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Review Article

UNDERSTANDING NANO-BIO-INTERACTIONS WITH CORRESPONDING BIOLOGICAL RESPONSES: INSIGHTS AND IMPACT ON NANO ASSEMBLY AND DISASSEMBLY

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ABSTRACT

Using stimuli-responsive Bio Interactions with controlled nano-assembly is proving a potent method for generating theranostic nanosystems that satisfy the needs of modern medicine for example, targeted delivery which is very helpful for cancer treatment with minimum side effects. However, because of the limitations in our knowledge, this promising topic is still in the proof-of-concept stage. This study provides an overview of the most recent theoretical and experimental advancements in biological fate, functional activity of nano-assemblies, and nano-bio interactions with exogenous stimulus-triggered systems (Light-responsive systems, Ultrasound-responsive systems, Magnetic field-responsive systems, and Thermal-responsive systems)endogenous stimulus-triggered systems (Ph-Responsive Systems, Redox-responsive systems, Enzyme-responsive systems) and multi stimuli system**.** Related biological consequences reactions. Firstly, we intend to thoroughly explain these relationships in this review. The relationship between interaction studies and nano-based stimuli; the important physicochemical characteristics of *in vivo* stimuli, such as responsive assembly and disassembly; biological applications; and pharmacokinetic (pk) parameters based on nano-bio interaction.

Keywords: Nano-bio interaction, Nanotechnology, 2-Dimensional, Assembly, Disassembly

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INTRODUCTION

The Introduction and all sections of this review article were searched from specialized databases such as Elsevier, PubMed, Science Direct, Springer, and Google Scholar, and online published articles from the International Journal of Applied Pharmaceutics, Nature, JDDST, Nanomedicine, Nano Today, ACS Omega, etc. with searching keywords nano-bio interaction, Assembly, Disassembly, stimuli responsive. The range of the year of literature review article 1989-2023.

The range for nanoscale is 1 to 100 nanometres. Nanotechnology plays a vital role in pharmaceutical sciences, disease treatment, identification, etc. Nanotechnology gives facility to the targeted delivery, which is a very interesting topic for understanding how Nanomaterials (NMs) interact with biological molecules, to understand that concept, we discuss some important topics in this review. First, Nanomedicine entering into biological fluids, engineered nanomaterial can rapidly interact with various biomolecules, which mainly contain the three following aspects;

(1) Absorption of a biomolecule on the surface of nanomaterials (2) reconstruction and change of functional proteins and (3) redox reaction between nanomaterial and biomolecule.

Then, NMsenter the cell with different uptake inhibitors and state-of-the-art techniques such as transmission electron microscopy or confocal microscopy are used to study the cellular trafficking of NMs. The NMs react with the cells with uptake pathways, including the clathrin-mediated, caveolae-mediated, and lipid raft-mediated endocytosis and phagocytosis, as well as pinocytosis and micropinocytosis. Phagocytosis is normally for specialized cells such as monocytes and macrophages. Small size and protein adsorption in cell culture media, NMs are mostly consumed by cells through endocytosis, trapped into endosomes, entered into lysosomes, and then excluded from the cells. However, some NMs can get out of endosomes and enter other organelles such as cytosol, mitochondrion, and nucleus [1, 2].

How nano-based stimuli connect with interaction studies

Nano-based stimuli

The influence of nanotechnology in medicine is substantial, particularly in utilizing nanomaterials like metallic Nanoparticles (NPs), which offer numerous advantages. These intelligent nanomaterials are highly sought after due to their responsiveness to a range of extrinsic (e. g., optical, ultrasound, magnetic fields, and thermal state) and intrinsic (e. g., pH, redox potential, and enzymes) stimuli. Leveraging their interaction with the biological system, they hold promise for the evolution of highly effective therapeutic administration systems [3, 4].

Exogenous stimulus-triggered systems

The extrinsic stimulus-triggered system engages drug delivery through external factors like light, ultrasound, magnetic fields, and temperature. This system aims to reduce inter-patient variability by directly applying physical stimuli to the specific tissue for triggering drug release. It offers numerous advantages, enabling controlled and targeted drug release while minimizing side effects on surrounding healthy tissues [5, 6] All the factors are discussed below.

Light-responsive systems

Light-responsive systems represent an extensively explored exogenous system in drug delivery. Electromagnetic radiation with diverse wavelengths, including ultraviolet, visible, and near-infrared light, can modify the structure of light-responsive nanocarriers, thereby enabling controlled drug release at specific locations. The versatility of light as a stimulant from its adaptable nature and high precision, makes it highly applicable for targeted drug delivery and control. Photothermal effects of light, converting it into heat, have been extensively investigated. This concept involves heat generated from light activating heat-sensitive nanocarriers, disrupting their nanostructure by breaking hydrophobic and hydrophilic linkages, thereby facilitating drug release at desired sites. For instance, Li *et al.* developed nanocarriers equipped with the hydrated moieties AMD3100 and the lipophilic NIR light-to-heat converters IR780 [7]. Guardado-Alvarez *et al.* capitalized on the high spatial resolution, subcutaneous delivery, and attenuated diffusion properties of NIR radiation to achieve drug release from developed siliceous mesostructured NPs jointly with a disulfide-attached β-cyclodextrin cap. Optical-responsive bio-inert micellar therapeutic delivery systems further underscore the significance of light as a stimulus. The creation of coumarin-modified block copolymers in micelle-drug conjugates demonstrated controlled drug emit of the oncolytic

mediator 5-FU under UV irradiation (254 nm) [8]. Peng and colleagues engineered a photo-responsive hydrogel by linking trans-configurated nitrophenyl groups to dextran and pairing it with a cyclodextrin-decorated dextran. Upon exposure to light, the azobenzene is isomerized, causing the release of encapsulated entities. Utilizing Upconverting Nanoparticles (UCNPs), dynamic optically triggered substances can be charged. Xiang *et al.* developed UCNPs containing an amphipolar di-block copolymer with a UV-responsive lipophilic sphere, releasing drugs under the influence of NIR radiation (wavelength 908 nm), altering the micelle structure due to UV light absorption by the copolymer and inducing disproportion in amphiphilic balance [9-11].

Ultrasound-responsive systems

Ultrasound waves possess thermal, mechanical, and radiation force properties, which contribute to targeted drug release. The medical field widely explores ultrasound technology for imaging-guided drug delivery because of its reliability, parenchyma-penetrating ability, non-intrusion, and precise space-time domination, enabling focused treatment on specific areas [12]. In the exploration of ultrasound potential, an innovative ultrasound-reactive system loaded with doxorubicin was devised employing poly (D, L-lactide-co-glycoside)-methoxy-poly (ethylene glycol) to complex doxorubicin. This system was transformed into stable nanobubbles through boiling. Minimal drug release was observed in the absence of ultrasound exposure [13-15]. Another study focused on Microbubbles (MBs) as ultrasound-enhancing agents carrying mRNA-lipoplexesNPs. Numerous studies have utilized MBs for ultrasound-facilitated gene delivery. For instance, Hossack *et al.* developed a method utilizing ultrasound-facilitated plasmid DNA delivery from cationic MBs for vascular myocytes. Microbubbles carrying reporter plasmid DNA were sonicated near smooth muscle cells in an *in vitro* setting using varying acoustic pressures (ranging from 0 to 950 kilopascals) and pulse durations (ranging from 0 to 100 cycles) [16-18].

Magnetic field-responsive system

Recently, magnetically sensitive systems attained considerable cognitive engagement medical field account of advancements in Magnetic Nanoparticles (MNPs) and their application in biomedical and clinical domains. These systems incorporate fabricated metal and superparamagnetic oxide MNPs that exhibit responsiveness to both internal and external stimuli [19, 20]. MNPs play a pivotal role in magnetic-responsive nano-systems due to their biocompatibility and facile synthesis via various techniques such as hydrothermal methods, ignition, thermal decomposition, chemical vapor deposition, and carbon arc, among others. Studies indicate that MNPs, being small with a substantial specific surface area, facilitate cellular activities and signaling for ex vivo and in situ remote control cellular, enabling a promising potential for drug delivery systems [21, 22].

Previously, magnetoactive nanomembrane-based PNIPAAM nanogels and NPs were developed. Results indicated that these membranes were cell-bio-friendly and maintained their modifiable flow characteristics post-45 days of subcutaneous embedding [23]. Various mechanisms, including magneto-driven hyperthermia and directed therapeutic delivery, have been investigated to comprehend magnetic-reactive systems [24]. For further exploration of these mechanisms, Thirunavukkarasu *et al.* fabricated Superparamagnetic Iron Oxide NPs (SIONPs) for therapeutic applications. In this study, SIONPs and Doxorubicin (DOX) were loaded into a poly (α-hydroxy acids) (PHA) medium, reacting to the thermal effects induced by SIONPs under magnetic field influence, consequently facilitating the release of DOX. Ex-vivo assay demonstrated thermotolerance of the PHA medium, showing approximately 37 °C, drug release reached 39%, while at 45 °C, it increased to 57% [25]. In separate work, Wang *et al.* developed an implantable chitosan-based hydrogel integrated with magnetic properties, incorporating hydrophobic (rifampicin) and hydrophilic (Adriamycin) medications, exhibiting controlled drug release at targeted sites [26]. Reports indicate that alternative magnetic fields can control the timing and dosage of drug release from nano-formulations. The formulation of Pluronic/poly (ethylene imine) polymeric nanospheres stands as an illustration of an alternative magneto-sensitive system, enabling the triggered delivery of siRNA at targeted sites. Stable nano-sized polyelectrolyte complexes containing anionic siRNA-PEG conjugates facilitated the release of drugs through cleavable disulfide linkages [27]. A study introduced the utilization of triblock copolymer, poly [(acrylic acid)-block-(N-isopropyl acrylamide)-block-(acrylic acid)], in magnetic field-responsive systems. These copolymers, self-assembled into magnetic nanocarriers (SAMNs) by immobilizing amine groups on iron oxides (Fe3O4-NH2), were further grafted with folic acid for additional targeting effects. Encapsulation of the hydrophobic anticancer drug curcumin, into SAMNs resulted in enhanced curcumin release upon exposure to the magnetic field because of the paramagnetic behaviour of SAMNs [29].

Thermal responsive systems

Thermal-responsive systems represent an area of exploration in extrinsic triggered systems within medicinal fields for both intervention and assessment techniques. Tumour sites typically exhibit higher temperatures (40–42 °C) compared to healthy tissues (37 °C). Thus, heat-sensitive nanospheres sustain their load at ambient temperatures and liberate upon exposure to hyperthermia in infected sites [30]. Two primary strategies dominate the exploration of thermo-responsive systems. In the first, drug loaders are synthesized to emit the drug when exposed to hyperthermia. For instance, polycaprolactone (N-isopropyl acrylamide) (PNIPAM) conjugated with nanostructured carbon effectively released drug molecules in response to higher temperatures (40 °C). This resulted in a substantial decrease in impaired cellular functionality was observed at 40 °C, showing a 20% reduction in viability relative to the baseline viability observed at 37 °C following nanotherapeutic intervention. The secondary approach revolves around utilizing pharmaceutical carriers engineered for an immediate or rapid release triggered by elevated temperatures induced via an external stimulus. This trigger initiated a thermo-responsive agent in the vector to generate thermal energy, prompting rapid drug liberation at the intended area [31, 32]. The integration of block polymers in thermo-responsive systems has provided a new area in the pharmaceutical field. Block polymers with thermo-responsive monomers enable the manipulation of the Lower Critical Solution Temperature (LCST) to a desired point. PEG-b-PNIPAAM copolymers formed micelles via Atom Transfer Radical Polymerization (ATRP) when exceeding the thermal threshold. These micelles, comprising PNIPAM-b-PMMA, exhibited enhanced drug liberation upon reaching temperatures beyond the LCST point of 38 °C [33, 34]. The therapeutic efficacy of hydrophobic anti-neoplastic agent Paclitaxel (PTX) was notably enhanced when loaded into nanoparticles, given the formulation's prolonged vascular transit time conditions, with the LCST surpassing normal body temperature [35, 36]. An innovative method using a temperature-responsive macromolecular drug carrier, Elastin-like polypeptide (ELP), effectively localized neoplasms. ELP clusters attached to tumor blood vessels only expose tumors to 41.5 °C heat. Upon returning to febrile temperature, these particles solubilized within the plasma, augmenting vascular density and facilitating increased recanalization of ELPs penetrating neoplastic vascular networks, leading to substantial extravascular accumulation [37-39]. Another approach to achieve thermal responsiveness in drug formulation is through cryotherapy. Zhang *et al.* fabricated nanospheres with a core-shell loaded with pluronic F127 and chitosan, leveraging their inherent heat-triggered swelling and shrinking characteristic. These nanospheres, when combined with cryotherapy, demonstrated a high permeable barrier and effective encapsulation of small therapeutic agents, showing promise in disease treatment [40-42].

Endogenous stimuli-responsive systems

Biological responses can be elicited through the utilization of endogenous stimuli, including fluctuations in pH levels, variations in tissue-specific enzyme concentrations, and gradients in reduction-oxidation (redox) potentials [43].

Ph-responsive systems

The biological system encompasses distinct pH gradients across various organs, offering an advantage for pH-responsive nanocarriers. These carriers undergo conformational changes or cleavage of pH-responsive bonds at particular pH values, releasing

their cargo drugs precisely at the intended site. Hemodynamic and healthy tissues typically maintain a pH of approximately 7.4; conversely, tumor interstitial spaces and inflamed areas have an approximate pH of 6.5. Intracellular organelles like endosomes exhibit a pH of 5–6, while late lysosomes have a pH range of 4–5 [44-47]. Numerous materials exhibit responsiveness to pH stimuli, encompassing both organic and inorganic substances. Recently, dendritic polymers have gained prominence in pH stimuli-responsive systems due to their manipulative properties, including solubility, volume, and conformation [48]. Their biological effectiveness is enhanced when combined with Polyethylene glycol, altering structure, size, and biocompatibility. Moreover, coupling dendritic polymers with antitumor drugs through hydrazine bonds has shown increased effectiveness in cancer treatment [49]. pH-responsive nano-systems have been employed to deliver hydrophobic anticancer drugs to specific sites. For instance, the fabrication of Curcumin (CUR) DOX-loaded polyethylene glycol nanoparticles combined with transferrin (Tf) demonstrated accelerated release of both CUR and DOX in mildly acidic environments, highlighting the pH-dependent drug release in this setup [50]. Another innovative approach engages emergent-organization hyaluronic acid NPs using calcium phosphate to create hydroxyapatite NPs incorporated DOX. These minerals dissolve upon exposure to low pH, thereby releasing the drug at specific tumor sites [51]. Moreover, polymers comprising ionizable clusters, like amines and carbonic acids, show promise in developing pH-responsive nanospheres. Utilizing a PMAA–PMA copolymer significantly enhanced the bioequivalence of cyclosporine A, exhibiting the drug emitted at pH>6, thereby preserving the drug from acid decomposition after passing through the stomach [52]. Ulbrich *et al.* developed an HPMA (N-(2-hydroxypropyl) methacrylamide) polymer linked utilizing hydrazone groups as pH-triggered linkers for attaching the antineoplastic agent DOX. These conjugates remained stable at pH 7.4 and effectively emit the drug at pH 5. Additionally, they coupled an antibody to the polymer backbone to attain efficient directing of T cell lymphoma EL 4 cells [53-55].

Redox-responsive systems

In our biological system, the extracellular and intracellular spaces exhibit a redox potential difference of approximately ~100–1000 fold, along intercellular environment being oxidative and intracellular being reductive. An emerging paradigm shift in therapeutics involves this redox potential gradient in redox-responsive systems for targeted drug delivery [56]. Redox-sensitive nanocarriers, particularly in gene delivery, offer promising avenues for protecting plasmid DNA or siRNA outside the cell and releasing them upon cellular entry [57]. Recent investigations by Xiao *et al.* highlighted an oxidation-reduction signaling system using silica nanoparticles conjugated alongside DOX via an amphiphilic peptide, including a disulfide bond. These nanoparticles securely retained the drug DOX, exhibiting minimal escape in blood circulation and normal cells. Intracellularly, rapid and substantial drug release occurred only upon cleavage of the disulfide bond interjacent the nanospheres and the drug due to the redox potential gradient. This system capitalizes on substantial variances in GSH levels amidst tumor cells, the extracellular matrix, and normal cells, resulting in mitigated toxicity and increased tumor selectivity [58]. Similarly, Zhang *et al.* employed DOX with a PFG polymer, exploring redox-responsive systems extensively by employing a preclinical breast carcinoma prototype. They integrated thioketal, a Reactive Oxygen Species (ROS) potential stimulator for tumor cells, resulting in enhanced intracellular drug delivery via Glutathione (GSH) activation. This redox-responsive nanocarrier exhibited significantly higher drug-loading efficiency, improved stability, and enhanced cellular uptake [59]. Studies have observed that GSH can upset disulfide coupling within NPs in redox-triggered systems [60]. Additionally, Tirelli *et al.* demonstrated that polysulfide-containing nanocarriers can respond to oxidants present in their surroundings [61].

Enzyme-responsive systems

Enzyme-triggered systems primarily depend on ester hydrolysis by various enzymes within the biological system [64]. Cathepsin B (CTSB) finds extensive use in enzyme-responsive systems for site-specific drug delivery due to its amplification of carcinoma [65]. Tarassoli *et al.* investigated CTSB for the emission of indocyanine green (ICG) from polyglutamate (PGA) NPs. They developed biodegradable and self-assembled PGA-NPs incorporating ICG, reporting tumour-targeted drug emission and low toxic profile due to CTSB overexpression [66]. Mao and Gan formulated hydrophilic-phobic poly(glycidol-block-ε-caprolactone) (PG-b-PCL) encapsulating a model compound. In addition to lipase, blockage of PCL decreased, suggesting that the enzyme could still split the ester bonds owing to the kinetics of amalgamation and segregation [67, 68]. Moreover, Minko and colleagues linked paclitaxel to PAMAM G4 dendrimers and then succinate. This system released the drug when ester bonds were broken by esterase, exhibiting superior cell toxicity than the unbound moiety [69]. Aimetti *et al.* investigated a 4-arm PEG norbornene hydrogel using a peptide cross-linker with terminus thiol moiety. Drug release from this system occurred upon contact with human neutrophil elastase [70]. Additionally, Ghavami *et al.* fabricated Phospholipase-Sensitive Liposomes (PSL) as a drug-delivery system, where liposome degradation was triggered by tumor cell-derived phospholipase A2 (sPLA2). The activation of PNA release by>80% of phospholipase indicated its potential as an agent to release drugs from enzyme-responsive systems [72]. An enzyme-responsive nanomaterial based on an HPMA triblock copolymer was developed, self-assembling into NPs approximately 85 nm in diameter. This system precisely emits the antineoplastic agent paclitaxel in the cancer microenvironment [73].

Multi stimuli-responsive systems

Multi-stimuli triggered systems, capable of responding to two or more distinct stimuli, are garnering significant interest in therapeutic applications. These systems combine stimuli like pH, temperature, redox potential, magnetic fields, and more within the same matrix [74]. They function as intelligent carriers, precisely releasing their payload at targeted sites in controlled amounts [75]. Examples of multi-stimuli responsive systems include pH-redox, photo-magnetic, and thermo-redox combinations [76]. Qian *et al.* investigated a multi-stimuli system where the outcomes of the principal stimulus served as an auxiliary stimulus to enhance specificity and synergistic efficacy. They developed a conjugated polymeric nanoparticle exposed to light irradiation, resulting in O_2 generation and inducing cellular apoptosis [77]. In a related study, Lu and associates explored a tri-stimuli delivery system (redox/pH/photo-responsive) comprising organo-silica and copper sulfide nanoparticles (DOX-CuS@PMO) cross-linked by thiol bonds. Their biological evaluation using the U87MG human glioblastoma cell line and a glioblastoma mouse model demonstrated enhanced cellular internalization upon mild laser irradiation of DOX-CuS@PMO [78]. Researchers have also employed bi-stimuli systems, where pH and NIR stimulus are used to fabricate hollow mesoporous copper sulfide NPs (HMCuS NPs) loaded with DOX and coated with hyaluronic acid (HA). This system efficiently delivers the payload to tumor sites as the outer layer of DOX-loaded nanoparticles degrades due to hyaluronidase, influenced by pH and NIR. Similarly, the sensitivity of multi-responsive systems to temperature and redox potential has been explored, enabling specific drug release in the tumor microenvironment [79-81].

Section snippets

The key physicochemical parameters of *in vivo* stimuli-responsive assembly-disassembly

Nanoparticle assemblies and disassemblies play an integral role in nanoparticle functionality, ensuring stability before reaching the target site and subsequently activating their function through assembly or disassembly in situ [82]. This stimuli-responsive assembly-disassembly can lead to unexpected biological outcomes [83]. Recent studies have shown the emerging selective "turn-on" performance of *in vivo* stimulus-responsive nano-assemblies and disassemblies, demonstrating their potency in various therapeutic conditions, such as tumor treatment. Comprising eco-friendly polymers, triggered groups, and pharmaceutically bio-active molecules, these *in vivo* stimulus-responsive systems are designed for targeted drug delivery. They energetically react to the intrinsic microenvironment, enhancing therapy efficacy and enabling control over degradation speed and

clearance from the body. The strategies for delectable assembly/disassembly mechanisms revolve around corrupting the delicate equilibrium between the entropy and enthalpy of nano-systems upon cellular/extracellular stimuli in target tissues. These stimuli include the acidity of the microenvironment, overexpressed proteins/enzymes, and high levels of reduced GSH and ROS among others. Dynamic nano assembly/disassembly-based drug delivery systems are adaptable structures that change in response to biological microenvironments [85-87]. Researchers are increasingly interested in exploring stimuli-responsive controllable assembly/disassembly strategies to enhance the efficiency of drug-associated nanosystems. Typically, small units are assembled into nanoscale assemblies to achieve tumor accumulation via the Enhanced Permeability and Retention (EPR) effect, minimizing rapid excretion. Upon reaching the complex tumor microenvironment, these triggered nano assemblies undergo disassembly, releasing their inner active substances, thereby enhancing their therapeutic efficacy. Stimulus-responsive modification can also alter the characteristics of nanoparticles, particularly their size and shape, to achieve desired effects in imaging, therapy, and bioelimination. Therefore, a detailed discussion on pH-stimuli-responsive assembly-disassembly, redox-responsive assembly-disassembly, and enzyme-responsive assembly-disassembly is needed [88, 89].

Ph stimuli-responsive assembly-disassembly

The pH conditions within various human body organs, including the blood (pH 7.2–7.4), endosomes (pH 5.0–6.2), and even the tumor interstitial environment (pH 6.5–6.8), can trigger pH-stimuli-triggered assembly-disassembly processes within cells. The design of pH-responsive diagnostic nanosystems primarily relies on the protonation of specific moieties (e. g., amines). These triggers disrupt the hydrophilic-lipophilic balance, resulting in direct drug release at the target site. The wide usage of pH values at the target site serves as a broad-spectrum stimulus, ultimately enhancing pH-stimuli-responsive assembly-disassembly [90, 91]. In tumor therapy, pH-responsive disassembly has shown promise. Molecules of interest encapsulated in pH-triggered amphiphilic polymers aggregate in the hydrophobic core and undergo self-quenching. They are triggered to disassemble into highly fluorescent molecular units within the acidic tumor microenvironment [92]. Distinguishing neoplastic tissues from surrounding healthy tissues can be achieved with high specificity through pH-responsive assembly-disassembly. For instance, glycyrrhizic acid-modified gold nanoparticles assemble at normal tissue pH (pH 7.4) and disassemble at the tumor extracellular pH (pH 6.8), facilitating cellular uptake of the nanoparticles. This reversible pH-stimuli-responsive assembly-disassembly process can enhance Computed Tomography (CT) imaging for tumor therapy [93]. Redox-responsive assembly-disassembly techniques have gained attention due to the differing redox potential between normal and abnormal tissues. Research focuses on redox-sensitive linkers, such as disulfide bonds, which play a crucial role in this strategy [94]. In redox-responsive nanosystems, payload drug release occurs through the reduction of disulfide bonds, breaking the cross-linkers used for assembly, and degrading hydrophilic bonds, leading to disassembly. Advancements in redox-responsive assembly-disassembly involve utilizing Nile red-based amphiphiles bearing redox-cleavable disulfide bonds that exhibit enhanced binding to the system [95]. Disulfide bonds respond differently in the tumor microenvironment, promoting the self-assembly of small units. For instance, Liang and colleagues developed a Cys(StBu)-Lys(Ru(bpy)3 2+)-CBT probe for tumor imaging that self-assembles into Ru(bpy)3 2+NPs within cells under the influence of the redox potential [96]. Enzyme-responsive assembly-disassembly strategies leverage the catalytic activity of endogenous enzymes. Diseases often involve the overexpression of specific enzymes like Alkaline Phosphatase (ALP), matrix metalloproteinases (MMPs), and furin, paving the way for enzyme-responsive assembly-disassembly. Nanoparticles carrying drug payloads reach the target site and release drugs upon catalysis by these overexpressed enzymes, so many stimuli actions with assembly mechanisms and responses are discussed below in table 1 [97]. Drugs combined with enzyme-sensitive linkers, incorporated into amphiphilic polymers, aggregate in the hydrophobic core. Upon contact with specific enzymes overexpressed at the target site, these assemblies disassemble and release the drug [98]. Furthermore, endogenous enzymes are explored to enhance the accumulation of nanoparticles in biological systems, particularly in tumor imaging. Combining tumor probes with in situ enzyme-responsive assembly-disassembly mechanisms can "turn on" tumor-associated enzyme activity, enabling imaging in living cells [99].

Table 1: List of stimuli-responsive assembly and disassembly

Stimulus		Preparation	Responses	Assembly mechanism	Ref
pH	3 amines	2-(Dipropylamino)ethyl methacrylate (DPAMA)	Disassembly	Lipophilic effect	[100]
	Imidazole	Octadecylamine-p(API-Asp)10, Pt NPs	Disassembly	Lipophilic effect	[101]
	2-Pyridylamine	Au-DNA-αCDs	Assembly	Complementary nucleotide bonding	[102]
	Hydrazone	AuNP(Au-AK), azide	Assembly	Click chemistry	[103]
	Cytosine rich i-motif array	DNA with G-quadruplex and cytosine rich i-module array, DOX, Au NPs	Assembly	i-motif shift	[104]
Redox	Disulfide bond	Paclitaxel-loaded poly(ethylene glycol)-disulfide-paclitaxel conjugate NPs	Disassembly	Lipophilic effect	[105]
	Disulfide bond	Polyethylene glycol-polylactic acid with disulfide	Disassembly	Hydrogen bond	[106]
	Disulfide bond	Poly(ethylene glycol)-b-poly(l-lysine)-bpoly(l-phenylalanine)	Disassembly	Disulfide cross-links	[107]
	Disulfide bond	5-[4-(Prop-2-yn-1-yloxy)benzyl]-1,3-dioxolane-2,4-dione Tyr(alkynyl)-O-carboxyanhydrides, bis-(azidoethyl) disulfide as a cross-linker	Assembly	Click chemistry	[108]
Enzyme	Gelatin	Gelatin, IONPs@Au	Disassembly	Lipophilic effect	[109]
	GCNSGGRMSMPVSNGG– HYD	Maleimide-functionalized HA	Disassembly	Ionic forces	[110]
	GPLGLAGGERDG	Carboxylic acid-functionalized norbornene with GPLGLAGGERDG	Assembly	Lipophilic effect	[111]
	GPLGLAGGWGERDGS	Alex647-PPA-l (l-amino acid peptide)	Assembly	Lipophilic effect	[112]
	Pro-Leu-Gly-Val-Arg-Gelatinase	Purpurin 18-Pro-Leu-Gly-Val-Arg-Gly (P18-PLGVRG)	Assembly	π–π stacking	[113]
	Phosphate bond	Indocyanine green	Assembly	NapFFKYp Head-to-tail arrangement	[114]

ADME (Absorption distribution metabolism excretion) in nano-interaction

The pharmacokinetics of nanoscale formulations differ significantly from those of conventional formulations. Understanding the relationship between drug pharmacokinetics, encompassing absorption, distribution, metabolism, and elimination, and nanoscale preparation is crucial. The impact of characteristics (such as size, surface polarity, charge, and bioadhesive properties) of NPs on ADME profiles is paramount [115].

Size

The size of NPs plays a pivotal role in the formulation of ADME as it influences uptake by enterocytes and M cells within the biological system. Additionally, cellular uptake through the paracellular route

depends on NPs size, particularly when the NPs substance inherently enhances transmissivity by opening a permeability barrier [116]. Studies have demonstrated size-dependent absorption mechanisms; for instance, carboxylated chitosan-grafted poly (methyl methacrylate) NPs of varying sizes (300, 600, and 1000 nm) were evaluated *in vitro* using caco-2 mono-cultures and co-cultures with M cells. Smaller particles exhibited greater transportation through all routes compared to larger NPs. Similar size-dependent ADME trends have been observed in studies with decomposable PLGA NPs using the Caco-2 model [117].

Surface polarity

Surface polarity significantly affects nano-bio interactions and ADME. Enhancing NP stability through surface polarity helps prevent NP aggregation in the gut lumen and may reduce enzymatic degradation [118]. However, increased surface polarity might decrease intestinal permeability [119]. This property is often utilized to reduce protein adsorption on NP surfaces, potentially leading to reduced hepatic clearance [120].

Charge

The charge on NPs affects formulation stability, influencing NPs clustering in the gut lumen and the absorption process. Upon contact with the biological system, the charge density of NPs can undergo alterations [121]. Assimilated into the peripheral circulation, charged NPs, specifically ones, interact with plasma proteins, leading to aggregation. Superiorly charged NPs are likely to exhibit increased accumulation in target tissues [122].

Bioadhesive properties

Bioadhesive NPs impact the ADME process by prolonging the dwell span in the gut and maintaining extended interaction with gut exterior barriers, potentially improving ADME [123-124]. Recent studies have explored the impact of bioadhesive NPs not only on absorption but also on NP distribution within the biological system. For example, attaching a biocompatible layer (poly(butadiene-maleic anhydride-co-L dopa to non-biocompatible Polystyrene (PS) beads resulted in exceptional enhanced cellular intake [125, 126].

Pharmacokinetic (pk) parameter based on nano-bio interaction

The comprehensive analysis of ADME parameters concerning drug-loaded NPs can be challenging due to variations in NP formulations and their interactions within biological systems. ADME data is often confined to Cmax, Tmax, and AUC, with limited research detailed parameters like $t_{1/2}$, C, V_{dss}, or MRT [127]. Sonaje *et al.* conducted a study investigating the pharmacokinetics, pharmacodynamics (blood glucose), and biodistribution of pH-triggered NPs comprising chitosan and poly(gamma-glutamic acid). The comparison was made between oral and subcutaneous administration in rats using Single-photon Emission Computed Tomography (SPECT). The investigation results revealed that orally given aspart-insulin was incorporated into the peripheral circulation, whereas the nanocarrier was mostly held in the gut following hypodermal administration. Peak aspart-insulin concentration in peripheral tissue/plasma occurred at 20 min post-injection. A comparison of PD/PK profiles between orally administered as part-insulin and SC infusion of NPH-insulin, moderate-acting insulin preparation, suggested the potential of this nano-bio system as a non-invasive alternative for basal insulin regimen [128]. Another study, inspired by this work, focused on hepato-selective agent delivery carriers comprising chitosan/poly (ethylene glycol)–glycyrrhetinic acid NPs. The PK analysis of these NPs was conducted using single-photon emission computed tomography (SPECT), while cellular uptake was assessed using human hepatic carcinoma cells (QGY-7703 cells). Results indicated the remarkable hepato-selective ability of CTS/PEG–GA NPs, maintaining high levels during the experiment, with liver accumulation reaching 51.3% at 3 h post-injection [129].

Two-dimensional (2D) nanomaterials interactions with biological moieties

2D materials refer to substances alongside a thickness of meagernanometres, typically existing as laminate materials with intense in-plane bonds and weak van der Waals-like linkage amidst laminae. These nanomaterials have gained attention in pharmaceuticals derived their unique structural and physiochemical characteristics [130]. Their sheet-like planar morphology, held together by weak van der Waals forces, endows 2D nanomaterials with exceptional optical, electrical, and mechanical properties, elevating their significance [131]. Moreover, their large surface area-to-volume ratio allows the loading of various pharmaceutically active agents onto their surfaces through non-covalent interactions [132, 133]. This high surface tunability enables the design of biocompatible nanomaterials for applications spanning drug delivery, bioimaging, biosensors, stimulus-responsive theranostic agents, and regenerative medicine [134-136]. The interaction of 2D nanomaterials with biomedical systems, encompassing cells, cytoplasmic organelles, and biomolecules, is remarkable due to their large surface areas providing high surface energy and numerous active centers. This enhanced interaction holds potential for numerous healthcare utilization, comprising tissue engineering, additive manufacturing, neoplastic treatment, biosensing, and more [137-139]. Research into new 2D materials and their interactions with biological moieties remains a focal area. Graphene, the ancient identified 2D nanomaterial, finds applications across diverse research fields, comprising therapeutics, sensing, and energy. For instance, graphene oxide (GO), derived from graphene modified with carboxylic acid, epoxide, and hydroxyl groups, exhibits amphiphilic properties and is highly useful in pharmaceutical applications for stabilizing hydrophobic drugs in solution [140-142]. Additionally, reduced graphene oxide (rGO) synthesized via spray drying forms iron oxide-decorated rGO microspheres, displaying synergistic neoplastic treatment. The photothermal properties of rGO enable NIR stimulus, accelerating doxorubicin release and increasing temperature, responding to NIR intensity. Contrasted to 1D or 3D nanomaterials, 2D nanomaterials have the supreme therapeutic application due to their particular surface area, resulting in an abundant quantity of surface atoms compared to volume atoms [143].

Biological applications

In recent times, nanotechnology has emerged as a ground-breaking field impacting pharmaceuticals, materials science, and electronics. Nano-bio interactions in pharmaceuticals have notably advanced with the availability of various nano-based formulations exhibiting superior responses compared to conventional ones. Among these, liposomes stand out as a pivotal carrier system, demonstrating excellent responsiveness to endogenous stimuli like temperature and pH conditions, significantly enhancing therapeutic agent delivery [144-146]. In the field of nanomedicine, exploring nano-bio interfaces remains pivotal for designing safe and effective drug delivery systems, targeting pathological sites, understanding metabolism, and ensuring biocompatibility [147-149]. While the application of nano-bio interactions in pharmaceuticals, especially in drug delivery systems and oral routes, presents numerous advantages, detailed mechanistic studies are imperative to understand the influence of nanoparticles on ADME profiles, thereby enhancing formulation safety and efficacy [150]. Studies by Pascal Ickrath *et al.* highlighted the impact of nano-bio systems on dermal zinc oxide NPs formulations in human mesenchymal cells, revealing cytotoxicity at elevated doses and genomic instability at average to minimal doses, with prolonged exposure exacerbating cell necrosis impact [151]. Additionally, the work of Luisana Di Cristo *et al.* delved into nano-bio systems' role in inhalation therapies delivered via aerosol [152, 153]. Moreover, nano-biosystems play pivotal roles not only in pharmacy but also in biosensing, electronics, and imaging—the vastness of their applications beckons further exploration [154, 155]. This is achieved by controlling drug release within the tumoral vascular and interstitial space, improving liposomal clusters in tumoral tissue through increased blood flow and tumor vasculature penetrability [156]. Responsive drug delivery systems targeting the tumor microenvironment are extensively employed to enhance selectivity in tumor imaging and therapy while minimizing normal cytotoxicity, ultimately elevating therapeutic effectiveness [157, 158]. The development of pH-sensitive dynamic nano assemblies, leveraging upconversion NPs (UCNPs), offers significant therapeutic potential in cancer therapy by capitalizing on the acidic tumor microenvironment the implementation of pH-responsive drug delivery systems facilitates the precise diagnosis of minor orthotopic

Hepatocellular Carcinoma (HCC) by functioning as a Magnetic Resonance Imaging (MRI) contrast agent, pivotal for monitoring the progression of cancer [159]. Neurological diseases like Alzheimer's, Parkinson's, ALS, Huntington's disease, epilepsy, and ischemic stroke possess complex, ambiguous pathogenic mechanisms. Current diagnostic methods fall short of meeting clinical demands. Hence, there's a pressing need for sensitive, specific probes for early diagnosis and therapy. Designing DNDDS offers a new ray of hope in initial assessment, evaluation, and rational treatment of neurological diseases [160, 161]. Tissue injuries and infections often accompany inflammation, recruiting various inflammatory cells and generating ROS. This oxidative stress exacerbates injuries. Additionally, the infected site exhibits a slightly acidic microenvironment. DNDDS designed based on these micro-environmental features alleviates oxidative stress at injured/infected tissues, thereby improving therapeutic efficiency in treating injuries and infections; nano-bio interactions studies play a pivotal role in the pharma industry; some approved products are also enlisted in table 2 [162].

Table 2: Nano-bio responsive approved formulation

Approved product	Drug release	Disease	Company	Ref
Depocyt	Cytarabine	Oncogenic	Pacira Pharma	[163]
Onivyde	Irinotecan	Pancreat cancer	Merrimack pharmaceuls	[164]
Arikace	Amikacin	Lung infections	Transave Inc.	[165]
T4N5 liposlotin	T4 endonucle V	Xeroderma pigmentosum	AGI DermaticInc.	[166]
DaunoXome	Daunorubicin	Kaposi's Sarcoma	NeXstar	[167]
Marqibo	Vincristine	Acute lymphoblastic leukemia	Talon Therapeutics	[168]
OSI-211	Lurtotecan	Ovarian cancer	OSI pharma	[169]
Thermedox	Doxorubicin	Metastatic liver cancer	Celsion	[170]

Future approach

For future study, so many research problems are still in the way of understanding: The first point is a lack of complete knowledge of the biological mechanisms of nanomaterials. The second point is to effectively use nanomaterials as more intelligent therapeutic and diagnostic modalities, a regulation approach for their catalytic activity needs to be developed. The third point is that the complex environment *in vivo* must be considered in research on nano-bio interactions. The fourth and last point is more attention should be paid to theoretical simulation to accurately and deeply investigate the nano-bio interactions. Thus, more efforts should be made in the research of nano-bio interactions.

CONCLUSION

If we are heading off to advance nanomedicine, research on the nano-bio interactions of stimuli-based nanomaterials is crucial. This is because drug delivery, metabolism, pathological site targeting, safe and effective nanomedicine, and biocompatibility with minimal side effects all are impacted by nano-bio interactions. We outlined recent developments in nano-bio interactions of nanomaterials in this review. With these developments, nanomaterials will likely play a significant role in biomedicine in the future, particularly in the treatment of cancer-related illnesses.

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ABBREVIATIONS

Nanomaterials: NMs, Nanoparticles: NPs, Utilizing Upconverting Nanoparticles: UCNPs, Superparamagnetic Iron Oxide Nano Particles: SIONPs, Doxorubicin: DOX, Self-Assembled into Magnetic Nanocarriers: SAMNs, Lower Critical Solution Temperature: LCST, Atom Transfer Radical Polymerization: ATRP, Paclitaxel: PTX, Elastin-Like Polypeptide: ELP, Curcumin: CUR, Glutathione: GSH, Reactive Oxygen Species: ROS, Cathepsin B: CTSB, Phospholipase-Sensitive Liposomes: PSL, Enhanced Permeability and Retention: EPR, Computed Tomography: CT, Alkaline Phosphatase: ALP, Polystyrene: PS, Single-Photon Emission Computed Tomography: SPECT, Hepatocellular Carcinoma: HCC, Magnetic Resonance Imaging: MRI

AUTHORS CONTRIBUTIONS

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CONFLICT OF INTERESTS

The authors declare no competing interest

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