and efficacy of drug through a single nanocarrier system for precise detection and therapy [9-17]. Many researchers worked on nanoparticle based theranostic agents have such as, magnetic, gold, silica Nanoparticles, carbon nanotubes and quantum dots [18-22].

Theranostics nanoparticles are mainly composed of polymeric, lipid based and metallic nanomaterials such as, organic and inorganic materials, nano capsules, micelles, liposomes, dendrimers, quantum dots, and carbon nanotubes as depicted in Fig. 2.



Fig. 1. Theranostic platform and applications in various disease and disorders

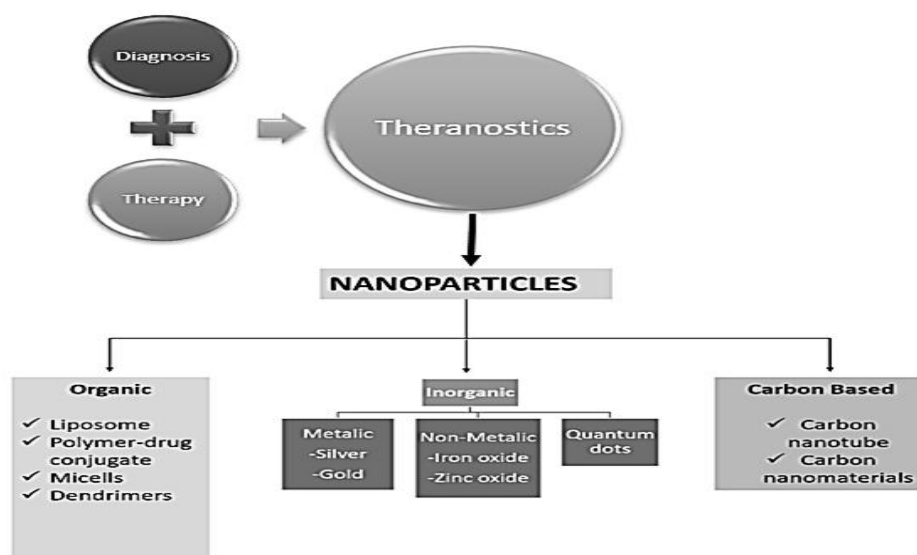


Fig. 2. Various types of nanomaterials for theranostics

2.1 Metallic Nanoparticles for Theranostics

Organic and inorganic nanoparticle used includes, gold, Silver and iron oxides.

2.1.1 Gold nanoparticles

Gold Nanoparticles (AuNPs) are biocompatible, possess excellent physical and chemical properties, prepared as cubes, spheres, rods, and cages and act as a promising agents in terms of both imaging and therapy [23-26]. AuNPs offer the advantage of fictionalization with drugs through covalent and ionic binding and useful for biomedical applications, specially on treatment of cancer. On account of its optical properties AuNPs act as an NIR-active imaging probe for cancer detection facilitating scanning of whole body. AuNPs showed promising results in treating MDR tumors by combining chemotherapeutic agent and photothermal treatment [27-30]. Functionalized AuNPs have wide applications in drug delivery, biological detection, clinical treatment and also reported to be efficient and improve the treatment of gliomas [31,32]. Recently, matrix metalloproteinase-2- sensitive gold-gelatin nanoparticles were developed to pass through the BBB, allowing a pH-triggered release to the glioma specific area [33].

2.1.2 Silver nanoparticle

Silver nanoparticles (AgNPs) have unique characteristics that make them ideal for cancer

diagnosis and therapy and reported to involved in biomedical applications such as drug delivery vectors and theranostics agents [33,34]. Many researchers have worked on preparation of silver nanocomposite particles for cancer theranostics [35] Many researchers worked on and developed AgNPs that showed anticancer activity against different cancer cells, as AgNPs modified by luminescent Ru(ii) complexes can target lysosomes Ru1-2 and can act as a potential theranostic agent [35,36].

2.2 Polymer Based Nanoparticles

Nanoparticulated polymer based systems proven to improve therapeutic efficacy and diagnosis sensitivity. Polymeric Nanoparticles prepared from poly(lactic acid)/poly(lactic-co-glycolic acid) PLA/PGLA, block copolymers, and chitosan are utilized in Theronostics due to their biocompatibility, better physiochemical characteristics, nontoxicity and storage stability [37,38]. Fluorescent polymeric nanoparticles (FNPs) were researched as theranostic agents for cancer detection and treatment [39,40].

Polymer based magnetic nanoparticles (PMNPs) have applications in targeted drug delivery, cell tracking, tissue engineering and bio separation and found to be an efficient nanotheranaostic system for diagnostics as well as drug delivery [41,42]. Dendrimers, highly branched macromolecules have found

many applications in theranostic nanomedicine. Many researchers have developed dendrimers for cancer theranostics [43].

2.2.1 Drug-polymer conjugates

Conjugated polymer nanomaterials (CPNs), found to be promising theranostic agent as it possesses both optically and electronically properties. CPNs include protein conjugates and drug conjugates with appropriate polymers and are used for theranostics because of high stability, non-toxic and biocompatible nature [44, 45]. These are easy to prepare, tunable in their size, and nonbleach able which makes ideal for for biomedical fluorescence and photoacoustic imaging as well as for theranostic applications [46] Yuan et al synthesized poly(HPMA) based theranostic copolymers loaded with Cu-64 and used as targeting ligand for targeting tumor angiogenesis [47].

2.2.2 Chitosan nanoparticles

Several researchers have conducted studies on chitosan Nanoparticles (CNPs) for CANCER drug delivery. CNPs generally used for a disease specific theranostic delivery system of different imaging agents and therapeutics CNPs also used as co delivery strategies in combination with diagnostics and image guided therapy to improve therapeutic effects [48]. CNPs developed as theranostic agents because of their good loading capability, biodegradability, biocompatibility, bioadhesiveness and physiological stability.

Loutfy et al. synthesized CNPs for evaluation of the in vitro human carcinoma cell model (HepG2) and reported that, CS-NPs are suitable for drug delivery proposes for cancer of the liver [49].

2.3 Lipid Based Nanoparticles

lipid-based nanocarrier (LNPs) because of their biocompatibility, biodegradability, structural simplicity, found to be safe and easy for manufacturing for cancer theranostics. Bondi et al, (2015) prepared LNPs for the controlled release of sorafenib. And found that, these nanocarrier can be a good delivery agent for liver cancer [50]. Zhao et al, (2015) developed doxorubicin and curcumin LNPs and reported to have excellent inhibitory effect on tumor growth [51].

2.3.1 Solid lipid nanoparticles (SLN)

The solid lipid nanoparticles (SLNs) consist of drug along with solid lipids, surfactants/co-surfactant and explored by many researchers for use in cancer Theranostics [52]. SLNs due to their small size and lipophilic surface gets easy access to the blood compartment to cross tight-endothelial cells of barrier for brain targeting. Kuang et al developed IR-780 iodide loaded tumor vasculature targeted SLNs to monitor PTT by imaging at glioblastoma tissue [53-55]. Bae et al. reported quantum dots loaded SLN for anti-cancer theranostics [56]. Videira, MA prepared and studied lymphatic uptake of pulmonary delivered radiolabelled solid lipid nanoparticles [57].

2.3.2 Liposomes

Liposomes used as a nanocarriers for the delivery of many drugs and diagnostic agents are most popular because of biocompatibility, biodegradability and their surfaces properties can also be modified for use in cancer targeting [58,59]. The liposomes can successfully protect the functional components from the external environment, prolong the systematic circulation time, and enhance their tumor accumulations [58]. Many researchers have worked on liposomal formulations that have applications in targeting, therapeutic, and imaging functionalities. Liposomes have capability to encapsulate diagnostic and therapeutic agents which ultimately led to utilizing liposomes as nanocarriers for theragnostic applications. liposomes as nanocarriers is used for theranostic applications such as for simultaneous detection and treatment of heavy metal toxicity and cancers. Hybrid liposomes (HL) reported to have ability to detect tumors in an orthotopic graft model mouse of breast cancer which found to have theranostic significance in patients with breast cancer [60-66].

2.3.3 Micelles

Polymeric micelles are self-assembling colloidal structure with a hydrophobic core and hydrophilic shell and used theranostic carriers and imaging probes [67]. Therapeutic/ diagnostic agents is loaded into hydrophobic core of micelles and also the outer hydrophilic layer with targeting agent, which might then be administered intravenously. Kumar R et al, Synthesized phospholipid based micellar system

encapsulating QDs /doxorubicin and showed a sustained release from the micellar core over a period of 7 days [68-71].

2.3.4 Dendrimers

Dendrimers are branched nano delivery with controlled functionality and efficiently tailored for the spatial distribution of varied functionalities on their surface. These versatile functions, which permit stimuli–response ability and also the ability to self-assembly, make dendrimers excellent candidates for theranostic applications [72]. Sk UH et al, discussed the in vitro and in vivo applications of dendrimers in many diseases including cancer and explored its use as imaging agents for fluorescence imaging and magnetic resonance imaging [73]. Saad and coworker designed, and evaluated a theranostic dendrimer to deliver paclitaxel and diagnostic agent [74]. Taratula et al. developed a novel dendrimer based theranostic platform for tumor- targeted delivery of phthalocyanines. Which revealed the significant potential of dendrimers as an efficient theranostic agent [75].

2.4 Carbon Nanomaterials

2.4.1 Nano carbons

Nano carbons, such as carbon nanotubes (CNTs), graphene derivatives and carbon dots (C-dots) possess inherent optical properties which makes them useful contrast agents in optical imaging and sensing [76-78] CNTs are useful for theranostic applications since they improve the effect of chemotherapeutic drugs and are adaptable to clinical applications [86-88]. Chen et al., reviewed the applications of functionalized fullerenes in tumor theranostics [89]. Xu and co-workers investigated the influence of oxidized multiwalled CNTs on macrophages and in cancer immunotherapy [90]. Shen H and co-workers reported the applications of graphene and graphene derivatives in drug and gene delivery, cancer therapy, biomedical imaging, biosensing and tissue engineering [91].

3. RECENT ADVANCEMENT OF THERANOSTIC NANOPARTICLES

The Table 1 summarized the recent applications and advancement of Theranostic Nanoparticles

Table 1. Recent advancement of theranostic nanoparticle

Types of theranostic nanomaterials	Theranostic advancement	References
Liposomes	Targeting and Imaging	[79]
Gold Nanoparticles	Improve the treatment of Cancer	[80]
	Stimulus responsive drug release	[81]
Magnetic Nanoparticles	Increase accumulation in brain tumors	[82]
Drug-polymer conjugates	Cancer imaging and radio chemo-therapy	[47]
Solid lipid Nanoparticles	Multimodal Therapy	[83]
Polymeric nanoparticles	Therapeutic efficacy and diagnosis sensitivity	[84]
Dendrimers	Stimuli–response ability	[75]
Micelles	Delivery of single theranostic agent	[85]
Carbon Nanotubes	Improve the effect of chemotherapeutic agent and translatable to clinical application	[86,87]
Carbon nanomaterials	Self-photoluminescent and photothermal property	[88]

4. CHALLENGES

The challenges associated with theranostic nanomedicine are interaction and compatibility between nano material and biological components which shows immunoreactions and inflammation along with the safety profile in humans [92]. The major challenge associated with thetheranostic nanomedicines is the difficulty in control and reproducibility of the formulation process. Since theranostic nanoparticles are multifunctional unit, more accurate formulation approach and control along with good manufacturing practice are needed [93]. Also, more stringent regulatory steps are needed to bring theranostic nanomedicine from research lab to clinical use.

5. CONCLUSION

Nano theranostics is a field that conglomerates the merits of diagnosis and therapy. Theronostics not only takes advantages to deliver the drug but also useful in imaging and diagnose functions. The NP based theranostic involves gold, magnetic, carbon nanotube,etc. and have shown potential outcome in cancer and other diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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