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Original Article

Smart Polymers is Controlled Drug Release

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ABSTRACT

In recent years, the development of novel drug delivery systems has gained immense attention in the pharmaceutical and biomedical fields. Among them, smart polymers, also referred to as stimuli- responsive polymers, have emerged as a revolutionary class of materials for controlled drug release. Unlike conventional polymers, which provide passive encapsulation and release of drugs, smart polymers are capable of responding to specific external or internal stimuli such as pH, temperature, light, enzymes, redox potential, or magnetic fields. This unique ability enables precise spatial and temporal control of drug release, thereby improving therapeutic efficacy, reducing side effects, and enhancing patient compliance. Despite significant progress, several challenges remain in the clinical translation of smart polymer- based drug delivery systems. Issues such as biocompatibility, biodegradability, large-scale production, reproducibility, and regulatory approval must be carefully addressed. Moreover, long-term safety and stability of these materials in biological systems need thorough investigation. Nevertheless, ongoing advances in polymer chemistry, nanotechnology, and biomedical engineering are continuously improving the design and functionality of smart polymers. Integration with emerging fields such as personalized medicine, targeted drug delivery, and nanotheranostics further enhances their potential.

Keywords: Nanotheranostics

INTRODUCTION

Nanoparticles (NPs) have been successfully adopted in electronics, food and agriculture, biosensing, and some areas of nanomedicine; however, their translation to clinical oncology remains limited. Although nanomedicine-based drug delivery has been dominating the field of cancer research over the past decade, only a dozen US Food and Drug Administration (FDA)-approved NPs are currently available. As such, there is a growing need for novel NPs in oncology to improve drug delivery for cancer treatment, mainly through target-driven design. Currently, poor patient outcomes are attributed in part to the low stability, drug solubility and bioavailability, poor pharmacokinetic (PK) and pharmacodynamic (PD) parameters, a specific distribution, cytotoxicity, and chemo resistance that are characteristic of traditional chemotherapeutic agents. As a result, nanomedicine-based drug delivery has been of increasing research interest because NPs have been shown to substantially improve the therapeutic efficacy of chemotherapeutic agents by overcoming the various anatomical, physiological, chemical, and clinical barriers associated with intravenous drug administration However, the lack of efficacy in the clinic has made innovative NP-design and -delivery approaches increasingly important in the translation of these promising therapies from bench to bedside.

Smart Nanoparticles

NP drug-delivery systems that can release the drug in response to specific physiological triggers, at the appropriate time, and at the correct target site are referred to as smart NPs. For this review, smart NPs refer to those incorporating all three delivery strategies: passive, active, and stimuli-responsive targeting, as summarized. The enhanced permeability and retention (EPR) effect, or passive targeting, is the most basic targeting strategy employed by smart NPs. The EPR effect and its limitations have been reviewed extensively elsewhere. the EPR effect is a complex phenomenon dictated by the degree of leaky tumor vascularization and poor lymphatic draining that varies significantly between tumor types, anatomical sites, and patients. However, the high intestinal fluid pressure in tumors can prevent successful uptake and

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homogenous drug distribution. Long-circulating liposomes, polymers, and micelles are examples of NPs that take advantage of the leaky vasculature of tumors that ultimately allows for the entrapment and accumulation of NPs.

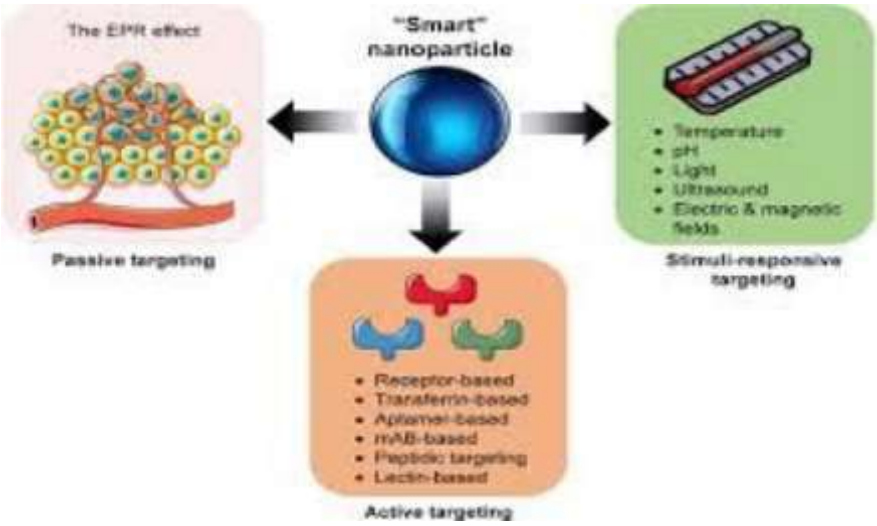

Figure 1 Multifunctional targeting employed by "smart" nanoparticles

Clinical importance of smart nanoparticle drug delivery Cancer patients often face severe cytotoxic effects, as most anticancer agents are administered at the maximum tolerated dose, leading to discontinuation of life-saving treatment. Intravenous delivery of anticancer agents is also limited due to low drug efficacy, the need for hospitalization, frequent administration, and high cost.4 Smart NPs can allow for the administration of lower doses of drugs while maintaining effective intracellular concentrations, thereby widening the therapeutic window of anticancer agents. For instance, nanopolymers possess high drug-loading capacity, which allows them to achieve the same efficacy with smaller doses while minimizing systemic side effects. Therefore, smart-NP formulations that can increase tumor accumulation and specificity for cancer cells through coordinated targeting strategies can provide a therapeutic option that significantly reduces systemic side effect.

Classification of Polymers

A) Based on origin

1) Natural polymers –

Natural Polymers are extracted naturally from plant origin which are water-based polymers. E.g. such as cellulose, keratins, etc.

2) Synthetic polymers –

Synthetic Polymers are man-made polymers with the help of chemical reactions Eg. such as polyethylene glycol, polyether's, etc.

B) Based on chemical structure

1) Natural polymers Natural Polymers are extracted naturally from plants-based resource which are water-based polymers.

2) Inorganic polymers Inorganic-

Polymers are those polymers that do not contain any carbon atoms in their backbone or chain Eg. such as polysulfide, polysiloxanes, etc.

3) Activated c-c polymers –

Activated C–C Polymers are the polymerization methods in which the reactive monomers are attached themselves to the active site of others

C) Based on the polymerization method

1) Additional polymers-

Additional Polymers are those polymers in which the simple linking of monomers takes place without co-generation. Eg. such as polystyrene, polyacrylates, polyethylene, etc.

2) Condensation polymers-

Condensation Polymers are those polymers that are formed through the condensation process. Eg. such as starch, cellulose, polypeptide chains, etc. 4.4. Based on interaction with water

3) Soluble polymer -

Soluble polymers are those polymers that are hydrophilic Eg. such as HPMC, PEG, etc.

4) Insoluble polymer -

Insoluble polymers are those polymers that are hydrophobic grade in the biological environment such as polyethyleneimine, etc. S.

Hydrogels are cross-linked hydrophilic polymers that do not dissolve in water Eg. such as polyvinyl pyrrolidine, etc.

E) Based on bio-stability

1) Biodegradable polymer –

Biodegradable Polymers are those polymers that are easily degraded in the biological environment Eg. such as polylactic acids, polyglycolic acids, etc.

2) Non-biodegradable polymer-

Non-biodegradable Polymers are those polymers that don't degrade in the biological environment. Eg. such as polyethyleneimine, etc. an important question is whether the drugs released from the NPs still have their original structure and bioactivity.

Development of Controlled Drug Delivery Systems - Control of Drug Concentration Levels Over Time

A) While newer and more powerful drugs continue to be developed, increasing attention is being given to the methods of administering these active substances. In conventional drug delivery, the drug concentration in the blood rises when the drug is taken, then peaks and declines.

B) Maintaining drug in the desired therapeutic range with just a single dose, or targeting the drug to a specific area (lowering the systemic drug levels), are goals that have been successfully attained with commercially available controlled release devices.

C) However, there are many clinical situations where the approach of a constant drug delivery rate is insufficient, such as the delivery of insulin for patients with diabetes mellitus, anti-arrhythmics for patients with heart rhythm disorders, gastric acid inhibitors for ulcer control and nitrates for patients with angina pectoris.

D) The onset of infection of medical device or biomaterial surfaces is an additional clinical situation where responsive delivery system of anti-inflammatory drugs can be useful.

E) Furthermore, studies in the field of chrono pharmacology indicate that the onset of certain diseases exhibit strong circadian temporal dependence. Therefore, time-dependent release of drugs, such as β-blockers, birth control, general hormone replacement, immunization and cancer chemotherapy, is required.

F) Treatment of all these clinical scenarios could be optimized through the use of responsive ('smart') delivery systems, which are, in essence, man-made imitations of healthy functioning.

Classification Of 'Smart' Polymers

A) 'Smart' controlled drug-release devices can be classified as open- or closed- loop systems

B) Open-loop control systems are those where information about the controlled variable is not automatically used to adjust the system inputs to compensate for the change in the process variables.

C) In the controlled drug delivery field, open-loop systems are known as pulsatile or externally regulated. The externally controlled devices apply external triggers for pulsatile delivery. Eg. such as: ultrasonic, magnetic, electric, light and chemical or biochemical agents.

D) Closed-loop control systems, on the other hand, are defined as systems where the controlled variable is detected, and as a result, the system output is adjusted accordingly.

E) In the controlled drug delivery field, closed-loop systems are known as self-regulated, in which the

release rate is controlled by feedback information, without any external intervention.

F) The self-regulated systems utilize several approaches for the rate control mechanisms. Eg. such as thermal, pH- sensitive polymers.

General Polymer Properties

A) Degradable polymers can be hydrolyzed in vivo and are usually classified according to whether their source is natural or synthetic. Commonly used polymers include the αhydroxy acids, polyanhydrides, and natural sugars such as chitosan, in addition to many other types.

B) Synthetic degradable polymers are favored in tissue-engineering or drug delivery applications, as they have less batch-to-batch variability and immunogenicity as compared to degradable polymers from natural sources.

C) Polymers can be rendered degradable through the inclusion of labile ester, anhydride, and amide chemical linkages, which are susceptible to common degradation mechanisms involving hydrolysis or enzymatic cleavage leading to the gradual scission (breaking of chemical bonds) of polymer chains.

D) Drug release from degradable polymers can be governed by

(1) surface erosion of the polymer matrix.

(2) cleavage of polymer bonds at the surface or within the bulk of the matrix.

(3) diffusion of the physically entrapped drug.

However, drug release is often a result of a simultaneous combination of all three.

Polymer Molecular Weight

The physical properties of polymers, such as Tg, solubility, viscosity, crystallinity, mechanical strength, and degradation rate, are related to the polymer's MW, with low-MW polymers degrading more rapidly. The MW of degradable polymers has a significant impact on the drug-release profile from NPs and can influence the biological properties of polymeric drug delivery systems, such as elimination, phagocytosis, and biological activity. For example, oestradiol-loaded NPs made with low-MW PLGA (14 500–45 000 Da) were found to exhibit zero-order release kinetics, compared to higher-MW (85 000–213 000 Da) PLGA, which exhibited a square root of time (Higuchi's pattern) dependent release. 120 Furthermore, drug Cmax in the plasma was shown to be polymer MW dependent (higher for the lower-MW polymers).

Biodegradability

Biodegradable polymers are designed to degrade into non-toxic by products upon completing their function, ensuring minimal long-term accumulation within the body. Commonly used materials such as polylactic acid (PLA) and polycaprolactone (PCL) have been extensively studied for their controlled degradation rates, making them suitable for prolonged therapeutic delivery. The degradation profiles can be further tuned by incorporating copolymers or functional groups to achieve site-specific release.

Biocompatibility

Biocompatibility is a non-negotiable attribute for any polymer intended for medical use. Smart polymers like polyethylene glycol (PEG) are often used to enhance the biocompatibility of drug carriers, reducing immunogenicity and prolonging circulation time in vivo. Recent advancements have focused on designing polymers that mimic natural biomolecules to improve their interaction with cellular environments.

Versatility

Smart polymers exhibit a range of functional properties, including responsiveness to external stimuli, self-healing capabilities, and the ability to encapsulate both hydrophilic and hydrophobic drugs. For example, amphiphilic block copolymers have demonstrated remarkable potential in forming micellar structures that protect encapsulated drugs during systemic circulation while allowing controlled release at the target site.

PLGA, PLA, AND PCL

A) Currently, PLGA, PLA, and PCL are part of the most widely used biodegradable polymers in the delivery of drugs. PLGA – a lactic and glycolic acid-based copolymer has been widely explored for its versatile degradation characteristics on varying bioactive compounds.

B) A recent study by Tong et al. (2023) using PLGA nanoparticles proved that siRNA could be effectively delivered to target cancer tissues.

C) The unique tunable degradation profile of PLGA makes it possible for the sharpening of the therapeutic index of nucleic acid-based drugs. [24] Based on the longer degradation profile of PLA than that of PLGA, PLA has been employed in numerous biomedical functions such as bioresorbable stents.

D) In another study that was conducted in 20,214, Zhao et al. proposed the use of PLA-based stents that have low restenosis since the polymer has potential in cardiovascular uses.

E) Amongst all these polymers PCL has a significantly slow degradation rate and thus can be used for longterm drug delivery applications.

F) Another study by Karbasi et al. (2023) came up with PCL-based scaffold for growth factor delivery in tissue engineering showing the versatility of PCL in regenerative medicine.

Applications in Controlled Release and Implants:

A) Biodegradable polymers have a significant role in current controlled-release systems because of their ability to deliver therapeutic agents in a controlled manner over a period of time.

B) As described by guo et al. (2023), a new anticancer preparation formulated from plga nanoparticles had better targeting efficiency and longer drug release time than the original preparation.

C) Pla has also been employed in the creation of bioresorbable stent to give half-term support to vessels while degrading to eliminate long-term adverse effects.

D) As about 2024, ahmed and colleagues studied the pla-based stents for treating the coronary artery disease where the effect of the stent reduced restenosis and benefited the patient.

E) Hence, its slow dissolution profile allows for sustained release making pcl ideal for implantation applications such as contraceptives or hormone-releasing implants.

F) Li et al. in 2022 further designed a pcl-based controlled drug delivery system for contraceptives where the controlled release of drug was maintained at several years.

Innovations In Smart Polymer:

Design Innovations in polymer science have significantly expanded the scope of smart polymer applications in drug delivery. Among these, stimuli-sensitive hydrogels, dendrimers, and micelles represent cutting edge developments.

Stimuli-Sensitive Hydrogels:

Stimuli-sensitive hydrogels incorporate responsive moieties that allow them to swell, shrink, or dissolve in response to specific triggers. For environment of tumors for targeted drug release Advances in hydrogel technology have also enabled multi-stimuli responsiveness, making these materials suitable for complex therapeutic scenarios.

Dendrimers:

Dendrimers are highly branched, tree-like macromolecules that provide precise control over drug loading and release. Their structural uniformity and abundant functional groups make them ideal candidates for conjugating multiple therapeutic agents or targeting ligands. Dendrimers have shown exceptional promise in delivering anti-cancer drugs, with studies demonstrating their ability to enhance bioavailability and reduce off-target effects.

Micelles:

Micelles are nanoscale structures formed by the self-assembly of amphiphilic polymers in aqueous environments. Their core-shell architecture allows for the encapsulation of hydrophobic drugs within the core while presenting a hydrophilic exterior, improving solubility and systemic stability.

Temperature- and pH-sensitive micelles have been particularly effective in achieving controlled drug release in response to localized triggers, such as the acidic and hypoxic conditions found in tumors. Recent developments in functionalizing micelle surfaces with targeting ligands have further enhanced their ability to achieve precision delivery.

Responsive Polymers: From Molecular Architecture to Emerging Response

- Responsive polymers belong to the class of smart materials capable of producing detectable responses under the effects of external stimuli. When properly understood and quantified, such a molecular-scale response can be conveniently exploited in various ways to obtain responsiveness at the meso and macroscale.
- The response of active polymers usually consists of nanoscale changes (molecular bond rearrangement/cleavage, molecular motion, morphology change, etc.) that can induce observable changes at greater scales, such as colour and/or shape changes or changes in physical properties, that can be exploited to achieve desired functionalities.
- Since responsiveness comes from their molecular architectures, the arrangements of polymer chains, and the nature of embedded active molecules, stimuli-responsive polymers can be tailored to have stimulus-specific chemical, physical (electrical, optical), and mechanical responses and can be engineered into different forms (thin films, micro/nanoparticles, composites, to name a few).

PH-Responsive Polymers

- pH-responsive polymers can change their configurations and properties with pH variation in the solution, as illustrated in Figure 3A. Usually, these materials contain ionizable functional groups that can donate or accept protons due to the environmental pH change.
- The typical ionizable groups are weak acids and weak bases such as carboxylic acids, phosphoric acid, and amines, which can be characterized by the acid dissociation constant (pKa) or base dissociation constant (pKb).
- For example, poly (acrylic acid) (PAA) has a dissociation constant pKa = 4.25 and above the pH value 4.25, its carboxylic group becomes ionized by denoting protons.It leads to electrostatic repulsions between polymer chains, which can then associate with water molecules for swelling.
- The physical properties of pH-responsive polymers, such as chain conformation, configuration, solubility, and volume, could be tailored by manipulating the charges along the backbone of polymer chains or electrolyte concentration, resulting in electrostatic repulsion forces to increase the hydrodynamic volumes of polymer chains.
- The transition between tightly coiled and expanded conformations can be influenced by any condition that changes the electrostatic repulsion, such as pH value, ionic strength, salt concentration, and type of counterions. The transition from collapsed state to expanded state of these polyelectrolyte chains has been explained by the change of osmotic pressure exerted by mobile counterions neutralizing the network charges (Tagliazucchi et al., 2010).

Dynamic Network Reorganization (Vitrimers, Ionic Polymers, And Others)

- The term “dynamic polymer network” refers to the class of network whose chains are not covalently bonded to the cross-links. Instead, these bonds are able to dissociate and reassociate in time under external stimuli or thermal fluctuation. Some examples of these bonds are covalently adaptable bonds (Bowman and Kloxin, 2012) or physical bonds such as hydrogen bonds and ionic interactions (Luo et al., 2014).
- These materials are of particular interest in several applications such as in renewable materials, self-healing, or materials with high energy dissipation.
- The dynamic nature of their microstructure comes from the weak nature of the bonds, such as the ionic ones, existing in some polymers (the Brownian motion induced by thermal fluctuations enables the bond exchange to occur) or can also take place in covalently bonded polymers (Leibler

et al., 1991; Wojtecki et al., 2011; Jin et al., 2013; Kloxin and Bowman, 2013; Meng and Terentjev, 2018).

- In particular, the socalled vitrimers—a class of polymers derived from thermosetting polymers consisting of molecular covalent networks are capable of changing their topology by thermally activated bond-exchange reactions. At sufficiently high temperatures they flow like viscoelastic liquids, while at low temperatures the bond-exchange reactions rate slow down, leading to a classical thermoset.
- Vitrimers are strong glass formers; their behaviour opens new possibilities in the application of thermosets such as self-healing or simple processability in a wide temperature range.

Polymers with Changing Topology

- Polymers with network rearrangement capabilities have the unique properties to reorganize their chains structure in t, so leading to a continuous relaxation of their microstructure that spontaneously tends to return to the reference stress-free state (Tanaka and Edwards, 1992).
- A class of gels with structural rearrangement capability (slide-ring gels) coming from their movable cross- links properties (Kato et al., 2013) also belong to such a group of responsive polymers.

Additive Manufacturing Methods

Additive manufacturing is the novel approach that allows producing full-scale 3D objects from computer-aided design (CAD) using modelling tools. It has remarkably decreased the processing time required for manufacturing and the related cost for multi-material and complex geometries. Unlike conventional techniques, 3D manufacturing can fabricate complicated geometries through precise implanting of thin layers skipping the assembly procedures, making the geometry in one part and lightweight. Consequently, it has reduced many complications related to the fabricated components and the necessity for inventory. However, conventional techniques are replaced with time due to their incompetency in small-scale and low-volume objects but are still considered for large-scale production. Therefore, the only limitation related to 3D printing is its unsuitability for large-scale production due to its slow printing rate, which is considered a benefit in precision medicine and compatible therapy, due to which AM is widely accepted in various biomedical applications. The advancement of AM techniques has offered new solutions driven by robust demands. Several procedures are established depending upon different types of material like polymers and their nanocomposites. Following, we introduce the working principles for the most relevant AM processes discussed in the subsequent sections.

Applications In Responsive Therapeutic Systems Disease-Specific Application

Smart polymers have demonstrated exceptional potential across a range of disease-specific therapeutic applications. By tailoring their responsiveness to the unique pathophysiological conditions of diseases, these polymers enhance drug efficacy while minimizing adverse effects.

Targeting Strategies for Kidney Diseases

Macromolecule is a very large molecule, which can accumulate in the kidneys. Generally, the molecular weight of the macromolecular vehicle is bigger than that of the prodrugs, so this kind of system can achieve the goal. Pro-drugs have the ability to select the target in the kidney because it can release the active drug by the action of renal enzymes. Some of the polymers have been eliminated rapidly from the systemic circulation but it does not excrete from the kidney, and its accumulated in the renal systems. So, it clearly proposed that the selection of effective and active multi-functionalized polymeric nanoparticles can uptake by the particular kidney cell types. So, the selection of polymers is one of the prime strategies for consideration to achieve the efficient kidney targeting.

Advantage of NPS Usage in Chemotherapy

NPs properties are related to shape, size, and particle material, surface charge, surface (PEGylation) or another coating, and targeting ligand. Use of NPs have

following advantages (A to H) over traditional CTX techniques.

A) Special surface coating on NPs (have large surface area to mass ratio) allowing them to escape from macrophage uptake hence half-life increases.

B) Small size NPs have larger surface area that also increases their efficiency. Small size particles easily flowing in the circulatory system.

C) Smaller particles easily penetrate the cell membrane and can also easily penetrate targeted organelle in the body.

D) For brain cancer treatment, to enhance brain delivery across the BBB nanocarriers have the potential to increase the therapeutic effects of drugs and to reduce their side effects.

F) Bioavailability of drug oligonucleotides is seriously reduced due to their fast degradation by enzymes exonucleases, and endonucleases after intra tumoral injection. These types of drugs must be encapsulated in NPs, giving them much more stability until they strike their target.

G) NPs can be changed in to target specified particles by applying some special ligands on their surface.

H) Overexpression of P-glycoprotein (P-gp) in cell membrane (P-gp), which cause drug resistance. NPs can be coated with some new polymer to solve this problem. With the time-lapse, cancer cells can develop drug resistance up to some extent; hence, high dosage is required to get excellent results.

Characterization of Drug Delivery System

- The delivery of CTX to the target cancer tissue by NPs is a passive and ligand-based targeting that either prolongs the duration of systemic therapy or focuses drug therapy on a particular tissue region.
- However, there are several barriers to reaching their site of action within cancer cells. The CTX must cross through capillary walls, and diffuse through the extracellular space, to reach the proper intracellular targets to overpass the cancer cell membrane.
- Important factors of ligand-mediated active tumor-targeting treatment modality, is particle shape and size, type and density of ligands. The effect of the attached ligand orientation, which blocks the recognition sites, needs density optimization.
- The NPs surface is coated with appropriate bio adhesive materials, and the emulsifier if loaded with CTX can significantly decrease systemic toxicity and increase therapeutic efficacy against drug-resistant and by their fast clearance by lymphatic drainage Different coating surfaces.
- For the treatment of drug-resistant cancers, the anticancer drugs and siRNAs are delivered into cancer cells to stop the gene's resistance, decreasing the drug efflux pumps and activating the apoptosis pathways of cancer cells, especially inaccessible solid tumours.

Types of Innovative Polymers in Drug Delivery

Advanced polymers for drug delivery include biodegradable polymers, for instance PLGA, PLA, polycaprolactone (PCL) and smart polymers, for instance pH and temperature responsive polymers have greatly influenced drug delivery systems making it possible to have controlled, sustained and targeted release of drugs. These advancements provide optimized and POLYMER-PLASTICS TECHNOLOGY AND MATERIALS 3 considerably more stable and precise drug delivery with less side effects; the research done in the recent years has demonstrated their utility in cancer treatment, cardiovascular stents, and tissue engineering rendering them foundational parts of modern pharmaceutical chemistry.

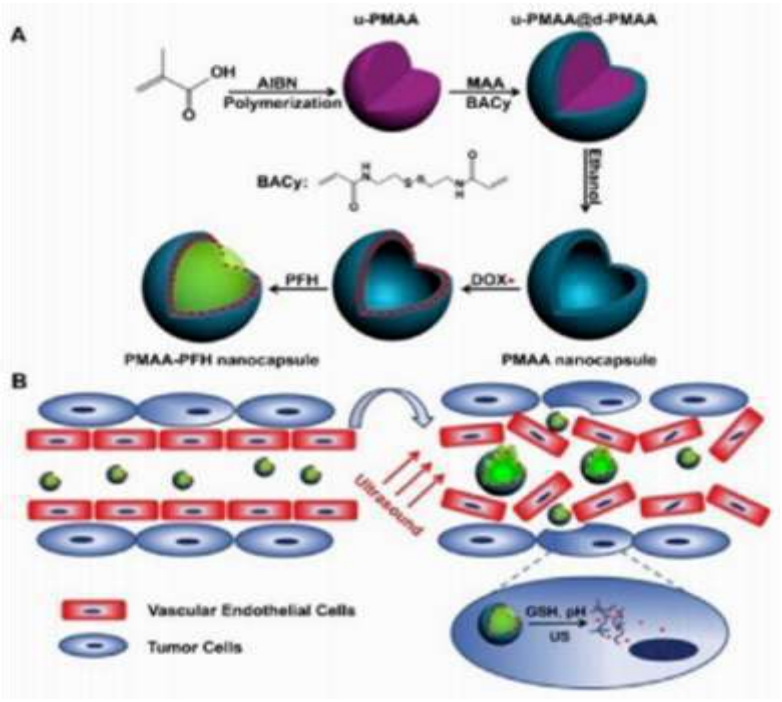

Fig: Drug delivery system utilizing phase-changeable nanocapsule triggered by ultrasound for enhanced anticancer therapy.

Cao et al. devised phase-changeable materials composed of lipid-base and PLGA nanodroplets that release DOX and perfluoro pentane when triggered by low-intensity focused ultrasound (LIFU) to improve anticancer drug delivery. The nanodroplets demonstrated improved inhibition of tumor proliferation over materials not treated with LIFU, leading to enhanced animal survival. Increasing the number of pulses improved the animal survival rate compared to a single burst of LIFU; an increase in vascular permeability of tumors was additionally observed. Salgarella et al. investigated the synthesis and evaluation of five different forms of poly(2-oxazoline) micelles for a possible carrier of a drug delivery system triggered with ultrasound. Micelles were tailored by controlling the ratio of hydrophilic and hydrophobic block copolymers and exhibited a significant release of dexamethasone. Gai et al. developed free-standing biocompatible polylactic acid (PLA) Nano and micro-chamber arrays using two different methods for encapsulation, one-step dip-coating and microcontact printing of air, NaCl, and rhodamine B dye. This work showed that the formation of microchambers can provide long-term encapsulation of small hydrophilic molecules and the release profiles of the microchambers with and without the use of HIFU.

CONCLUSION

Smart polymers are a transformative advancement in controlled drug delivery systems. Here's the info from the conclusion:

- They respond to specific physiological or external stimuli like pH, temperature, enzymes, and light.
- This responsiveness allows for site-specific, sustained, and tunable drug release. Benefits include minimizing side effects and enhancing therapeutic efficacy.
- Challenges remain in large-scale production, long-term biocompatibility, and regulatory approval. Ongoing research is expanding their potential in clinical applications.
- Smart polymers hold promise for personalized and targeted medicine with further optimization.

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