



(REVIEW ARTICLE)



Polymeric nanoparticles with stimuli-responsive properties for drug delivery

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Abstract

In the last few decades, polymeric nanoparticles have been emerged as a most promising and viable technology for targeted and controlled delivery of drugs as well as delivery of bioactive compounds such as genes, drugs, nucleic acids and proteins among other things, in biomedical and pharmaceutical applications. They not only improve the solubility, bioavailability, and circulation time of previous medications, but they can also be tailor made to selectively release the drug at the target site. Furthermore, these polymeric nanoparticles can be transformed into stimuli sensitive systems based on either exogenous stimuli (such as ultrasound, light, electric pulses, magnetism) or by endogenous stimuli (such as PH, redox, enzymes, temperature, hypoxia, glucose) for efficient targeting and biodistribution of genes and drugs at specific sites. Polymeric nanoparticles for delivery of drugs and bioimaging has attained a considerable interest in various cancer therapies. In the present content, we discuss various types of stimuli-responsive-nanocarriers and their applications in different fields like bioimaging, drug delivery.,etc.

Keywords: Stimuli-Responsive DDS; External Stimuli; Internal Stimuli; Bio Imaging; Gene Delivery; Drug Delivery

1. Introduction

Nano technology has a major effect on practically every subject of study [1-3]. Because of their small size scale they are concerned with synthesis, evaluation and application of materials with novel properties. Due to this unique phenomenon of nanocarriers there is a possibility of manipulating biological structures at nanoscale or atomic level by the use of these systems. These polymeric nanocarriers now offer a wide range of uses in cancer treatment and detection. These polymeric nanocarriers can boost anticancer efficacy and reduce cytotoxicity by enhancing the solubility of poorly soluble drugs. Additionally, these polymeric nanocarriers can incorporate imaging agents such as inorganic nanoparticles and organic dyes for simultaneous cancer surveillance and treatment. Chemical or physical conjugation can be used to insert diagnostic and therapeutic substances into these nanoparticles [4]. Genes or proteins having anticancer activity can be enclosed by forming nano-sized complexes with polymers, in addition to standard chemical entities. Cationic polymers can produce stable nanoparticles in aqueous solution by electrostatically interacting with anionic proteins or DNA. When compared to normal blood vessels, tumour blood vessels are often more permeable. Depending on the location of tumour the size of pores of tumor microvasculature range from 100-780 nm when compared to normal healthy blood vessels. Due to this property of tumour microvasculature, it's assumed that nanoparticles smaller than a particular size that is less than 200 nanometers can be deposited at tumor site by IV administration with increased Retention and Permeation Effect (EPR). The passive targeting process can also be achieved by conjugating the targeting substances to the nanoparticles surface.

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2. Types of stimuli

In order to improve the treatment efficacy and to reduce or eliminate unwanted effects the delivery of drugs should be at the targeted sites in controlled manner. Stimuli responsive delivery of drugs has shown a tremendous potential for an efficient drug targeting by this method (Figure 1). Multiple types of stimuli were utilized in the design of stimuli-responsive-drug-delivery systems, which were classified into exostimuli or external stimulus & endostimuli or internal stimuli as shown in (Figure 2) [5] [6]



Figure 1 Stimuli responsive polymeric nanoparticles

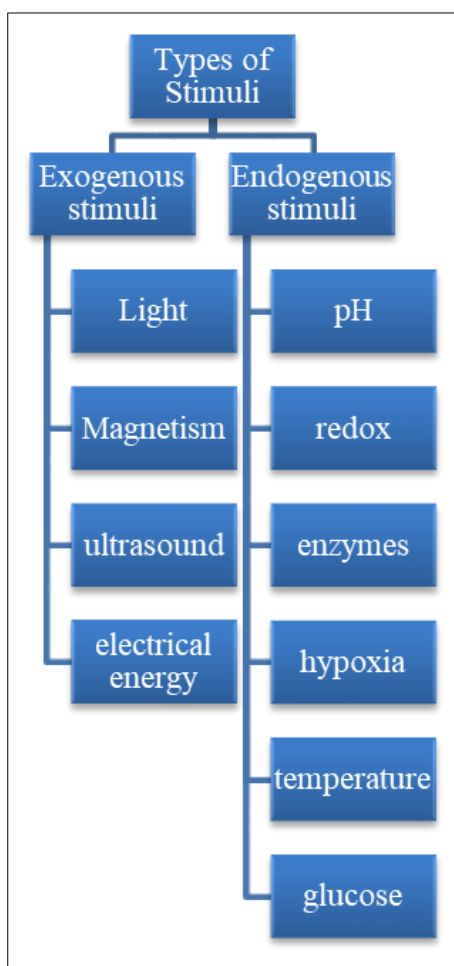


Figure 2 Various types of stimulus in stimuli responsive DDS

2.1. External stimuli

Advances in the medical sciences have enabled the utilization of various exostimuli based energy sources for efficient triggering of drug release from nanocarriers for efficient delivery to the target sites. There are various types of exostimuli used in formulating stimuli responsive DDS (stimuli responsive drug delivery systems).

2.2. Light

Light responsive DDSs have an on and off type of release of drug in response to the light. Different wavelengths of lights like UV, Near IR, Visible light are investigated for controlled release of drug [7]. Photo activatable micellar systems were created for lipophilic substance drug delivery using a co-polymer system comprising 2-Nitrobenzyl scaffold / 7-diethylamino - 4 - (hydroxymethyl) coumarin. The produced micelles dissolved and disseminated the drug encapsulated into aqueous solution after being exposed to two – proton near IR irradiation with a laser [8] [9].

2.3. Magnetism

Magnetic stimuli are used as a noninvasive technique for medical imaging via MRI or for developing controlled release drug delivery platforms because of their freely permeable nature [10]. Magnetic nanoparticles with a center/shell structure, for example, have a range of unique magnetic properties and, when appropriately constructed, can provide additional benefits such as increased plasma half-life, improved bioconjugation sites and so on [11] [12]. Two important strategies for regulated release of the drug in the presence of external-magnetic-stimulation are drug targeting guided by a magnetic field and hyperthermia [13].

2.4. Ultrasound

Due to its numerous advantages, such as enhanced spatiotemporal control, intrinsic tissue penetration and increased safety, the ultrasound has been widely used as a stimuli in clinical experiments [14-16]. The utilization of a technology known as “sonoporation” causes permanent or temporary openings in the blood vessel membranes, considerably boosting extravascular transfer of therapeutic substances in the site of action, due to its safety and intrinsic tissue penetration [17-18].

2.5. Electrical-energy

By application of a mild electrical field to a particular location of tissue after administering an electro sensitive medication can result in programmed-drug-delivery via a variety of mechanisms such as redox reactions [19], breakdown of carrier structure [20], and heat production from electrical stimulation [21]. Electrical stimuli-responsive hydrogels based on aniline and dextran trimers for regulated medication release were recently developed [22].

2.6. Internal-stimuli

Endostimuli-responsive nanoparticles for drug delivery and effective targeting have benefited from these properties.

2.7. pH

Under altered pathological situations, such as cancer, inflammation, or ischemia with dramatic pH variations, pH has also been exploited to release drug moieties as shown in (Figure 3) [23]. The extracellular pH in healthy tissue and blood is kept at 7.4. Because many tumours have high glycolysis rates, extracellular pH levels are frequently acidic [24]. A low pH can help to identify the tumour region, allowing for more targeted drug delivery. pH-responsive polymers allow for mild conformational changes and are often utilized in these systems. They can donate or accept protons at pathological pH. Modified poly-(caprolactone) (PCL) nanoparticles were used to boost tamoxifen concentrations in oestrogen receptor (ER)-positive breast cancer [25].

2.8. Redox

Redox stimulus systems had gotten a great deal of interest over the years for its potential to treat a variety of illnesses, and it's been extensively studied for the intracellular delivery of drugs [26]. Glutathione (GSH) concentrations in malignant tissues are 100-1000 times those in blood and around 100 times those in healthy tissues [27]. GSH is a powerful reducing agent that reduces the accumulation of reactive oxidative species (ROS) in sick tissues and is an intriguing stimulant for the delivery of anticancer medications due to its inherent thiol group [28].

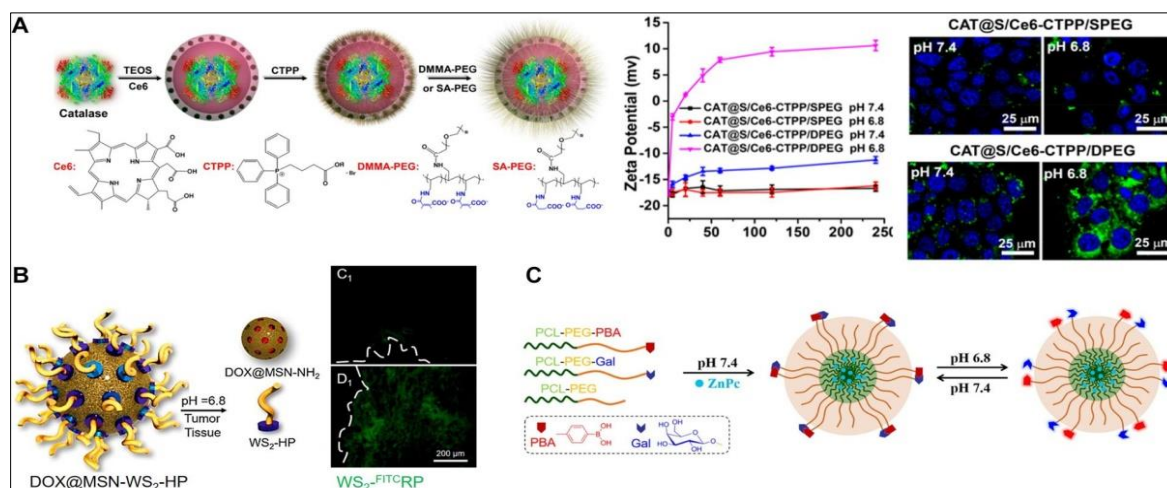


Figure 3 Pathological pH sensitive polymeric nanobiosensors for cancer theranostics which were recently developed

2.8.1. Enzymes

Because of their tremendous substrate specificity, the enzyme-responsive drug delivery systems have intensively been explored as potential therapeutic sector. Protease, lipase, glycosidase, trypsin, oxidoreductase, phospholipase and other enzymes had used to increase medication delivery to the cancer cells [29] [30]. Trypsin, a key digestive protease, regulates exocrine-pancreatic-secretion, which affects release of a range of the other digestive enzymes [31].

2.9. Hypoxia

Epithelial to mesenchymal transition, angiogenesis, metastasis and invasiveness are all affected by hypoxia in malignancies [32]. Tumor hypoxia appears to be a potential strategy for slowing tumour growth. Various reducing agents such as CYP450 reductase, NADPH, azoreductase, nitroreductase, NADH, and alkaline phosphate, accumulate in hypoxic cells [33]. Hypoxia causes plenty of changes that could pose a threat to nanomedicine architecture's key concepts. The hypoxia metabolic-cellular-pathway in hypoxic tumour cells can produce lactic acid which makes tumour microenvironment very acidic [34] [35].

2.10. Temperature

Temperature-responsive, smart-drug-delivery systems have been intensively studied in cancer therapy [36]. Nonlinear abrupt alteration in characteristics of a component in relation to the temperature in the surroundings governs the mechanism of release of drugs. Thermosensitive drug delivery systems rely on fast delivery of encapsulated drug when tumour microenvironment at a raised temperature, such as 40 to 42 degrees Celsius [23]. ThermoDox® (Celsion Corporation) a radiofrequency or temperature ablation sensitive doxorubicin liposomes, is now in phase II trials for colorectal liver cancer, breast cancer and hepatocellular carcinoma [24]. The use of functional modified thermosensitive liposomes to specifically target the antibody against the human epidermal growth factor receptor II in the treatment of breast cancer is also being investigated [37].

2.11. Glucose

Many researchers are interested in using glucose responsive composites that create smart insulin drug delivery systems. A insulin vector that monitors blood glucose levels [38] and a glucose responsive substance make up these systems. Insulin carrier, which governs the insulin release rate [39], undergoes several alterations such as crosslinking, pH and hydrophilicity.

3. Stimuli responsive polymeric nanoparticles for gene and drug-delivery

3.1. Pharmacotherapy with target specific Nanocarriers

Traditional DDS have substantial disadvantages and constraints, which were typically caused unpredicted drug release behavior and unpredicted biodistribution, resulting in systematic adverse effects. The target specific nanocarrier systems were most popular nano carrier technologies for the delivery of API's. These systems had helped to overcome limitations of traditional DDS. The stimuli sensitive drug delivery systems improves therapeutic efficacy of the loaded

molecules by targeting them accurately to the damages cells, organs or tissues, by preventing the loaded compounds from first pass metabolism, therefore raising their therapeutic index. In addition, in presence of stimuli, these DDS have showed considerable reaction & change in the features (external/ internal). Mechanisms of the drug loaded nanocarrier systems for the targeted delivery at cellular level or molecular have been demonstrated to play simultaneously critical roles & function for effective disease management and diagnosis.

3.2. Active and passive targeting

To obtain effective systemic therapy, passive and active techniques have been widely utilized for targeting various nanoparticles-based DDS. The incorporation of specified ligands to the nanoparticle's surface improves recognition ability of the cells in the disease sites, which is how active targeting in some cases, as polyethylene glycol-modified nanocarriers increase time of circulation in blood and achieve passive targeting.

4. Stimuli-responsive polymers in biomedical applications

A variety of interesting biological uses for stimuli-responsive polymer systems have been proposed, including drug administration, cell culture surfaces, and diagnostics. Different stimuli-responsive NCs for gene targeting and drug delivery.

4.1. pH responsive nanocarriers

The Ph factor is more important at the cellular and subcellular levels, as the abnormal tissues such as diseased, inflamed and cancerous cells, frequently has low PH. Extracellular pH of cancerous cells can be easily dropped to 6-7, with some malignancies reaching even lower levels. Following endo-cytosis, the NCs system encounters highly well defined compartments based on significantly varied levels of pH. pH of the early endosome is around 5 to 6, while pH of the effected lysosome will be in acidic compartment, which is around 4 to 5. These intracellular and extracellular pH gradients could be exploited for creating DDS that release the drug selectively at the targeted site.

4.2. Thermo responsive nanocarriers

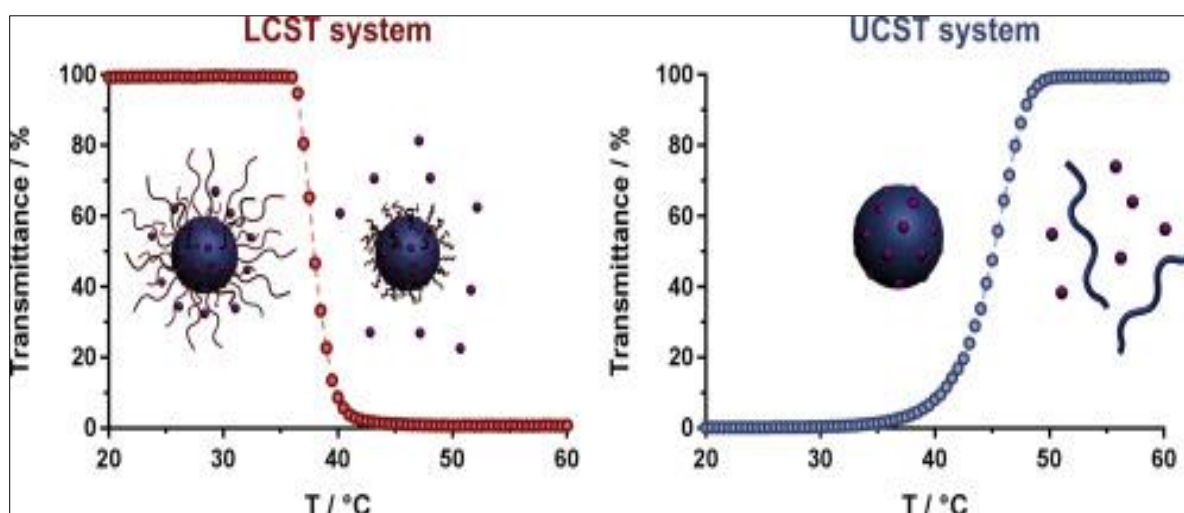


Figure 4 Biomedical applications of thermoresponsive polymeric nanocarriers

Thermo-responsive polymeric materials are excellent for creating molecular patterns that respond reversibly to change in temperature across a short temperature range (Figure 4). Because block copolymers of two thermo responsive monomers form micelles in water, they can be utilised to not only set the LCST to a certain value, but also to transport medicines.

4.3. Self-assembled thermo-responsive nanoparticles

For localised hyperthermia drug delivery, self assembled thermo responsive nanocarriers consisting of poly (N,N-diethyl acrylamide-co-acrylamide)-block-poly(-benzyl L-glutamate) were produced. The lower critical solution temperature of the nanoparticles was designed to be the halfway between normal body temperature (37 °C) and local hyperthermia (43 °C).

4.4. Hydrogels

Hydrogels are thermo-responsive and, depending on their composition, shrink or expand when heated. These hydrogels were densely packed especially at the surface so it aids in the on and off mechanism of release. IPN which is made up of PNIPAAm and (PTMEG) poly (teramethylene ether glycol) is an example of hydrogel. This system had shown a release rate of Indomethacin at 30°C, but it showed an enhanced release rate at lower temperatures. A required on and off release mechanism was achieved by this system, despite the fact that the reaction temperatures are not yet acceptable for an in vivo use. Copolymerization of PNIPAAm-containing hydrogels with other monomers, such as acrylic acids, can fine-tune the reaction temperature. Furthermore, this alteration increases the responsiveness of these hydrogels to pH fluctuations.

4.5. Redox potential-responsive nanocarriers

It is widely documented that the intracellular space is reductive and the extracellular space is oxidative, which was significantly related to the extra and the intracellular glutathione content, the given redox potential difference (100 to 1000 times) between the intracellular and extracellular spaces. Based on the above principles, redox-sensitive-nanocarriers could be used for intracellular distribution, notably for gene delivery (Figure 5).

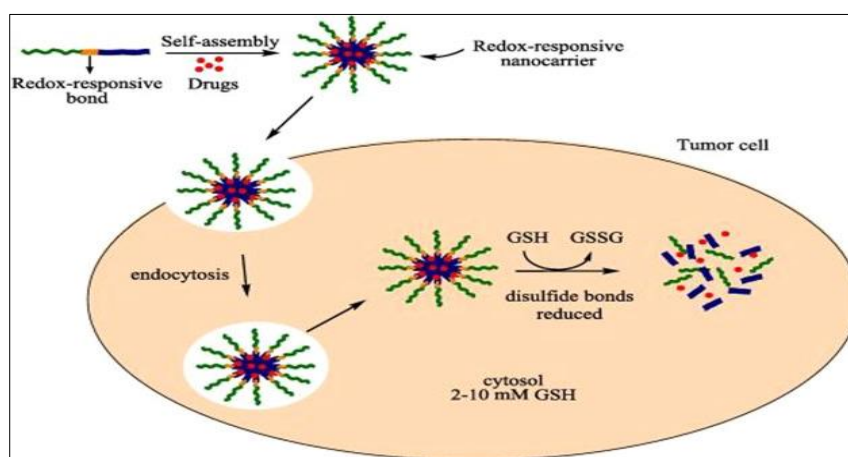


Figure 5 Redox-responsive drug release schematic illustration

4.6. Enzyme-responsive nanocarriers

Nanocrystals that respond to enzymes In comparison to non-cross-linked complexes, direct plasmid DNA complex formation with linear PEI followed by cross-linking with a cross-linker containing disulfide resulted in higher liver transfection and blood concentrations. Recently, a micelle that can alter shape in response to specific enzymes was identified. The peptide sequences in this micelle were recognised to be substrates for specific hydrophilic block enzymes [40](Figure 6).

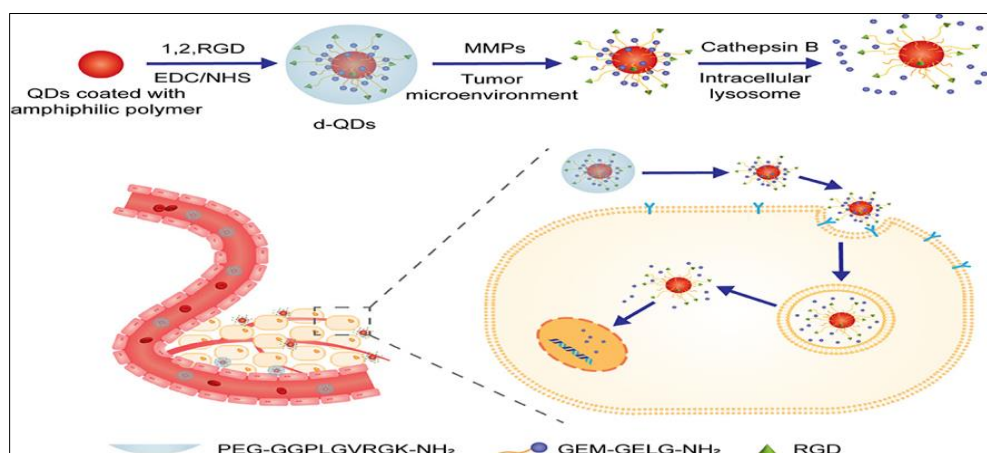


Figure 6 Anti-tumour drug delivery using enzyme-responsive nanoparticles

framework BioMOF-1 has been reported, and its potential as a drug delivery material has been researched. Procainamide hydrochloride, a local anaesthetic is administered into pores of BioMOF-I via a simple-cation-exchange approach.

4.13. Glucose-responsive nanocarriers

It has always been tempting to be able to control bio-responsive systems using endogenous and metabolic chemicals. To produce a glucose-responsive nanocarrier, researchers coupled the enzymes GOD (glucose catalase) and CAT (glucose oxidase) in the nanocapsule containing insulin solution. The LbL assembly procedure was used to create the capsules' multilayer shells, which incorporated imine bonds. The conversion of the glucose to gluconic acid & subsequent cleavage of imine bonds, the capsule disintegrated after being exposed to glucose solution, releasing the insulin.

4.14. Electrical-field-responsive-nanocarriers

The electrical field responsive release of drugs, which involves the ability to release and modify the carrier system remotely, is other intriguing way for constructing stimuli responsive DDSs. When subjected to a low electric potential of anode of atleast +0.5 V, nanoscale thin films are said to release precise doses of a tiny molecule medicine. Films containing positively charged gentamicin nanoparticles and negatively charged Prussian blue and a small hydrophilic antibiotic were created via LbL assembly. Whenever the Prussian blue nanoparticles are oxidised, they went from -ve charged to neutral, causing the film to dissolve. Controlling the release of drug by adjusting the thickness of the film and the amplitude of the voltage applied.

4.15. Substrate-responsive nanocarriers

This system uses unique ligand induced volume change at pre-determined timings initiated the release of the VEGF (vascular endothelial growth factor), model medication [43].

4.16. Dual-responsive-nanocarriers

Dual-responsive-nanocarriers are a relatively recent concept in a realm of environmentally-sensitive DDSs. Such system can respond orthogonally to two distinct inputs. Dual-responsive systems are commonly made by combining two monomers with different stimuli responsiveness.

4.17. Stimuli-Responsive-Polymeric-Nanocarriers for Bioimaging

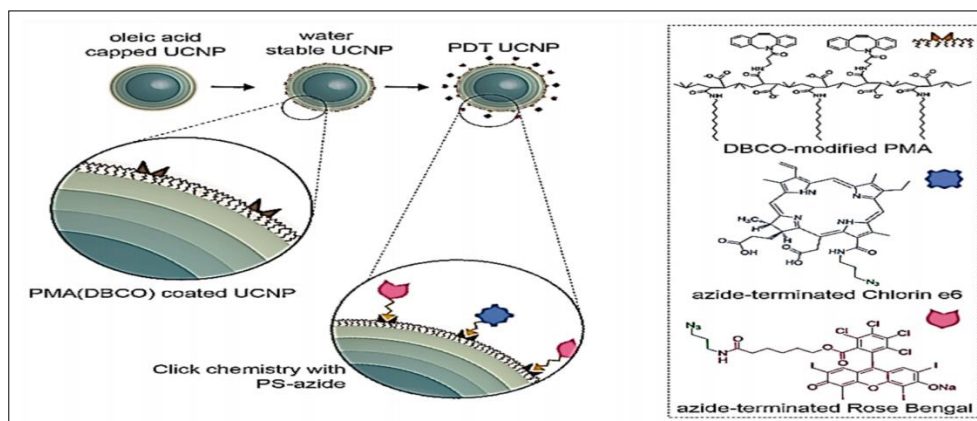


Figure 8 The phases of UCNP synthesis, including exchange of water and two PSs functionalization and water exchange, are depicted [6]

Polymeric nanocarriers have a substantial benefits over inorganic nanomaterials in terms of low preparation costs, biocompatibility, biodegradability, stability and tailoring capability. Smart-polymers are highly efficient polymers that respond to the triggered environment. Stimuli-responsive-polymers are affected by temperature, humidity, pH, chemical compounds, wavelength and light intensity as well as magnetic and electric fields. These materials could change their transparency or colour, become water conductive, or change shape, among other things. Change in the characteristics of polymers are mainly caused by minor environmental changes. Bio-imaging is a noninvasive method for observing biological processes over time while causing minimal discomfort to different life cycles like respiration, movement and documenting the 3D structure of the specimens. It's important for subcellular linking structural

observations to all tissues in the multicellular organisms. Ultrasound (US) [47], single photon computed tomography (SPECT), nuclear imaging [46], optical imaging [44], photoacoustic imaging (PA), magnetic resonance imaging (MRI) [45], positron emission tomography (PET) and other imaging techniques have all been used widely in clinical applications as shown in (Figure 8).

5. Applications in regenerative medicine and tissue engineering:

Tissue engineering and tissue regeneration are subgroups of greater field of the life sciences that often integrate biological and engineering elements to restore ill or injured cells, organs, and tissues. This field have been shown to have a lot of biomedical potential. Biopolymers and their mixes have been played a key role in the creation of tissue engineering materials and they are one of the most promising elements. Stimulus-responsive biopolymer-mediated systems have also used to generate biocompatible and biodegradable substances for regenerative medicine applications and bone/tissue engineering. In addition, the mechanical properties and the physical properties of materials can also be changed by the mixing and producing films and porous assemblies with certain designs. Chitin, collagen, chitosan, and other natural polymers have all been used to make stimuli-responsive scaffolds and structures. Tissue engineering-mediated materials require cell-associated structures which provides the propagation, cellular linkage, advancement, variance and displacement. In addition to polymer linked system, lipid-based systems have been shown a great promise in development of the regenerative therapeutics for the cancer and the other maladies or diseases. Researchers has developed the stimuli-responsive and chitosan based di-functional polymerized nanocarriers as a promising material for the tissue engineering and drug delivery, according to a study. Polymeric nanoparticles were studied under a variety of redox and pH conditions that were similar to those observed in cancer cell settings. The polymeric nanoparticles were shown to be biocompatible and biodegradable, although they disassembled in presence of the two stimuli. However, due to their characteristics, these polymeric nano-particles could be used as nanocarriers for targeting the drugs in chemotherapeutics. Hydrogels possessed similar mechanical properties to soft tissues, but were more prone to swelling. The addition of gelatin to the hydrogel had a significant impact on it, forcing it to form or deform into a helical pattern. In recent years, the number of regenerative-medicine based techniques for targeted and effective distribution of the biomaterials via stimuli responsive biopolymers has dramatically expanded. As a result of the findings, customised hydrogels could be used as the regenerative therapy for the central nervous system disorders.

6. Conclusion

Many smart-polymer-drug delivery, tissue engineering and diagnostic applications are in the works but have yet to make it to clinical use. Some of the reasons for this were best explained in the terms of smart polymer's potential biological toxicity, especially for the intra-cellular delivery of biomolecular medications such as nucleic acid, proteins and peptide pharmaceuticals that act predominantly within the cells. Many Smart-carrier systems use acrylic acid polymers and acrylamide that are not hydrolytically degradable, such as PNIPAAm and PPAAc. Concerns about PNIPAAm's possible toxicity have been raised in the past, but they have yet to be properly addressed, to the author's knowledge. The fact that AAm monomer is known to be neurotoxic may be a source of concern. NIPAAm monomer is unlikely to be present in PNIPAAm formulations that has been evaluated because they are normally thoroughly cleaned before integrating medicines. As a result, the possibility that PNIPAAm is toxic in and of itself must be thoroughly examined in animal testing and cell culture, sometimes known as preclinical-implant studies. Furthermore, many smart polymer carriers with higher molecular weights are more successful in reaching their cellular targets; such a polymers are not easily removed by kidneys after delivering the medicine, and they are not a biodegradable, so they tend to be accumulate in the body. This might be another reason they haven't investigated in the clinical trials. The clinical trials are too expensive, and the companies the prefer to use well known, FDA-friendly polymers like PLGA and PEG instead.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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