Next Generation of Drug Delivery: Stimuli Responsive Drug Delivery Overview

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ABSTRACT

Conventional drug delivery systems (tablets, capsules, syrups, ointments, etc.) suffer from poor bioavailability and fluctuations in plasma drug level and are unable to achieve sustained release. Without an efficient delivery mechanism, the whole therapeutic process can be rendered useless. Smart drug delivery systems offer various advantages over conventional drug delivery methods. Smart systems can deliver drugs directly to the target site, hence reducing damage to healthy tissues and minimizing side effects. They also enhance drug stability and bioavailability, especially for sensitive drugs. They provide controlled and sustained release of drugs at a specific rate and time, improving therapeutic effectiveness. These features also reduce the frequency of dosing and improve patient compliance, making smart drug delivery more efficient and reliable than conventional approaches. Over the past three decades, research in this field has developed in many different directions. Each new generation of scientists has discovered new physical and chemical methods to control how materials release drugs. Because there are so many approaches, stimuli-responsive drug delivery systems are highly specific because they release drugs only in response to particular internal or external triggers or stimuli such as pH, temperature, and enzymes, which allows precise and site-specific drug action. This targeted and controlled release minimizes drug loss, reduces side effects, and enhances therapeutic effectiveness, making these systems more precise than conventional drug delivery methods.

Keywords: Smart and Stimuli sensitive drug delivery, targeted drug delivery, pH sensitive delivery, Thermosensitive delivery, enzyme sensitive drug delivery.

How to cite this article: Nanaware HT, Patil VN, Shete SS, Patil AS, Sangale ND, Patil AS, Salokhe SV. Next Generation of Drug Delivery: Stimuli Responsive Drug Delivery Overview. Int J Drug Deliv Technol. 2026;16(24s): 315-325. DOI: 10.25258/ijddt.16.24s.36

Source of support: Nil.

Conflict of interest: None

Introduction:

The drug delivery system enables the release of the active pharmaceutical ingredient to achieve a desired therapeutic response. Conventional drug delivery systems (tablets, capsules, syrups, ointments, etc.) suffer from poor bioavailability and fluctuations in plasma drug level and are unable to achieve sustained release. Without an efficient delivery mechanism, the whole therapeutic process can be rendered useless. Moreover, the drug has to be delivered at a specified controlled rate and at the target site as precisely as possible to achieve maximum efficacy and safety. Controlled drug delivery systems are developed to overcome the problems associated with conventional drug delivery. There has been a tremendous evolution in controlled drug delivery systems from the past two decades ranging from macroscale and nanoscale to intelligent targeted delivery. (21)

The initial section of this review provides a fundamental overview of drug delivery systems. It highlights conventional drug delivery approaches along with their associated limitations. The discussion then progresses to controlled drug delivery systems, emphasizing their advantages over traditional methods. Furthermore, recent advances in nano-drug delivery, targeted drug delivery, and smart drug delivery systems based on stimuli-responsive and intelligent biomaterials are comprehensively reviewed, with a focus on key recent findings. Finally, the review outlines the current challenges in stimuli-responsive drug delivery and discusses potential future directions in this field.

Conventional vs. Controlled Drug Delivery Systems :

Conventional DDS (tablets, capsules, syrups, etc.) get eliminated from the body very quickly and the dose is not well maintained within the therapeutic window. After taking a single conventional dose, the drug metabolizes very quickly and the drug level increases, immediately followed by an exponential decrease. The time frame may not be long enough to produce a significant therapeutic effect and result in a sub-therapeutic response. Hence, to maintain the plasma drug concentration above the minimum effective concentration (MEC) and below the toxic concentration, multiple approaches have been sought.

Administering multiple doses at regular intervals of time might seem to be an alternative to a single dose, but the former results in fluctuations in plasma drug levels and often reaches below effective levels and above toxic levels. Taking several doses within a day result in poor patient compliance. Another approach is by administering a single dose greater than the required dose, which leads to adverse effects other than the effects intended by the drug . Hence, controlled release DDS are required to maintain the plasma drug levels at a constant rate within the therapeutic window and offer the desired therapeutic effect for a longer duration of time. (28)

Drug delivery (DD) refers to the methods, formulations, technologies, and pro cesses involved in transporting a pharmaceutical substance in the body to achieve the desired therapeutic effect.

It encompasses the approaches of administering medicinal compounds in humans and animals to attain therapeutic effectiveness. Recent developments in drug delivery systems (DDSs) are primarily been focused on smart DD, which focuses on drug administration at the appropriate time, dosage, and location with maximum safety and efficacy.

The advancement of novel DDSs (NDDSs) has attracted pronounced attention in recent years. These systems enhance the therapeutic effectiveness of new and existing drugs with targeted, managed, and sustained delivery while meeting real and appropriate drug demand.

DD is a growing field in pharmaceutical science. There are five generations of DDSs, and targeted delivery belongs to the fourth generation.

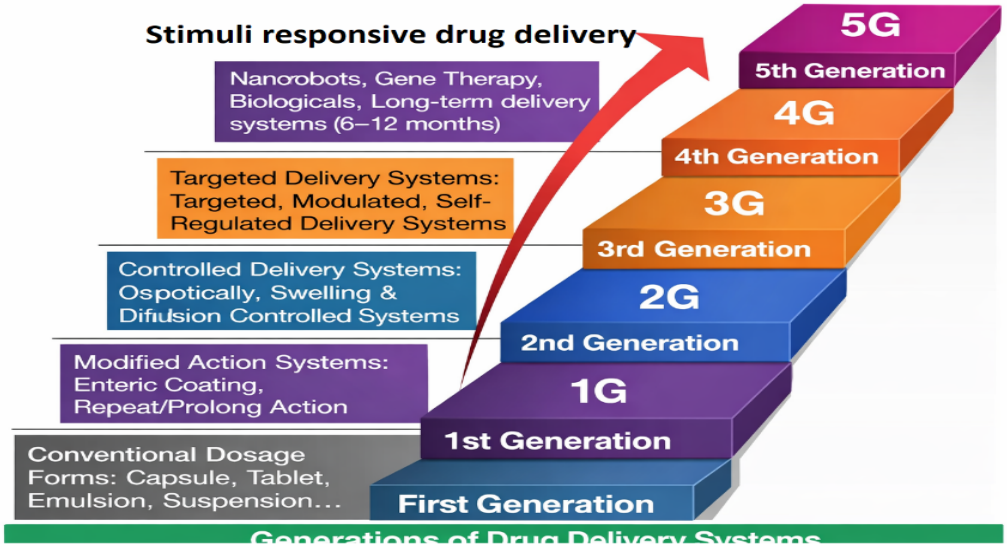

Fig.1-Generations of drug delivery

Over the last few decades, developing sustained or controlled DDSs has been a focus, with the objective of controlling and/or sustaining drug release, reducing dose frequency, or increasing drug efficacy compared to conventional delivery. Bilayer tablets are one example of an NDDS, used with modification of conventional drug-preparation and -delivery approaches.(17)

TDDSs are where a drug is delivered to a specific location, rather than the whole body or organ, and combine diverse fields of science, such as polymer science, pharmacology, bio-conjugate chemistry, and molecular biology. TDD is aimed at managing and controlling the pharmacokinetics, pharmacodynamics, aspecific toxicity, immunogenicity, and biorecognition of therapeutic agents.

The end goal is improving treatment effectiveness while reducing side effects. TDDSs differ from conventional or traditional DDSs in that they acquire site-specific release of drugs from a dosage form, while the former depends on drug absorption through biological membranes.(17)

Magic bullet theory :

The Concept of the Magic Bullet The concept of targeting of drugs to their site of action dates back to the postulation of the "magic bullet" concept.

A century ago, Paul Ehrlich envisioned the concept of selectively targeting a pathogen without harming the host organism using "magic bullets." Analysts in cancer treat ment were particularly inspired by the idea.(31) Ehrlich approached his magic bullet concept in two consecutive steps: screening for toxic drugs, followed by modifying toxic drugs to be more specific and less toxic.(32) He strongly pictured that achieving a cure would be very stress-free with substances that had exclusive affinity toward the causative bacteria alone, with no affinity for the host. This would finally result in the least harmful effect on the human body by exerting an exclusive lethal action on the parasite within the organism, hence the term "magic bullet"(33). Ehrlich anticipated site-specific therapies to acquiring knowledge on how to cast magic bullets, as the magic bullets of a gunman hit the enemies exclusively. This fascinating idea pressed scientists to investigate further for more than a century, and led to the discovery of different nanometer- scale devices, called "nanomedicines" nowadays.(17)

According to the magic bullet philosophy of Ehrlich, drugs should go straight to their anticipated targets in the body and only interact with the target molecule. However, drugs pass complex pathways and contacts during their transport to reach their targets and possibly interact with multiple targets, resulting in side effects. Unfortunately, there has never been a drug or a DDS that has directly reached the bodily target without these pathway interactions. This interference with several targets makes the drug a "magic shotgun," rather than a magic bullet. To meet the magic bullet target, we still have a long way to go.(17)

The Need for Targeted Drug Delivery :

The need for TDD over conventional DSs is fourfold: unsatisfied peformance of drugs in terms of pharmacodynamic, pharmacokinetic, pharmaceutical, and pharmacotherapeutic features with conventional delivery. Targeting of drugs to a particular area through optimized DD methods is not only important to enhance therapeutic effectiveness but also to reduce the toxicity associated with a small therapeutic index and high doses. Targeting is needed to achieve solutions to these constraints and innate disadvantages of conventional DDSs. Parenteral delivery is highly invasive, oral administration cannot be used for protein- or peptide- derived drugs, and topical creams and ointments are limited to local effects. Furthermore, the effectiveness of drug–target interactions is compromised unless the drug is delivered to its site of action at a dosage and rate that produces minimal side effects while maximizing therapeutic effects. In addition, simpler drug-administration procedures, decreased drug quantity, which reduces therapeutic costs, and the potential to sharply increase drug concentration in target compartments without adverse effects on non-target compartments are promising benefits of TDD. Generally, drug targeting results in increased efficacy, modulated pharmacokinetics, controlled bio-distribution, increased specificity of localization, decreased toxicity, reduced dose, and improved patient compliance,(17)

The ideal nanocarrier-based DDS not only protects the cargo but enables control over both the timing and location of release. These systems should be able to be directed to a specific tissue or cell type and release the payload only when exposed to cancer-specific physiology. In addition, along with conventional small molecule drugs, DDSs that can effectively deliver macromolecule biologics are needed. These new requirements have stimulated significant research on nanoplatforms, targeting techniques, and the use of both exogenous and

endogenous stimuli to control the release of therapeutics.(6)

This drug delivery system represents a major therapeutic milestone that allows drugs to release during specific biological events and environmental triggers . The "smart" delivery platforms exhibit predictable physicochemical variations in their properties during stimulus exposure to pH changes, temperature fluctuations, enzyme effects, or light radiation and magnetic fields, therefore providing accurate drug release regulation. Responsive delivery developed its basic principles during the 1970's through temperature-sensitive liposomes, although major breakthroughs appeared in the late 1990s with pH-responsive polymers that sought tumors' acidic microenvironments. This drug delivery system surpass traditional drug delivery methods by releasing their content based on physiological conditions only and minimize unintended side effects, which helps solve longstanding pharmaceutical science difficulties of inadequate pharmacokinetics and drug resistance and poor bioavailability (11)

Drug Delivery System Stimuli-based drug delivery systems have constituted a new platform under Reference of diseases at the molecular level. For this purpose, nanotechnology-based drug

1. Temperature Liposomes, Micellar nanoparticles, Hydrogels, Polymeric nano particles, Dendrimers delivery systems offer tremendous and promising advantages in the prevention, diagnosis Docetaxel Micelles, Hydrogel, Liquid Suppository, Liposomes and therapy of many diseases. The stimuli-based drug delivery system includes the phenomenon that influences an activity at a particular site or target tissue to bring about useful

2. Magnetic Field Doxorubicin Magneto-liposomes, FeCo/Graphite shell Nanocrystals, Alginate embedded Magnetic Nanoheaters, Magnetic iron oxide nanoparticles activities for the drug release via various mechanisms and is known as "stimuli responsive materials" or "environmentally-responsive materials".

Stimuli-responsive materials are those that undergo a physical or chemical change in response to an external stimulus. These materials exhibit the environment responsive behavior phenomenon and respond to the external stimuli due to biomimetic nature. The stimulus-based drug delivery system is of great importance in the field of nanomedicines and nanotechnology due to controlled and targeted release at the site of action. Stimuli-responsive systems respond to specific triggers to release their cargo at the desired site, hence they can enhance drug efficacy and overcome the adverse effects related to oral or parenteral drug delivery. Drug delivery systems with the ability to respond to temperature, pH change, enzymes, light, magnetic field, ultrasound or electrical stimuli have been heavily investigated over the past few decade. Many intelligent designs of these delivery systems are based on polymers, hydrogels and nanoparticles . The stimuli-responsive drug delivery systems may be classified as physical and chemical stimuli-responsive drug delivery systems which are summarized(1)

Historical background and its development :

The development of drug delivery systems with stimulus-responsive capabilities began in the 1950s through the creation of implantable silicone rubber capsules used for sustained drug release during 1964 . Researchers achieved a fundamental change in the 1970's through their discovery of controlled macromolecule release from polymeric materials . Acid-sensitive linkages entered the pharmaceutical field through polymer-drug conjugate research during the 1980's. Scientists added temperature-sensitive models to their research by creating poly (N-isopropyl acrylamide) (PNIPAm) hydrogels that had reversible phase characteristics during the 1990s . In the early parts of 2000, scientists achieved advancements in enzyme responsive and redox-responsive systems . The field of light responsive materials became significant after photodegradable polymer research began . During the mid-2000's, scientists developed pH and temperature dual-responsive hydrogels, which represented multi-stimuli responsive systems. Superparamagnetic nanoparticles spurred significant advancement in magnetically triggered delivery systems when they were used for on-demand drug release during 2008. The 2010s brought rapid growth to commercial translation as ThermoDox® (Temperature-sensitive liposomal Doxorubicin) started its clinical trials.

Aim :

Stimuli-responsive hydrogels, also known as smart hydrogels, are materials that can respond to different external stimuli. These hydrogels can undergo reversible or irreversible changes in their physical or chemical properties when exposed to specific triggers. Because of this behavior, they allow controlled and targeted drug release.

This property helps in achieving precise drug administration, improving treatment effectiveness,

and reducing side effects. In this review, we discuss the basic principles involved in designing responsive hydrogels. Special focus is given to important stimuli such as pH, temperature, light irradiation, redox conditions, and specific biomolecules.

Recent advances in materials chemistry and drug delivery have made it possible to develop smart systems that can release drugs in a controlled way at the right place, at the right time, and in the right amount.

Implementation of such devices requires the use of biocompatible materials that are susceptible to a specific physical incitement or that, in response to a specific stimulus, undergo a protonation, a hydrolytic cleavage or a (supra) molecular conformational change. In this Review, we discuss recent advances in the design of nanoscale stimuli-responsive systems that are able to control drug biodistribution in response to specific stimuli, either exogenous (variations in temperature, magnetic field, ultrasound intensity, light or electric pulses) or endogenous (changes in pH, enzyme concentration or redox gradients).(7)

Stimuli :

Tumor physiology is significantly different from that of normal tissues. Rapid and uncontrolled cell growth, poor blood supply, and altered cellular metabolism lead to the formation of an acidic and low-oxygen (hypoxic) microenvironment. The pH of the tumor extracellular matrix (ECM) is typically around 6.8, which is lower than that of normal tissues. This acidity increases further inside the cell, with pH values of about 6.0–6.5 in endosomes, 5.0–5.5 in late endosomes, and 4.5–5.0 in lysosomes.The reduction–oxidation (redox) balance is also altered in cancer cells. Due to the abnormal cellular activity and rapid propagation, the concentration of reactive oxygen species (ROS), primarily generated through mitochondrial metabolism, is typically elevated in cancer cells. Reductive agents such as glutathione (GSH) are usually overexpressed in cancer cells to relieve the high oxidative pressure that results from elevated mitochondrial metabolism. As a result, GSH levels are elevated in inflammations, neurological diseases, and tumors, and can be several orders of magnitude higher in cancer cells than the ECM . Similarly, several enzymes, including hydro lases, proteases, and oxidoreductases, are overexpressed in tumors. Finally, many inflammatory disease processes lead to hyperthermia, and temperature elevation is observed in tumors . All of these unique properties of tumors and cancer cells can be considered endogenous stimuli and have been exploited to stimulate the release of therapeutic agents from DDSs. Exogenous stimuli such as photoirradiation, ultrasound, oscillating magnetic fields, and locally induced hyperthermia have also been exploited to activate the release of payloads from DDSs. In this section, recent advances in the application of each of these stimuli to enhance efficacy in DDSs are reviewed.(6)

Exogenous and endogenous :

Endogenous stimuli response -

Ph sensitive response:

pH-sensitive systems. pH variations have been exploited to control the delivery of drugs in specific organs (such as the gastrointesti nal tract or the vagina) or intracellular compartments (such as endosomes or lysosomes), as well as to trigger the release of the drug when subtle environmental changes are associated with pathological situations, such as cancer or inflammation. Two main strategies exist: the use of polymers (polyacids or polybases) with ionizable groups that undergo conformational and/or solubility changes in response to environmental pH variation; and the design of polymeric systems with acid-sensitive bonds whose cleavage ena bles the release of molecules anchored at the polymer backbone, the modification of the charge of the polymer or the exposure of targeting ligands.(7)

The pH value in different tissues and cellular compartments varies inside the body. These variations of pH in different diseased conditions such as inflammation, infection, ischemia and cancer can be exploited for pH-responsive drug delivery systems (1).

In tumor tissue, within the interstitial matrix, the metabolic profile is different due to poor perfusion of oxygen, resulting in a high level of lactic acid and pH drop from 7.4 to 6 (slightly acidic). The changes in pH can be exploited for drug targeting in two ways:

(1) by targeting the extracellular tissue, where pH ranges between 6.5 and 7.2 or

(2) by targeting the lysosomes with pH range of 4.5–5.0. In lysosome targeting, hydrolytic enzymes such as cathepsin B may also be utilized to release the drug.

The pH-responsive systems must incorporate pH-tunable moieties. These moieties can utilize a variety of functional groups such as hydrazone, ortho ester, amine, acetal and vinyl ether, which function as pH

sensors because their insolubility in water is changed by protonation and deprotonation.

Different delivery systems for achieving pH-responsive drug release have been reported such as liposomes, polymers, micelles and den drimers. Hira et al., 2020, has recently developed doxorubicin-loaded pH-responsive nanomicelles for treatment of murine lymphoma. The drug was effectively released from the nanomicelles at low pH conditions, i.e., tumor microenvironment [198]. In vivo results showed pH-responsive nanomicelles loaded with doxorubicin have a prolonged blood resident time owing to minimal drug leakages.(14)

Enzyme responsive:

Enzyme-sensitive systems. The altered expression profile of specific enzymes (such as proteases, phospoholipases or glycosidases) observed in pathological conditions, such as cancer or inflammation, can be exploited to achieve enzyme-mediated drug release with accumulation of drugs at the desired biological target. Most of the systems devoted to enzyme-mediated drug delivery exploited the presence of enzymes in the extracellular environment. Recent 998 studies reported the use of short peptide sequences, cleavable by matrix metalloproteinases, as linkers between surface PEG chains and either TAT-functionalized liposomes or CPP decorated, dextran-coated iron oxide nanoparticles. After cleavage of the PEG shell in the tumour microenvironment, surface bioactive ligands became exposed, and this enhanced intracellular penetration compared with nanocarriers without cleavable link ers. Using this approach, systemic administration of siRNA-loaded nanoparticles resulted in an almost 70% gene-silencing activity in tumour-bearing mice. Similarly, protease-sensitive polymer coatings or lipopeptides were designed to achieve triggered release from porous silica nanoparticles or liposomes. It is also possible to deliver drugs to intracellular compartments by usng enzymes. For instance, mesoporous silica scaf folds grafted with polysaccharide derivatives enabled the specific delivery of doxorubicin after lysosomal enzyme-mediated cleavage of the glycoside bonds and reduction of the polysaccharide chain lengths. Similarly, lysosomal enzyme cathepsine B, overexpressed in several malignant tumours, enabled cargo release by means of fast enzymatic degradation of polymersomes. Transgene expres sion with high cell specificity has been achieved through polymer based delivery systems bearing a cationic peptide as substrate of intracellular proteases (or kinases) that are exclusively expressed in cells infected with human immunodeficiency virus or inflamed cells. The enzyme-mediated disintegration of the polymer–DNA electrostatic interaction promoted gene release and transcription. Enzyme responsiveness can be extended to bacterial-infection treatments. For example, on-demand release of antibiotics, achieved with vancomycin-releasing lipase-sensitive nanogels, significantly inhibited the growth of Staphylococcus aureus and was also effective in killing intracellular bacteria. These representative examples highlight the potential of enzyme triggered drug delivery. However, work is still needed to obtain precise information of the target enzyme levels at the desired site to fine-control cell uptake and to demonstrate that in vivo drug release is correlated to enzymatic activity.(14)

Redox:

Redox-triggered drug delivery. The difference in redox potential between normal and tumour tissues, and between the intracellular and extracellular environment, can also be exploited for drug delivery in cancer. For example, the concentration of glutathione in cancer cells is 100 to 1,000 fold higher than in the blood, and in a tumour mass the glutathione concentration is also markedly (100 fold) higher than the extracellular level of glutathione in normal tissue. Reduction sensitive liposomes that have two forms of disulphide conjugated multifunctional lipids on their surface have been tested in a breast cancer cell line. The cleavage of the disulphide bond resulted in the removal of the hydrophilic head group of the conjugate, membrane reorganization and the release of encapsulated calcein. The disulphide bond has been widely used as the cleavable and/or reversible linker in NDDSs to confer redox sensitivity. (8)

Thermoresponsive systems:

Thermoresponsive drug delivery is among the most investigated stimuli-responsive strategies, and has been widely explored in oncology. Thermoresponsiveness is usually governed by a nonlinear sharp change in the properties of at least one component of the nanocarrier material with temperature. Such a sharp response triggers the release of the drug following a variation in the surrounding temperature. Ideally, thermosensitive nanocarriers should retain their load at body temperature (~37 °C), and rapidly deliver the drug within a locally heated tumour (~40–42 °C) to

counteract rapid blood-passage time and washout from the tumour.(7)

Thermoresponsive Drug Delivery Systems Among different stimuli-responsive systems, temperature-responsive systems are the most investigated especially in the field of oncology . In such a system, drug release is governed by variation in temperature of the tumor environment. Within normal body temperature (~37◦C), the thermoresponsive carriers retain the drug load. However, the drug is released at the local temperature of the tumor environment (~40–42◦C). A thermoresponsive drug delivery system is considered as an adjunct to hyperthermia therapy. In hyperthermia therapy, the body tissue is exposed to high temperatures via microwave, ultrasound or radiofrequency, which can kill or make the cancer cells more susceptible to specialized effects of radiation or chemotherapeutics agents. Along with the cancer cells, the hyperthermia therapies (microwave, ultrasound or radiofrequency) have toxic effects on the normal cells as well. Likewise, the chemotherapy also has toxic effects on normal cells as well as cancer cells. So, collectively, the combinations of chemotherapy and hyperthermia as a combinatorial strategy have toxic effects on the normal cells as well as cancer cells. Therefore, thermoresponsive drug delivery systems that utilize the tumor micro environment-based temperature,i.e., mild hyperthermia (~40◦C) which is not toxic for normal cell sand causes the tumor- specific drug release, are proposed. Thermoresponsive systems are generally nanoparticles, liposomes or polymeric micelles that release the drug in appreciable rates only at targets having higher temperatures than Cancers to normal cells of the body (e.g., cancer tissue). Thus, thermoresponsive liposomes, for example, function by minimizing the metabolism, uptake and clearance of drugs and concentrate the drug to the vasculature of the heated tumor. The released drug diffuses into the tumor, enhancing the drug concentration and the penetration at the tumor site. This approach does not depend upon passive targeting of the tumor. For abrupt release of the entrapped drug with in the tumor, the thermoresponsive liposomes are administered during the mild hyperthermia treatment . In thermoresponsive liposomes, lipids with suitable gel to liquid phase transition temperatures such as dipalmitoyl phosphatidyl choline or lysolipids are usually used . Examples of such types of liposomes include doxorubicin loaded thermoresponsive lysolipids-based liposomes (ThermoDox®, Doxil®, Myocet®) that have shown improved efficacy for cancer targeted delivery . Thermoresponsive polymers exhibit lower critical solution temperature (LCST) and in response to LCST, the drastic change in aqueous solubility of polymers occurs. Below LCST, these polymers dissolve in water, whereas, above LCST, they are insoluble in water , get precipitated and disrupted the drug delivery system to release the drug . Polymers such as poly (N-iso-propylacrylamide) (PNIPAAm) and poly (N-alkylacrylamide) compounds have been investigated as temperature-responsive polymeric micelles . Block polymers can be synthesized by different polymerization techniques that consist of at least one thermoresponsive block with the ability to self-assemble in water to form thermoresponsive micelles. A copolymer can be synthesized by attaching a permanently hydrophilic block with a thermoresponsive one, which is hydrophilic below the LCST and micelles are formed once the transition in the phase of the thermoresponsive block occurs .(14)

Mechanism of SRDDS :

Drug delivery systems based on stimulus responsiveness achieve their clinical goals because of the mechanisms by which external cues activate precise therapeutic drug delivery, as Temperature-sensitive PNIPAm derivatives use conformational changes to transform into hydrophobic globules that collapse when the lower critical solution temperature is exceeded, thus enabling precise drug release . Exchange forces in drug carriers use chemical reactions activated by stimulus to break drug-carrier bonds through disulfide bond containing nanoparticle examples that quickly decompose after exposure to tumor levels of GSH and release the drugs . Such assembly-disassembly strategies use the dynamic characteristics of supramolecular interactions to generate either self-assembled products or their dissociation through stimuli changes; innovative pH-responsive micelles utilize amphiphilic block copolymer destabilization at acidic tumor microenvironments triggered by protonation processes . The clinical implementation of pH responsive systems encounters multiple obstacles because they tend to leak drugs prematurely due to inconsistent patient pH variations and variable tumor pH gradients and because normal tissue pH and pathological tissue pH are difficult to distinguish effectively. The pH responsiveness of controlled releases becomes harder to maintain because biological fluids possess

a buffering capacity, which reduces their sensitivity to pH changes.(11)

The physical state transformations of thermosensitive liposomes through mild hyperthermia conditions result in drastic membrane permeability increases for accelerated drug diffusion . The swelling/deswelling properties of hydrogel based systems depend on stimulus-triggered water intake or output that controls mesh size and drug diffusion speed because such systems trigger insulin release through blood glucose level changes . Surface properties alter through subtle yet effective mechanisms that control carrier surface characteristics among nanoparticles with zwitter ionic coatings, which transform into positive charges in tumor surroundings while retaining circulation stability.(11)

Enzyme-responsive nanofibers serve as examples of degradation triggered release mechanisms that break down due to stimulus generated breakdown while showing rapid degradation when exposed to matrix metallo proteinases over expressed in tumor tissues .

Devices utilizing pore-opening mechanisms contain trigger-sensitive channels or gates within impervious materials for making controlled drug delivery possible with precision; mesoporous silica nanoparticles under specific light wavelengths activate their molecular gates to release drugs (11).

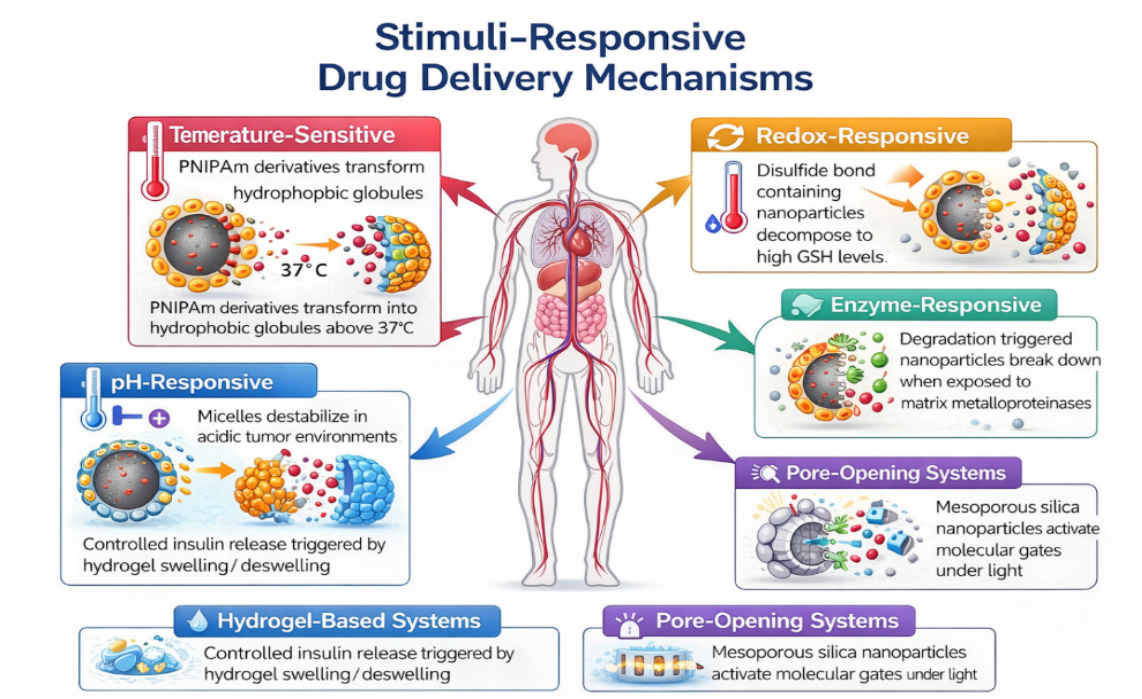

Fig.2- Stimuli responsive drug delivery mechanism

Future perspective and advances:

Stimuli-responsive drug delivery systems (SRDDS) are designed to release therapeutic agents selectively in response to specific internal or external triggers, enabling spatially and temporally controlled drug delivery. The fundamental principle underlying these systems is the conversion of a physiological or externally applied stimulus into a physicochemical change within the carrier matrix, which subsequently triggers drug release at the target site. These mechanisms enhance therapeutic efficacy while minimizing systemic toxicity.

Temperature-responsive systems operate through reversible conformational changes in polymer chains. Polymers such as poly(N-isopropylacrylamide) (PNIPAm) exhibit a lower critical solution temperature (LCST), above which they undergo a coil-to-globule transition. This structural collapse results in reduced hydration, increased hydrophobicity, and expulsion of the encapsulated drug. Similarly, thermosensitive liposomes undergo lipid bilayer phase transitions under mild hyperthermia, leading to increased membrane permeability and accelerated drug diffusion.

Redox-responsive systems exploit differences in intracellular and extracellular redox environments. Tumor cells contain elevated concentrations of glutathione (GSH), which cleaves disulfide bonds incorporated into polymer backbones or

crosslinkers. This bond cleavage destabilizes nanoparticles or micelles, resulting in rapid intracellular drug release. Such systems ensure minimal drug leakage during circulation and efficient release after cellular internalization.

pH-responsive drug delivery systems utilize the acidic microenvironment of tumors, inflamed tissues, or intracellular compartments such as endosomes. Protonation or deprotonation of ionizable functional groups causes swelling, micellar disassembly, or carrier destabilization, leading to drug release. However, clinical translation of pH-responsive systems is challenged by buffering effects of biological fluids and small pH differences between healthy and diseased tissues.

Hydrogel-based stimuli-responsive systems rely on swelling and deswelling mechanisms governed by water uptake or expulsion in response to stimuli such as glucose, pH, or temperature. Changes in network mesh size regulate drug diffusion rates. Glucose-responsive hydrogels, for example, release insulin in response to elevated blood glucose levels, mimicking physiological feedback mechanisms.

Surface-responsive nanocarriers modulate drug delivery through changes in surface charge or hydrophilicity. Nanoparticles with zwitterionic or charge-switchable coatings remain stable during circulation but convert to positively charged surfaces in tumor environments, enhancing cellular uptake and localized drug release. Enzyme-responsive systems utilize disease-associated enzymes such as matrix metalloproteinases to trigger carrier degradation, allowing site-specific drug release.

Externally triggered systems provide precise, on-demand drug delivery. Light-responsive carriers use photo-cleavable bonds or photothermal effects to open molecular gates or destabilize carriers. Mesoporous silica nanoparticles with light-activated gatekeepers exemplify pore-opening mechanisms that enable controlled drug release only upon external stimulation.

Overall, stimuli-responsive drug delivery systems integrate molecular design with biological cues to achieve controlled, targeted, and efficient drug release. Despite challenges related to stability, reproducibility, and clinical translation, continued advancements in smart polymers and nanotechnology are expected to expand their therapeutic potential.(18)

In recent years, micro sponges, solid-lipid NPs, and nanostructured lipid carriers have been used and further investigated as carrier systems/vesicles for DDSs. Micro sponges are synthetic, biologically porous, inert polymers that can carry up to their own weight in drugs. They have the ability to protect the drug from the external environment and to provide controlled release. Nanotechnology has been implemented in several fields of nano medicine, such as drug/gene delivery, imaging, and diagnostics. Ab–drug conjugates or immune conjugates are being investigated as alternative recombinant Abs by covalently binding through a linker to a drug to target potent drugs to specific sites using the specificity of mAbs, thus avoiding non targeted-organ toxicity. There are also other advances, such as micro- and nanoemulsions, nanocapsules, smart capsules, cyclodextrins, microspheres, nanotubes, nano shells, quantum dots, hydrogels, metal and magnetic NPs, and natural and synthetic polymeric NPs that are being investigated for local and systemic targeting.Though there have been promising recent advances, there are also associated challenges in their application.(17)

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