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Review Article

A REVIEW ON RECENT ADVANCES ON STIMULI BASED SMART NANOMATERIALS FOR DRUG DELIVERY AND BIOMEDICAL APPLICATION

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ABSTRACT

The advancement of numerous interdisciplinary fields of science, engineering, and medicine has been integrated into the rapid growth of nanomedicine (NM) over the past few decades. Many aspects of NM need to be investigated, even though a few clinical successes of nanomaterials have significantly altered the landscape of disease diagnosis and treatment. One such topic is the complex interactions between NM and its post-administration chemical, physical, and biological interactions and how these interactions impact NM biological performance. Because of the increased prevalence of metabolic disorders, neurological illnesses, heart diseases, and cancer, as well as the hunt for effective therapies for these and other diseases, there is a larger demand for unique, inventive, and drug-delivery systems that can transport medications to the desired place. The many cutting-edge drug delivery systems are becoming more and more dependent on nanotechnology. In this review, developments in the field and talk about how nanomedicine interacts with the physical, chemical, and biological material, with a focus on biological stimuli research. We also show how nano-bio interaction can create a variety of multifunctional platforms of biomedical applications with a wide range. The potential difficulties and opportunities in the study of nano-bio interactions are also discussed.

Keywords: Nanomedicine, Nano-bio interaction, Nanomaterials, Intelligent material, Nanoparticles, Stimuli-responsive

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INTRODUCTION

While nanoparticles have improved notable over time and are regard a main strategy for improving drug delivery, remains to be improved is therapeutic efficacy, as there are still challenges with their structure design and performance that have to be overcome. Withstanding advances in nanoparticle design for drug delivery, with lack of association targeting organism, identification and targeting of specific site of action and thus toxicity following acute and chronic, drug release before reaching site of action, insufficient drug release at specific site of action with still exist of intravenous nanoparticles formulations. Therefore, to overcome from these challenges researchers are developing stimuli-responsive systems have been widely studied and reported for drug delivery system.

Nanomaterials any recent studies it was found that the alarming incident of metabolic disorders which leads to cancerous disease and many associated disorders which results in neurodegenerative disorders, now a days it becomes the most challenging tasks for the medical practitioners for providing effective treatment by using the novel approaches that have a unique process of targeting the infected tissues or organs [1-3]. Nanotechnology has been playing a more and more important role in the different innovative methods of drug delivery that are being studied to get the drugs where they need to go. Nanomaterials have been made and tested in many different ways, such as polymeric, lipidic, inorganic and inorganic-organic hybrid nanoparticles, nanocrystals microemulsions, polymersomes, dendrimers, nanogels, nanofibers [3-6]. These nanocarriers may be designed with a range of surface and volume chemistries, sizes, geometries, and architectures to optimize medicine release, targeting, and blood circulation time. Positively charged surfaces, for example, often facilitate nanoparticles uptake by cells [7, 8]. For examples polyethylene glycol (PEG) to nanocarriers, causes blood opsonin to repel one another and considerably improve the duration that Nanomaterials are in circulation. The size of Nanomaterials has an impact on their bio distribution and cellular absorption [9-11]. It is common knowledge that cells can easily ingest Nanomaterials between 10 and 100 nanomaterials in size through endocytosis. Nonetheless, through various endocytosis pathways, large size of Nanomaterials may enter cells at a remarkably modest rate. For instance, oh, J. M the layered double hydroxide NPs range showed 50>100>200>350 nanomaterials were taken up by human MNNG/HOS cells, with nanoparticles in the range of 50 to 200 nanomaterials being particularly internalized by clathrin-mediated endocytosis. Nanomaterials with a diameter of 5 nanomaterials are very likely to be excreted by the kidneys, while those with sizes>150 nanomaterials are significantly more likely to become lodged in the liver and spleen [12, 13]. Nanoparticles with diameters between 100 and 200 nanomaterials have demonstrated excellent tumor-targeting potential, which can be attributed to their improved permeability and retention inside diverse cancers. However, typical nano-formulations have not yet been able to accomplish the requisite level of medication targeting and release, and despite decades of work, only a few nano-formulations have made it to market [14, 15]. The demand to programmed Nanomaterials with better structural and functional characteristics for useful therapeutic effects remains unfulfilled [16]. In various disorders, such as ischemia, inflammatory diseases, infections, and malignancies, Nanomaterials that respond to stimuli can benefit from these changes [17, 18]. Most chemically stimuli-responsive Nanomaterials have their roots in these circumstances, as an alternative, they can be engineered to respond to a wide range of physically induced stimuli from the outside, such as X-rays, light, ultrasound, magnetic fields, and temperature. External stimuli are typically less unpredictable and manageable than internal urges. The type of stimuli-responsive nanocarriers that should be utilized is determined by several considerations, including the intended use, the target location, the cost of therapy, and any safety concerns. In addition, much effort has gone into strengthening the programmability of various stimuli-responsive Nanomaterials in order to improve therapeutic benefits. For example, functionalizing nanomaterials surfaces with particular ligands and targeting agents like as antibodies, peptides, nucleotide aptamers, and other small molecules may increase medication targeting dramatically. Another idea is to add linkers or groups that can react to a variety of external or endogenous stimuli, which would make the nanoparticles sensitive to a wider range of stimuli and give better platforms for highly advanced programmability. This paper meticulously goes over the design strategies for both basic and complicated physically stimuli-responsive nanotherapeutics [19-22].

The examination of associations between nanoscale substances and biological systems such as amino acids, fatty acids, genetic material, and other molecules in nature, cells and cellular receptors, and life forms such as humans is known as "bio-nano interactions.

"Therefore, an urgent need for smart Nanomaterials without any of the limitations mentioned above is a demand of the current time. Different types of smart Nanomaterials with controlled capacities must be created [23, 24]. The continuous efforts of scientists resulted in the development of a particular kind of material that, in response to slight changes, experiences significant. The existence of natural living systems has the capacity to adapt their properties dynamically and intelligently. The Venus flytrap, an insectivorous plant that captures insects to feed its nutritional demands, and the Mimosa pudica plant, whose leaves change direction in response to stimuli like temperature and light, are just two instances of how living things adapt to their circumstances. Other examples include pinecones, wheat awns, and orchid tree seedpods. Researchers developed "stimuli-responsive" materials with incredibly intriguing applications in smart materials as a result of the biological systems' outstanding powers for energy conversion and multitasking [25-27].

Researchers are paying increasingly more attention to the concept of "intelligent material," also known as "stimuli-responsive material" or "smart material," as a result of the advancement of technology and the growing demand for novel materials that may satisfy the resulting needs. Smart Nanomaterials has been created as a result of this need for adaptation. Whether or not the response is reversible depends on the nanomaterials capacity to return to its initial state [28].

Herein, we provide a comprehensive review of stimuli-responsive nanoparticles for drug delivery and biomedical applications. Initially, the review provides a theoretical overview of the different types of stimuli responsiveness with biomedical applications, design approaches of the nanoparticles and advances in nanomaterials. We also highlighted the applications and limitations associated with drug delivery systems. Additionally, this review puts an emphasis on avenues in research area yet to be explored. This review creates a rigorous platform for the integration of stimuli-responsive nanomaterial into Nano-Bio Interactions studies.

The data availability on this review article were compiled from academic publications up to 1942-2023. Web of Science, PubMed, google scholar, and semantic scholar was used to find all the information. Search terms were used in this review, 'Nano-bio interaction studies, recent advances of smart nanomaterials, stimuli responsive, Nano-bio interactions, Physical responsive nanomaterial. Chemical responsive nanomaterial, biological responsive nanomaterial, dual responsive nanomaterials. The specific criteria included in the significance of title, data and its availability, appropriate referencing, presentation, and other key points.

Smart materials and nanomaterials

Materials that are smart, intelligent, or active are defined as "materials that can change their properties according to specific stimuli." Certain stimuli, it is asserted, can lead materials to alter form, density, color, modulus, rigidity, and harshness on demand. Previously, "smart materials" were frequently classified as those that could react immediately to their surroundings [29, 30]. After that, the definition of smart materials was enlarged to include materials that may respond to inputs from outside sources and display a new class of functional characteristics. Temperature variations, light wavelengths, pressure, stress, electric fields, magnetic fields, chemical concentrations, and other specific stimuli can be used as agents, and the results can include colour, heat, hyperthermia, magnetic fields, deformation, and other things [31-33].

These materials can alter their own characteristics in response to particular stimuli, alterations in size, shape, permeability, optical and mechanical characteristics, surface area, solubility, and other nanoparticles. In general, the majority of smart materials show five distinguishing traits: immediacy, transiency, self-actuation, directness, and selection. When a stimulus first appears, a material is said to be immediate if it can react fast [34-36].

These substances include, to name a few, micelles, liposomes, and polymeric nanoparticles as well as metal-and carbon-based Nanomaterials (such as metal oxides, nanogold, and nano silver) [37].

Stimuli-responsive smart nanomaterials types

The smart Nanomaterials are divided into many groups by applying stimuli. Smart Nanomaterials characteristics can be modified by external stimuli in a controlled manner. And the 4 different types indicated in fig. 1, these stimuli: physical, chemical, and biological and dual responsive [38-41].

Chemical-responsive nano-materials and their application

Chemical responsive has been worked into the design of various technologies for the diagnostics of several diseases and therapeutics [42]. Chemical-sensitive Nanomaterial Examples and their uses are listed in table 1.

Table 1: Chemically responsive nanomaterials and their use in medicine

S. No.	Nanomaterial	Stimuli	Application	References
1.	Poly (ethylene glycol)-ag nanoparticles	pH	Antibiotics, natural healing	[43]
2.	Hybrid ultra-pH-sensitive, nanotransistor) Nanotransistors HyUPS	pH	Endocytosis by receptors in tumour cells	[44]
3.	Nanohybrid composed of layered double hydroxides and zinc (II) phthalocyanine that contains octasulfonate)	pH	Theranostics	[45, 46]
4.	Similar to melanin nanoparticles	pH	Tumour photoacoustic imaging	[47]
5.	Resveratrol-polylactic acid PLA-RSV	pH	delivery of drugs	[48]
6.	Poly (carboxybetaine methacrylate)-nanodiamonds	pH	Theranostics	[49]
7.	Vancomycin Nanoparticles	pH	Antibacterial effects	[50]
8.	Trans-cinnamaldehyde chitosan nanoparticles	pH	Antibacterial effects	[51]
9.	Amoxicillin Poly (γ-glutamic acid)-g-arginine poly peptide chitosan complexed NPs	pH	Antibacterial effect against H. pylori	[53]
10.	Vancomycin Liposomes	pH	Against S. aureus and MRSA	[54]
11.	Cefazolin Porous Nanoparticles	pH	MRSA and Escherichia coli and Pseudomonas aeruginosa	[55]
12.	Vancomycin Micelles	pH	Staphylococcus aureus and MRSA	[56]
13.	Poly (ethylene glycol)-Pluronic F68-nanoscale covalent organic frameworks	Redox	Cancer treatment	[57]
14.	Mesoporous silica NPs	Redox	Antibacterial effects	[58]
15.	Silver Nps Nanogel	Redox	E. coli and S. aureus	[59]
16.	Chlorhexidine nanoparticles	Redox	Streptococcus mutants	[60]
17.	Folic acid Nanogel	Redox	E. coli and S. aureus	[61]
18.	Hyaluronic acid–chitosan–lipoic acid nanoparticles	Redox	Breast cancer treatment	[62]
19.	Folate redox-responsive chitosan nanoparticles FTC-NPs	Redox	delivery of cancer drugs	[63]
20.	Poly (ethylene glycol) conjugated to paclitaxel via disulfide linkage PEG2000-S-S-PTX	Redox	Breast cancer cell prodrug	[64]
21.	AgNPs hybrid nanoparticles/Prodrug	Redox	Delivery of drug	[65]
22.	P [(2-((2-((camptothecin)-oxy) ethyl) disulfanyl)ethylmethacrylate)-co-(2-(D-galactose) methylmethacryl-ate)] and silver nanoparticles	Redox	Release of drug	[66]

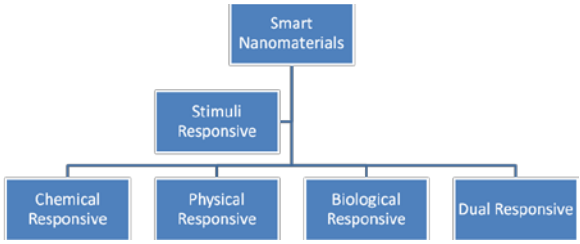

Fig. 1: Schematic diagram for the chemical, physical, biological and dual responsive

pH-responsive nanomaterials

Smart nanomaterials that respond to pH changes by exhibiting novel functional characteristics are especially interesting in the biomedical area since pH fluctuations are common in many specialized or diseased systems. The benefit of employing such substances is that different areas of the human body have varying pH levels (for chronic wounds, pH values are 7.4-5.4; for saliva, 6.5-7.5; throughout the gastrointestinal tract, the pH shifts from the stomach (4-6.5) to the intestine (5-8)). Additionally, compared to the healthy condition, the sick state has odd pH levels. An inflammatory tissue has a pH value of 6-7, bacterial infections produce acidic pus, and tumour micromedia have a lower extracellular pH between 6.5 and 6.9 [67, 68].

As a result of these extreme pH variations, many pH-responsive materials have so far been found. Polymers with ionizable moieties and polymers with acid-labile links make up the majority of the pH-sensitive polymers' classifications. The presence of ionizable, delicate, basic, or acidic moieties (amines and carboxylic acids) that attach to a hydrophobic backbone, such as polyelectrolytes, is essential for the first group. This type of polymer's most prevalent pH-responsive material exhibits protonation/deprotonation processes by distributing the charge throughout the molecule's ionizable groups [69-71].

The second category consists of polymers having a covalent backbone that is acid-labile. The breakage of these bonds with the decrease in pH determines whether polymer aggregates or chains will dissociate or break [72]. Due to the presence of covalent bonding, the second group undergoes a slower inner modification, which promotes their use in the drug release industry. In pH-responsive polymers, a phase abrupt transition is caused by pH. Normally, the phase shifts between pH values of 0.2 and 0.3. Poly (L-lysine), poly (N, N-dimethylaminoethyl methacrylate), poly (methacrylic acid), poly (acrylic acid), poly (N, N-dialkyl aminoethyl methacrylates), poly (ethylenimine), chitosan, aginate, and hyaluronic acid are the most well-known pH-sensitive polymers [73, 74].

Redox responsive nanomaterials

The process of oxidation and reduction-responsive nanomaterials have shown to be useful biomaterials, with dendrimers, nanogels, and micelles made from polymers in particular being studied as excellent transporters for medications, genes, and antigens. Labile group polymers are a viable choice for developing redox-responsive biological systems. Poly (b-amino esters), polyanhydrides, and poly (lactic/glycolic acid) are common examples of redox-responsive polymer compounds, which they include acid-labile moieties. Thiol groups, platin conjugation, and thioether, disulfide, or diselenide linkages are the most often used redox-responsive substances for controlled drug release applications [75, 76].

Physical responsive nano-materials and their applications

These materials respond to externally supplied physical stimuli like temperature, light, ultrasound, magnetic field and an electric field have a lot of examples for targeted and controlled drug delivery [77]. In table 2 shown some examples of physical responsive nanomaterials and their uses.

Table 2: Physical responsive nanomaterial and their biomedical application

S. No.	Nanomaterials	Stimuli	Uses	References
1.	Poly (ethylene oxide), Poly (propylene oxides)	Temperature	Oral drug delivery	[78]
2.	Gold nanoparticles—PluronicF127-Hydroxypropyl methylcellulose	Temp.	Wound healing, and photothermal platform	[79]
3.	Poly (oligo (ethylene glycol) methacrylate–co-poly (glycidal methacrylate) copolymers/poly (lactic acid-co-glycolic acid)	Temp.	Tissue engineering	[80]
4.	Collagen or Chitosan Based	Temp.	Delivery of drug	[81]
5.	Poly (N-Isopropylacrylamide-co-Sulfobetaine Methacrylate) nanogel-PNS	Temp.	Diagnosis and chemotherapy	[82]
6.	Poly(N-isopropylacrylamide)-Poly (N, N-dimethylacrylamide) Poly(acrylic acid)	Temp.	Delivery of drug	[83]
7.	Cholesteryl succinyl silane Micelle	Laser light	Photoresponsive Drug Release	[84]
8.	PEG coating gold shell	Laser light	Drug release	[85]
9.	Dna coating AU nanorod	Laser light	Photoresponsive drug release	[86]
10.	PLGA hollow spherical AuNM	Laser Light	Drug release	[87]
11.	AuNm liposomes	Laser light	Drug release	[88]
12.	DNA linker Spherical AuNM	X-rays	Radiotherapy	[89]
13.	PEG Spherical AuNM	X-rays	radiotherapy	[90]
14.	Mesoporous silica nanocapsules	Ultrasound	High intensity focused ultrasound therapy	[91]
15.	Au shell silica core	light	Photoresponsive targeted therapy	[92]
16.	Oligonucleotide spherical AuNm	temperature	Optical Multiplex biosensors	[93]
17.	PEG-PCL spherical gold nanomaterial	light	Photoacoustic imaging	[94]
18.	PLGA Au shell	light	Photoresponsive targeted therapy	[95]
19.	Poly(3,4-ethylenedioxythiophene)-coated Poly (lactic acid-co-glycolic acid) nanofiber	Electrical	Deliver y of drug	[96]
20.	Fe3O4/Polyaniline	Electrical	Delivery of drug, Antimicrobial	[97]
21.	Polyaniline/gold nanocomposite	Electricals	Immunosensor for chronic kidney disease detection	[98]
22.	Polyaniline, poly(3,4-ethylenedioxythiophene)	Electricals	Artificial Nerves	[99]
23.	Biosynthesized gold nanoparticles/poly(catechol)/graphene sheets/glassy carbon electrode	Electrochemical	DNA mutation, biosensor, and acute lymphoblastic leukaemia detection	[100]
24.	Poly (ethylene glycol)	Light	Fluorescent switches probes	[101]
25.	Ruthenium-containing block copolymer and nanoparticles of Poly Ru	Light	Photodynamic treatment and photochemotherapy performed *in vivo*	[102]
26.	Fe3O4/methoxy pol y ethylene glycol)-poly-(lactide) composite nanocapsules Fe3O4/MePEG-PLA composite nanocapsules	Magnetic	MRI	[103]
27.	Trastuzumab, doxorubicin poly (vinyl alcohol)/single-component thiol-functionalized poly (Methacrylic acid) T-DOX PVA/PMASH magnetic nanocapsules	Magnetic	Cancer Treatment	[104]
28.	3d hydrogel collagen	Magnetic	Directed neuronal regeneration	[105]

Temperature-responsive nanomaterials

The temperature-responsive polymers have received greater interest in medical research since 1942, when Huggins and Flory first theorized polyesters-solvent interaction in solution with different temperatures and the notion of free volume (used to explain the threshold temperature lower/upper a trend in solution). Thermo-sensitive polymers are a particular class of substance that undergoes a sudden change in solubility response to a slight temperature change and given that particular infections exhibit temperature variations, they have drawn researchers' attention in the field of biomedicine [106].

One polymer phase manifest above an upper critical solution temperature (UCST), and a phase separation exists below this. An LCST often occurs in polymer solutions as a coil-to-globule transition, reducing solvent contact. Normally, soluble polymers contain the UCST. The polymers that exhibit both LCST and UCST capabilities, but at different temperatures, is a single generation of temperature-responsive materials.

The initially loaded drug is released when the LCST value of a stimuli-responsive system rises to about 42 °C as a result of a change in the environmental condition, which is close to the body temperature for better outcomes [107].

Electrochemical stimuli-responsive nanomaterials

Electrical responsive materials that change their shape or size in reaction to a slight variation being applied electric current. The vast majority of ionizable groups are present in electro-responsive polymers, which are capable of mechanical work is produced by converting electrical energy. These types of smart materials were primarily used for energy transductions, muscle actuation, and artificially tailored medication delivery [108]. These materials give the advantage of exact control over an electrical pulse's duration, current strength, or pulse spacing. The application of electric current alters the pH, which disturbs the hydrogen bonds that hold polymer chains together and ultimately results in the pdelivery of drugs and polymer chain bending or breakdown. Charged drug electrophoresis implicated from electrosensitive polymers drug delivery. Charged drug electrophoresis, diffusion, and drug release after erosion of electro-erodible polymers were all important phenomena in drug delivery from electro-sensitive polymers [109, 110].

There are two recognized groups of electro-responsive materials. The first class is made up of current-responsive polymer materials, where a change in the local concentration of ions in the materials or solution is caused by the ions. Hydrogels, conductive polymers, and layer-by-layer coatings, as examples, to the ions' mobility caused by the electric field. The Second Group is subdivided according to preVoltage-responsive polymers are mostly used in biomedical applications like dielectric gels, elastomers, polymers for controlled drug release, accumulating on electroresponsive nanoparticle drug release, and so on [111].

Ha *et al.* developed a microfluidic actuator platform for photothermal treatment (PTT) and brain tumor targeting applications on the basis of an electro-responsive hydrogel. Collagen I gel and highly conductible silver nanowires (AgNWs) were used to create the hydrogels. Cells reacted to electrical stimulation. Also, they successfully demonstrated PTT adequacy for brain cancers utilizing gold nanorods linked to the acid peptide. Electrochemical biosensors are an important class of electrically sensitive device due to their various advantages, such as simple operation and long-lasting tracking at a favourable cost-benefit ratio. These qualities improve electrochemical biosensors. The identification of acute lymphoblastic leukaemia is one example of a clinical test that can be utilised as a support tool in the search for DNA alterations and cancer markers [112].

Light-responsive nanomaterials

Due to its adjustable and adaptable characteristics, light is viewed as an attractive stimulant. Light-responsive materials are extremely useful for applications because light can be applied instantaneously and with remarkable high accuracy with an on/off regulating mode. Light-sensitive smart Nanomaterials are biomarkers that's how the location of medications and their ability to target them, as well as malignancies, by fitting a wide range of characteristics. This stimulus material has the benefit of being easily adaptable when it comes to input characteristics like intensity, wavelength, light, beam width, and exposure period for particular purposes.

Smart Nanomaterials, such as nanopolymers, can be used to regulate medication distribution to target regions and achieve the optimum concentration of drug delivery at a given time, resolving challenges related with accurate drug release or light-mediated theranostics. Chromophores, such as azobenzene groups, can be found in a variety of light-sensitive polymers, spiropyran groups, or nitrobenzyl groups [113].

Mena-Giraldo *et al.* changed chitosan by adding molecules of azobenzene that react to ultraviolet light. This made a photoresponsive polymeric nanocarrier. They thought about how UV light might affect the release of the payload in a controlled manner using nano bioconjugates. They demonstrated the encapsulation/release concept using Nile red and dofetilide as cargo models. They employed cardiac transmembrane peptide-functionalized photoresponsive polymeric nanocarriers. The effect of UV light irradiation increased the feasibility of the treatment plan by increasing the concentration of intracellular delivery and reducing the amount of cargo reactions [114].

Magnetic-responsive nanomaterials

Magnetoresponsive Nanomaterials are stimulated by an applied magnetic field. Better theranostic devices can be made especially well with magnetic nanoparticles. These substances can improve, to mention a few, Cellular labeling, immunoassays, magnetically guided medications, magnetic separation, magnetic hyperthermia therapies, magnetic resonance imaging diagnostics (MRI). Numerous processes, such as the hydrothermal technique, ignition, thermal decomposition, chemical vapour deposition, carbon arc, high-temperature thermal breakdown and, have been used to create polymeric magnetoresponsive Nanomaterials. It is significantly easier to understand cellular activities and signalling for *in vitro* and *in vivo* remote control of cells when using magnetic nanoparticles made of iron and metal oxides [115].

Conventional methods like thermal ablation and magnetic hyperthermia, which kill cancer cells via thermotherapy by elevating the temperature over 45 °C in a localised location or throughout the body, have limitations such as inadequate targeting and deep tissue penetration. An MRI was developed in 1973 by Paul Lauterbur, and since the FDA approved its clinical usage in hospitals around the world in 1985, it has been widely used. The MRI operates because protons present align when they are exposed to a magnetic field from the outside [116].

MRI distinction materials are a type of medicine that improves image contrast by increasing the pace at which water protons unwind in the target tissue. The vast majority of MRI contrast materials are based on clinical gadolinium. Current MRI approaches must now be modified to address a number of limitations, such as toxicity in some contrast media or delayed imaging pace and accuracy. Many other compounds based on iron nanoparticles systems were created to further increase the signal-to-background noise ratio. Magnetically responsive Nanomaterials of the future must be stable, biocompatible, and have a high contrast capacity. The system created by Antman-Passig *et al.* is an illustration of how Magneto is responsive [117]. Nanomaterials are used.

Due to the presence of magnetic nanoparticles (MNP), they were able to align collagen fibres (red). The collagen suspension containing neurons (orange) solidified both naturally (up) and in the presence of an external magnetic field (red-green bars) (down). The collagen fiber orientation (blue lines) and MNP distribution in the first gel (up) were arbitrary (red). The second gel (below) showed aligned collagen fibers (blue lines) and an accumulation of MNPs (red particles), while neuronal growth after a week produced neuritis, proving the system's ability to regenerate the human brain in three dimensions under the control of a magnetic field [118].

Biological responsive nano-materials and their applications

In reaction to certain stimuli like biological signals and pathological disorders, bio-responsive Nanomaterials are created specifically for biomedical purposes. Hence, it demonstrates remarkable progress in the creation of unique, precise treatments for a variety of disorders in recent years. These theranostic smart Nanomaterials are typically in a "OFF" state in healthy conditions, switching "ON" when exposed to certain stimuli like enzymes, glucose, H2O2, H2S, or glutathione. Because of their excellent sensitivity and selectivity and little adverse effects, clever Nanomaterials are used [119].

Some biologically-active Nanomaterials and their applications are listed in table 3.

Table 3: Biologically-active nanomaterial and their biomedical uses

S. No.	Nanomaterials	Stimuli	Uses	References
1.	Acetalated dextran nanoparticles	Glucose	Diabetic Control	[120]
2.	Boronic acid-derived polymers	Glucose	Delivery of Drug	[121]
3.	Glycidyl methacrylated dextran/Concanavalin A Dex-GMA/Con A ConAMicro/Nanospheres	Glucose	Insulin Therapies	[122]
4.	Chitosan-g-polyethylene glycol monomethyl ether nanocomplex CS-g-(mPEG) NP	Glucose	Insulin Oral Deliveries	[123]
5.	Hyaluronic Acid (HA)-coated calcium carbonate NPs	Glucose	Insulin Oral Deliveries	[124]
6.	Chitosan/poly (gamma-glutamic acid) nanoparticles	Glucose	Insulin Oral Delivery	[125]
7.	Carboxymethyl chitosan-phenylboronic acid-Lvaline nanoparticles	Glucose	Insulin Oral Delivery	[126]
8.	Polyhexanide nanomaterial	Enzyme	Antibacterial Activity	[127]
9.	Silver Nanomaterials	Enzyme	Antibiotic Activity	[128]
10.	Ciprofloxacin Nanomaterials	Enzyme	Antibiotic Activity	[129]
11.	Doxycycline nanomaterials	Enzyme	Antibiotic Activity	[130]
12.	Nanoplatform formed from Ti substrates modified with layer-by layer mesoporous silica nanoparticles-silver nanoparticles LBL MSN-Ag nanoparticles	Enzyme	Concurrently cure implant-associated bacterial infection and promote tissue development *in vivo*	[131]
13.	Activates low-molecular weight Protamine-poly (ethylene glycol) poly (caprolactone) Nanoparticles-loaded with paclitaxel ALMWP-NP-PTX	Enzyme	Glioblastoma Treatment	[132]
14.	ATP-Ag nanoparticles silver nanoparticles coated on adenosine triphosphate.	Enzyme	Participate in protein activity and signal transduction	[133]
15.	layer-by-layer construction of materials-based poly(2-oxazoline)	Enzyme	Therapeutic delivery	[134]

Glucose-responsive nanomaterials

Glucose-responsive nanoparticles can prevent diabetes complications and administer the bioactive chemical in a targeted manner. This mimics the normal endogenous insulin synthesis that occurs in glucose presence. Particularly in light of their application in the fields of glucose detection and insulin delivery, polymers have attracted considerable attention [135]. The polymer responds to a pH shift by transitioning to a different volume, and in this way, conformational polymer changes control the body's glucose level.

Drug delivery systems that are enzyme-responsive are often made of inorganic or polymeric nanoparticles. Various tumor-specific enzymes can affect the peptide structure or ester bonds of nanocarriers, causing the loaded medicine to release at specific sites. Proteases and phospholipases are the most often employed triggers in enzyme-responsive drug delivery systems.

For instance, a few authors showed how well the phospholipase-responsive liposome (PSL) delivered drugs because sPLA2, which is present in tumour cells, causes liposome breakdown. Peptide nucleic acid (PNA) release is started and carried out by sPLA2 [136].

Enzyme-responsive nanomaterials

Because they are extremely selective, simple to degrade, tolerant of moderate conditions, and possess characteristics including Enzyme-responsive systems are appropriate for use in biomedical applications because they are sensitive to biorecognition, catalytic efficiency, and process efficiency. Polysaccharides like cyclodextrin, pectin, dextrin, and chitosan can be broken down by hydrolytic enzymes (like glycosidases) or reductive enzymes (like azoreductases) produced by microorganisms in various organs in nature. Enzymes are utilized to break up the polymer in the case of enzyme-responsive polymeric nanoplatforms in order to get desirable features.

In order to cure S. aureus infections and promote bone tissue growth in living beings, Ding and his team created an enzyme-sensitive nanoplatform. They discussed the creation of an implant made of titanium (Ti) that contained silver nanoparticles, modified Ti substrates with multilayer layers of poly (L-glutamic acid) and polyallylamine hydrochloride, and mesoporous silica nanoparticles (MSNs) (Ag NPs). They used a model of a rat femur that was bacterially infected [137].

Dual and multi-responsive nanomaterials biomedical applications

The creation of multi-stimuli-responsive polymeric nanoparticles as means of delivering drugs to certain targets the most promising area for nanotechnology development is the creation of nanoparticles with therapeutic and diagnostic capabilities. These technologies are widely used because of their benefits in terms of targeting, synergistic medications, and multimodal imaging. To only use the medicinal and/or diagnostic properties at the diseased spot, then another theranostics system depends on biological, chemical, and physical triggers. The dual and multi-stimuli-responsive approach is unquestionably ideal for theranostics in this era of the "war on cancer" since some qualities can launch therapy and cure while others can offer diagnostics. As a result, the benefits of multi-stimuli-sensitive polymers in the biomedical field are gaining increasing attention. The development of multi-stimuli-sensitive polymeric nanoparticles as drug delivery methods for specific targets the action of several internal and exterior stimuli is detailed [138. Table 4 provides examples of multi-sensitive Nanomaterials and their uses. The creation of novel diagnostic and therapeutic approaches is essential in the current global battle against cancer. The scientific community has created many systems using Nanomaterials with multiple response stimuli that have been successfully used to cure cancer.

Yu *et al.* created a multi-responsive system with regulated drug release and tumor cell eradication by distillation, precipitation, and polymerization. The penetration and accumulation of the tumor, as well as targeted medication administration, are made possible by the pH-, redox-, and temperature-responsive drug release mechanisms [139].

Table 4: Dual and multi responsive nanomaterial and their biomedical uses

S. No.	Stimuli	Nanomaterial	Uses	References
1.	pH and GSH	DOX Nanoparticles	Tumor treatment	[140]
2.	pH and thermal	DOX @SiO2-PMAA-b-PNIPAM Silica Nanoparticles	Ideal carriers for anticancer drug delivery enhance the drug release in controlled manner of DOX.	[141]
3.	Redox and pH nano-materials	Micelles of Doxorubicin	Reduce side effect, enhanced extremely targeting	[142]
4.	Redox and light nano-carriers	Dextran nanoparticles	Carrier composition preparation drug	[143]
5.	pH and GSH	Quantum Dot-based Nanoparticles	Breast cancer	[144]
6.	Redox and enzyme	Redox responsive nanocarriers	Increase the medication released by synergistic effects	[145]
7.	Oxidoreduction responsive drug delivery nanoparticles	β–CD attaching poly ethylenimine MNPs	Chemotherapy and Magnetic resonance imaging	[146]
8.	pH/light/enzyme	CuS NPs	Theranostics	[147]
9.	Liposomes	pH and Enzyme Responsive	Actibacterial Activity against Francisella novicida	[148]
10.	Redox/pH/temperature	Nanogels based on alginate and cystamine	Anticancer Activity	[149]

Redox dual-stimuli responsive DDSs

Redox-responsive DDSs are still having significant difficulties, although having a lot of potential for improving tumor targeting. It should be highlighted, however, that unfavorable drug release behavior from redox-responsive DDSs would be seen at non-targeted tissues, resulting in unfavorable toxicities. Despite the nanoscale size of DDSs, there is still a long way to go before the number of chemotherapeutic drugs produces a satisfying effect [150]. To get around the issues outlined above, redox responsive DDSs have been given additional sensitive external or intracellular groups or materials. Table 4 displays sensitive groups of substances that are external to or within cells. Additionally, it was estimated that two unique reactions such as enzyme-mediated DDs as well as the specially used redox reactions show the more decrements in the normal sizes in order to reach the cancer cells which reveals its potent anti-cancer activity of the drugs [151].

Redox and light dual responsive DDSs

It is also known as photodynamic therapy which is based on the photodynamic effect. It has been recognized as a valid method. The photosensitize delivered in the body, tumor tissues were treated by the specific wavelength of light with the single molecule of O_2 it increases the necrosis of cancer cell and activate an immune response against cancer [152]. The following two significant issues are still being faced by photosensitize delivery methods notwithstanding this. One problem is the possibility of trapping the created singlet oxygen inside cells as a result of the matrix of nanocarriers, which slows down or even entirely prevents the out-diffusion. Additionally, the photosensitize kept in the nanosystem maintains the state of self-quenching to lessen the PDT impact and the effectiveness of NIR imaging through hydrophobic interactions, which is known to be beneficial for reducing side effects in blood circulation [153, 154]. The PDT effect is, however, restricted to tumor locations for this reason. The ideal outcome is to preserve the fluorescence in the bloodstream and have it self-extinguish after it reaches the target areas. Delivering photosensitizer: PDT has lately gained popularity as a cutting-edge tactic thanks to its advantages of being selective, repeatable, and largely noninvasive. Nevertheless, due to the photo sensitizer's self-quenching in the center of nanoparticles in blood circulation and the NIR light's low penetration, the concentration of singlet oxygen produced by photo sensitizer was unable to reach the optimal level. To address the difficulties highlighted above, substantial research has been conducted on the development of new redox-sensitive DDSs to regulate drug release under high levels of GSH in cancer cytoplasm [155].

Redox and pH dual responsive DDSs

Among the intracellular drug release stimuli DDSs, the pH sensitive DDSs achieved by the differential in acidity is a relatively developed system. More energy is required for tumor tissues to maintain their growth. As a result, rather than the regular oxidative phosphorylation that results in greater H+production as a byproduct of glycolysis, their energy is mostly obtained via glycolysis. Moreover, the Warburg effect lowers the pH of the tumor microenvironment material. Cancerous endosomes and lysosomes have lower pH values than blood and normal cells, which have a pH of 7.4. It has been discovered that positively charged nanoparticles are more likely than negatively charged nanoparticles to enter cells by the endocytosis of proteoglycan adsorption in cell membranes. Positively charged nanoparticles, on the other hand, are quickly removed from the bloodstream. Charge reversal achieved by the acid gradient between blood and cancer cells and pH-responsive DDSs have been developed as a better approach to address this problem [156].

Redox and enzyme dual-responsive DDSs

The human body contains an abundance of enzymes, which are crucial for sustaining the body's regular functioning. In a number of serious clinical disorders, it has also been found that enzymatic activity is dysregulated. For instance, tissues with cancer overexpress certain enzymes. In order to construct enzyme-responsive DDSs, enzyme-sensitive materials have been used extensively [157].

The redox-responsive DDSs have higher tumor-targeting and drug release efficiency due to the enzyme's excellent biocompatibility, selectivity, and efficiency. The primary components of enzyme-responsive DDSs are typically starches and peptides, which are degraded by enzymes such phospholipases, cancer-associated proteases, kinases, and acetyltransferases [158].

Redox responsive and magnetic guide DDSs

In recent research on redox dual-stimuli responsive DDSs, which intended to further deliver medications to specified locations while safeguarding the healthy tissues from damage, magnetic guidance has emerged as a hotspot. These studies are in addition to the dual sensitive DDSs already discussed. Fig. 2 depicts the medication distribution of magnetic and redox-responsive DDS. The precise regulation of medication release into tumor cell cytoplasm is the fundamental component of the smart magnetic guide drug delivery system [159].

Advances in nano-materials

Organic/inorganic hybrid nanomaterials

Two hybrid organic/inorganic materials are formed as a result of interactions between the organic and inorganic components. For instance, iron oxide (Fe3O4) nanoparticles, carbon dots, semiconductor quantum dots (QD), and gold nanoparticles (AuNPs) are some water-insoluble inorganic nanoparticles. The size of these mixtures of organic and inorganic elements is submicron. Hybrid nano-composites are organic and inorganic matrices with a size higher than a micron. Nanoscale organic and inorganic materials are used to make hybrid nanoparticles [106]. Nanoparticles and nanocomposites, the two types of organic/inorganic hybrids, can be further divided into classes 1 and 2 based on the strength of their

links. Depending on the manufacturing process, the binding strength varies. The class 1 hybrid materials are held together by weak hydrogen bonds, Vander barriers, electrostatic bonds, or electrostatic interactions between organic and inorganic components. However, class 2 hybrid materials have strong and stable covalent or ionic connection. With little phase separation and clearly defined organic-organic interfaces, new materials from functionalized alkoxides can be synthesized using Class 2 hybrid materials that contain covalent linkages [160, 161].

Chemo dynamic cancer therapy (CDT) using nano-material

Due to how quickly nanotechnology is growing, Nanomaterial is used in a lot of cancer treatments. Several cutting-edge therapies for sensitive reaction activity, starvation therapy (ST), and other sensitive reactions have been made using Nanomaterial. This is usually done by causing a lot of oxidative damage on the outside and then using the low oxygen material inside the tumour to turn the overproduced hydrogen peroxide (H2O2) inside the cells into the very dangerous hydroxyl radical (OH) (TME). It is critical to compare CDT based on the Fenton-and Fenton-like responses elicited, which have tumour selectivity and are caused by TME's endogenous chemical energy and are beneficial in preventing oxidative damage to normal tissues. Furthermore, CDT does not require a separate oxygen energy source (O2). Additionally, increasing anti-tumor sensitivity and effectiveness by combining CDT with other treatments Metal Nanomaterials, noble metals, organic frameworks, mesoporous carbon-based Nanomaterials, etc. are some NANOMATERIAL-based nanoplatforms utilised for CDT [162, 163].

Photodynamic therapy (PDT) nanomaterials

A rapidly evolving technique for cancer diagnosis and treatment is photodynamic therapy (PDT). Cytotoxic reactive oxygen species (ROS) eventually cause the death of cancer cells in the presence of endogenous molecular oxygen because they accumulate in tumor tissue and are triggered by light sources of particular wavelengths. Even if its constituent components are non-toxic, PDT is associated with the production of harmful ROS like singlet $^1O2$, $O2\bullet-$, OH. Photosensitizer (PS) is filled with light. This method allows PDT to safely eliminate tumor cells as PS medicines have extremely high toxicity in the absence of outside photo-activating light [164]. Additionally, PDT considerably decreases side effects and enhances target specificity when compared to conventional cancer treatment alternatives like radiotherapy and chemotherapy since only the targeted cells and tissues are exposed to radiation during PDT. It represents a possibly improved method of successful cancer treatment. Wideband light from non-laser sources and monochromatic light from laser sources, such as metal-lamps lasers and argon-pumped dye lasers, fluorescent lights, and xenon arc lamps, are just a few examples of sources that can be employed for PDT. The selection of the light source is based on the PS used, the location of the tumors, and the light intensity. Evidently, a wavelength that may activate PS and create ROS is required to induce PDT [165, 166]. Since only target cells are affected by light irradiation, cancer treatment techniques like radiotherapy and chemotherapy are possibilities. PDT stands for a potentially enhanced form of effective cancer treatment. Gold nanoparticles, silver nanoparticles, Silica and silicon nanoparticles, Quantum Dots (QDs), Upconversion Nanoparticles, Carbon-Based Nanomaterials and Carbon nanotubes are some Nanomaterials for photodynamic treatment [167].

Wound-healing therapeutics using nanomaterials

Hemostasis, inflammation, bacterial growth, and remodeling of bacterial infection are four biological processes that happen in order and overlap as a wound heals. These are highly coordinated processes for rebuilding wounded tissue. Bio-sensing, Bio-imaging, Drug Delivery, Anticancer activity, Antibacterial activity, medical diagnostics, medical devices, the Food industry, Cosmetics, medicine, and Wound healing are just a few of the biomedical uses for wound-healing treatments based on Nanomaterials [168]. The main reasons for the extensive usage of Nanomaterials in wound healing are their favorable physicochemical properties and high surface area to volume ratio at the nanoscale (1-100 nanomaterials). In particular, their compact size and high surface area to volume ratio allow them to quickly penetrate the epidermal layers and interface with the wound site. Because of this, Nanomaterials can not only act as healing agents for wounds but can also transfer healing agents to the wound site in a steady, controlled manner. Nanomaterials-based strategies have created novel antibacterial alternatives that can eradicate various pathogenic bacteria. For instance, metal or metal oxide nanoparticles (such as Ag, Au, and ZnO) have been created for their ability to treat wounds and their inherent antibacterial activity [169, 170].

CONCLUSION

This brief overview outlines the incredible developments in nanotechnology over the past two decades and explains why they are crucial to the further investigation of smart materials for biological applications. To create drugs and polymers that react to biological cues like the pH and temperature differences between healthy and diseased tissue, creative drug and polymer formulation are required. The induced response results in a controlled and sustained release of the load. The prospect of developing materials that individually respond to local stimuli will increase with a better knowledge of the physiological changes and the distinctions between healthy and sick tissue. According to the therapeutic objectives, the production of nanoparticles for drug release following encapsulation must be customized. Designing multifunctional nanoplatforms will enable new methodologies and tactics for clinical cancer nanomedicine, improving the efficacy of diagnostics and treatment. In conclusion, stimuli-responsive nanomaterials will surely lead to effective methods and deliver a significant advantage in the biomedical area given the growing advancement and ongoing innovation of science and technology.

ABBREVIATIONS

NM: Nanomedicine, ZnPc58: Zinc (II) phthalocyanine, MelNP: Melanin-like nanoparticle, PLA: Polylactic acid, RSV: Resveratrol, CPT: Camptothecin, PTT: Photothermal treatment, AgNWs: Silver nanowires, MRI: Magnetic Resonance Imaging, MNP: Magnetic Nanoparticles, Gox: Glucose oxidase, PSL: Phospholipase-responsive liposome, PNA: Peptide nucleic acid, MSNs: Mesoporous Silica Nanoparticles, MNPs: Magnetic Nanoparticles, QD: Quantum Dots, AuNPs: Gold nanoparticles, ST: Starvation Therapy, ROS: Reactive Oxygen Species, PS: Photosensitizer, CDT: Chemodynamic Therapy, TME: Tumor Microenvironanomaterialent, DDs: Drug Delivery, GSH: Glutathione, DOX: Doxorubicin, LCST: Lower Critical Solution Temperature, UCST: Upper Critical Solution Temperature, LDH: Layered Double Hydroxides, HIV: Human Immunodeficiency Virus, DNA: Deoxyribonucleic acid.

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CONFLICT OF INTERESTS

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