Int. J. Sci. R. Tech., 2025 2(12)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Stimuli-Responsive Drug Delivery; Mechanism and Multi-Route Application: A Comprehensive Review

Ajinkya Kure*, Aishwarya Jadhav

K. V. N. Naik S. P. Sanstha's, Institute of Pharmaceutical Education & Research, Nashik, 422 002, Maharashtra, India

ABSTRACT

Stimuli-responsive drug delivery systems (SRDDS), which provide regulated, accurate, and adaptive drug release in response to particular internal or external stimuli, have become a revolutionary platform in contemporary therapies. Passive diffusion, low site specificity, systemic toxicity, and uneven patient adherence are common problems with traditional delivery methods. By taking use of diseased microenvironmental characteristics including acidic pH, increased enzyme activity, hypoxia, and redox imbalances in addition to externally applied stimuli like light, magnetic fields, ultrasound, and electrical impulses, SRDDS overcomes these constraints. The development of complex carriers' hydrogels, nanoparticles, micelles, dendrimers, and metal-organic frameworks that experience physicochemical changes like swelling, contraction, phase transitions, or cleavage of labile chemical bonds to achieve triggered release has been made possible by developments in polymer science. These processes lower off-target exposure and greatly improve treatment accuracy. Clinical translation is still hampered by issues with biocompatibility, early drug leakage, immune recognition, and scalability despite significant advancements. Furthermore, there is still a lack of consolidated knowledge regarding the optimisation of SRDDS for various administration routes, each of which presents distinct physiological opportunities and barriers. This study summarises current developments in SRDDS, categorises stimuli and their release mechanisms, assesses polymeric materials utilised in the creation of smart carriers, and addresses the systems' suitability for oral, ocular, transdermal, nasal, pulmonary, and parenteral routes. Emerging directions, existing limitations, and future prospects are highlighted to support the advancement of next-generation intelligent drug delivery technologies.

Keywords: Stimuli-responsive polymers; Smart drug delivery systems; Controlled release; pH-responsive carriers; Redox-sensitive nanoparticles; Thermo-responsive polymers; Targeted drug delivery

INTRODUCTION

Recently, the domain of drug delivery has undergone significant transformations, evolving from traditional dosage forms to cutting-edge "smart" systems that enable precise control over timing and location for therapeutic release. Standard formulations such as tablets, injections, or transdermal patches primarily rely on passive release methods and often face considerable challenges, including non-specific distribution throughout the body, insufficient concentrations at the desired target site, increased systemic side effects, and reduced compliance from patients [1]. To tackle these challenges, stimuli-responsive drug delivery systems (SRDDS) have been developed as an encouraging type of nanocarrier that modulates drug release in reaction to internal (endogenous) or external (exogenous) stimuli. Diseased tissues often exhibit unique changes in their microenvironment, such as acidic pH levels in tumours or inflamed areas, elevated enzyme activity, hypoxia, redox imbalances, and varying temperatures. By capitalising on these signals, SRDDS can maintain stability while circulating in the body and deliver their payload specifically at the target site, enhancing therapeutic precision and minimising off-target side effects [2]. Moreover, external factors such as light, magnetic fields, ultrasound, and electric fields offer an extra layer of precision, enabling on-demand control over drug release that can be activated by either a clinician or a patient with high spatial and temporal accuracy. Advanced materials such as polymers, hydrogels, liposomes, dendrimers, and metal-organic frameworks (MOFs) have been

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

researched extensively for the creation of these sophisticated systems [3]. Recent studies have revealed multifunctional stimuli-responsive drug delivery systems (SRDDS) that can simultaneously react to multiple stimuli such as pH alongside redox or temperature combined with enzyme levels, providing synergistic control for managing complex illnesses like cancer and diabetes. For example, researchers are creating peptide-based and ionic-liquid polymer hybrid hydrogels designed for the co-delivery of anticancer medications and imaging agents, aiming to enhance both therapeutic outcomes and diagnostic results [4]. Although there have been notable advancements, several challenges, including the biocompatibility of carriers, stability, recognition by the immune system, premature drug release, and the potential for large-scale manufacturing, still impede their clinical usage. Furthermore, while numerous reviews have analysed the mechanisms of stimuli responsiveness, fewer have focused on how stimuli-responsive drug delivery systems (SRDDS) can be successfully adapted for administration via various routes (oral, ocular, transdermal, nasal, pulmonary, and parenteral), with each path presenting distinct physiological hurdles and possibilities [5]. Thus, this review aims to (i) classify different stimuli and their associated drug release mechanisms, (ii) explore the development and effectiveness of SRDDS for various administration pathways, and (iii) highlight emerging trends, challenges, and future prospects in the field of stimuli-responsive and multi-route drug delivery systems.

1. Classification of Stimuli:

Stimuli-responsive drug delivery systems have either endogenous (internal) triggers, those inherent to tissue or cellular environments, or exogenous (external) triggers applied from outside the body. These stimuli dictate carrier behaviour (swelling, degradation, link-cleavage, conformational change) and thereby the controlled release of therapeutic agents.

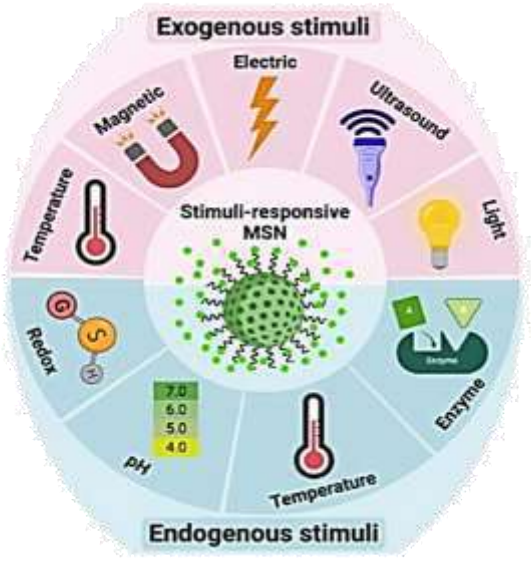

Figure 1. Classification of Stimuli

1.1 Endogenous (Internal) Stimuli

1.1.1 pH-Responsive Systems

The biomaterials that respond to pH levels detect variations in pH and experience physical and chemical alterations in their polymer chains, initiating the release of the drug. These materials are predominantly utilised for drug release triggered by pH changes compared to other types of stimuli. The conventional pH-responsive carriers exhibit their effectiveness based on the pH levels found in various organs, such as the stomach and intestines [6]. pH-sensitive polymers can be classified as either polyacids, which detect and release at alkaline pH, or polybases, which respond to acidic pH and release the drug. Eudragit S100 is a pectin nanoparticle coated with citrus that specifically aims to deliver the anticancer drug, 5-Fluorouracil, to the colon [7]. Carriers designed for this purpose can detect changes in pH levels at particular disease locations, such as ischaemic tumour areas and inflamed tissues.

Additionally, they can distinguish pH variations in different organelles, such as lysosomes and endosomes. Healthy tissue typically maintains an extracellular pH of 7.4, while in solid tumours, the pH drops to 7.0 due to an increased rate of glycolysis. This lower pH present in tumours serves as a trigger for controlled drug delivery systems [8,9]. The pH stimulus can be paired with other triggers, including redox conditions and temperature, to ensure targeted release at specific sites, such as poly(2-(diisopropylamino) ethyl methacrylate) (PDPAEMA) [8].

1.1.2 Enzyme-Responsive Systems

Enzymes serve as catalysts in drug delivery systems. They possess distinct characteristics such as specificity to their substrates and a high degree of selectivity under mild conditions. Given their close association with biological and metabolic functions, enzymes can facilitate the targeted release of drugs at sites of inflammation. A significant challenge in utilising enzyme-responsive drug delivery systems is the need for precise control over the initial release phase. These systems are classified based on their interactions with effector molecules [10]. Enzymes like glycosidases, lipase, phospholipases, and proteases are involved in nearly all biological and metabolic processes, making them useful for facilitating drug release through enzyme-mediated mechanisms in cancerous or inflamed tissues [11].

1.1.3 Redox-Responsive Systems

The alteration in redox potential initiates the release of drugs from redox-sensitive biomaterials. These materials are commonly utilised in disease treatment through intracellular drug delivery mechanisms. The redox potential differs across various tissues in microenvironments, which is beneficial for the development of redox-sensitive drug delivery systems [12]. The reduction of glutathione (GSH) is a widely recognised redox system found in cancer cells. While GSH concentrations in blood and normal extracellular matrices are noted to be between 2 and 20 μM, levels within cancer cells vary from 2 to 10 mM, representing an increase of 100- to 500-fold compared to normal levels. The substantial disparity in GSH levels between cancerous and normal cells has rendered redox-responsive delivery systems an appealing approach for designing drug delivery systems aimed at targeting specific intracellular sites within tumours [13].

1.1.4 Temperature-Responsive Systems

Temperature serves as the trigger for the release of drugs. Thermo-responsive polymers feature a lower critical solution temperature (LCST). When the temperature is below LCST, these polymers are soluble, hydrated, and tend to swell, which is the state during drug loading. Conversely, when the temperature exceeds LCST, these polymers shrink and dehydrate, leading to drug release. An example of a thermosensitive polymer that demonstrates these properties is poly (N-isopropyl acrylamide) [14].

1.2 Exogenous (External) Stimuli

1.2.1 Light-Responsive Systems

Light activation enables precise regulation of drug release both spatially and temporally. Near-infrared (NIR) light is more effective at penetrating tissues than UV or visible light and is frequently used in NIR-responsive nanocarriers. The mechanisms involved include the breaking of photochemical bonds, photo-isomerisation (as seen with azobenzene and spiropyran), and photothermal effects. A recent review centred on metal–organic framework (MOF)-based carriers emphasises the significance of light-triggered release, alongside sensitivity to internal stimuli. Critical design considerations encompass wavelength penetration, phototoxicity, thermal management, and safe usage in living organisms [15].

1.2.2 Systems Responsive to Magnetic Fields

In drug delivery systems that respond to magnetic fields, the release of medication can be controlled remotely by using an external magnetic field. These magnetic systems consist of a drug carrier, such as nanoparticles, and materials like magnetite (Fe_3O_4), maghemite (α-Fe_2O_3), iron, nickel, cobalt, and samarium-cobalt, which react to an applied magnetic field. The magnetic characteristics of these materials are determined by their magnetic susceptibility, which is the ratio of the induced magnetisation to the applied magnetic field [16].

1.2.3 Ultrasound-Responsive Systems

Ultrasound can induce cavitation, produce shear forces, facilitate acoustic droplet vaporisation, or generate localised heat, all of which can enhance delivery systems or improve the permeability of tissues. A recent pre-print discusses how employing microbubbles to generate cyclic jetting in the presence of ultrasound can breach cell membranes and enhance cellular uptake, suggesting that ultrasound-sensitive carriers are progressing towards improved mechanistic accuracy [17].

1.2.4 Electric Field / Electro-responsive Systems

Electrical stimulation can trigger redox reactions, ion movement, changes in polymer shape, or variations in swelling in electro-responsive materials. These technologies are often employed in implantable or wearable devices, where an applied voltage regulates drug release. Although they are not yet commonly used in clinical settings, these systems are gaining traction for transdermal patches and implantable delivery methods [18].

2. Polymers used in stimuli-responsive drug delivery:

Polymers capable of altering their characteristics in reaction to external or internal stimuli are gaining attention as a promising basis for drug delivery systems. Polymeric nanoparticles can help reduce the toxicity of medications, enhance the circulation of hydrophobic drugs, and boost a drug's effectiveness. Additionally, polymers that react to particular stimuli can be utilised to facilitate the controlled release of drugs into targeted regions of the body [19].

2.1 pH-responsive polymers:

A defining and distinguishing trait of pH-responsive polymers is the existence of either acidic or basic groups, which function to either accept or release protons when there is a shift in pH.

Natural origin polymers:

- Alginates: these are acidic polysaccharides with a pKa of approximately 3-4, attributed to the presence of -COOH groups. They form gentle gels in the presence of divalent cations such as Ca^{2+}, Ba^{2+}, Sr^{2+}, and Zn2+.
- Hyaluronic acid: this linear polysaccharide has a pH range of 3-4. It can absorb water up to 1000 times its own volume, resulting in the formation of a loose network.
- Chitosan: this polysaccharide exhibits pH sensitivity due to the amino groups present in its structure. Under low pH conditions, these amino groups get protonated, causing it to dissolve in acidic conditions while showing poor solubility in more alkaline environments.

Synthetic polymers:

- Polyacids: These contain acidic functional groups in their structure, such as carboxylic: poly (acrylic acid) -PAAc, boronic: poly (vinylphenyl boronic acid) - PVPBA, phosphoric: poly (ethylene glycol acrylate phosphate)-PEGAP, and sulfonic acid: poly (vinyl sulfonic acid)-PVSA.
- Polybases: These include functional groups such as amino: poly[(2-dimethylamino) ethylmethacrylate] - PDMA, pyridine: poly(4-vinylpyridine)-P4VP, and imidazole: poly(N-vinylimidazole) - PVI [20].

2.2 Ion-Responsive Polymers:

This collection of materials reacts to variations in ionic conditions in the environment. They demonstrate reversible physical and chemical changes in response to shifts in pH or ionic concentration. An alteration in the ionic strength around these materials impacts the interactions between the solution's ions and the polymer's ions, resulting in swelling or dehydration. Instances of polymers that react to ions include alginate (Ca2+) and chitosan (Mg2+) [21].

2.3 Redox Potential-Responsive:

Numerous redox reactions take place within the intracellular environment, including NADP+/NADPH, O_2/O_2^-O2-, and glutathione (GSH). In particular, GSH has garnered attention in the field of drug delivery. GSH's full chemical name is γ-L-glutamyl-L-cysteinyl-glycine, and it is a peptide made up of glycine, cysteine, and L-glutamic acid. Research has shown that GSH concentrations in tumour tissue can be four times greater than in healthy tissue in mice, indicating that GSH levels make a

suitable trigger for drug delivery systems [22]. The concentration of GSH is important for drug delivery because of the significant difference between its levels inside (1–10 mM) and outside the cell (1–10 μM). Doxorubicin was delivered using polymer micelles. These micelles were created with a graft copolymer of poly (acrylic acid)-g-poly (ethylene glycol) (PAA-g-PEG), which features a disulphide bond [23, 24].

2.4 Temperature-Responsive Polymers:

As indicated by the name, temperature-responsive polymers can alter their characteristics (frequently solubility) in reaction to variations in temperature (heating or cooling) in the surrounding environment. Temperature is a factor that can be easily measured and monitored, and the systems for such measurements are well established. For this reason, it is commonly utilised in the creation of smart polymers. An example of a temperature-responsive polymer includes poly(N-isopropylacrylamide) (PNIPAAm), along with poloxamers and prolastin.

The parameters related to the evaluation of this type of polymer include:

- UCST - Upper critical solution temperature. UCST remains largely underexplored.

- LCST- Lower critical solution temperature, denotes the highest temperature at which the polymer remains soluble, allowing for a single phase to be observed. When this temperature is exceeded, phase separation occurs.

The first polymer that was employed in the development of thermo-responsive materials was PNIPAAm (poly(N-isopropylacrylamide)). Its application is attributed to its comparable LCST temperature of 32–33°C, which is close to human body temperature [25,26].

2.5 Magnetic Field-Responsive Polymers:

Magnetic field-responsive polymers are materials that can alter their characteristics, including density, optical properties, and shape, when exposed to a magnetic field. These specific attributes can be achieved by incorporating magnetic particles, such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), into a formulation with polymers like poly (ethylene glycol) (PEG), dextran, poly (vinyl alcohol) (PVA), and poly (ethylene imine) (PEI) [27].

2.6 Ultrasound-Responsive Polymers:

Ultrasound refers to a wave generated by alternating current due to the mechanical vibrations of a piezoelectric material. Waves can be categorised based on frequency: low (<1 MHz), medium (1–5 MHz), and high (5–10 MHz). Ultrasound can influence materials in several ways: (a) thermal, resulting in a rise in temperature; (b) nonthermal, known as cavitation, where ultrasonic vibrations lead to the formation of gas bubbles. An example of a polymer that responds to ultrasound is dodecyl isocyanate-modified PEG-grafted poly (2-hydroxyethyl methacrylate), polyglycolides, or polylactides [28].

2.7 Electric Field-Responsive Polymers:

Polymers that respond to electric fields exhibit alterations in their physical properties when exposed to slight variations in electric current. The alterations in the electric field result from the transformation of electrical energy into mechanical energy.

Electro-responsive polymers include:

- Polypyrrole (PPy) is known for its excellent biocompatibility and high conductivity.

- Polyaniline (PANI) is recognised for its strong chemical stability, good processability, and conductivity.

- Poly (3,4-ethylene dioxythiophene) (PEDOT), which not only demonstrates biocompatibility and excellent conductivity but is also hydrophobic;

- Chitosan (CS), a naturally derived polymer known for its high availability, biocompatibility, antimicrobial properties, ability to form gels, and ease of processing [29, 30].

Table 1. Polymers used in Stimuli Responsive Drug Delivery.

Stimulus Type	Definition / Mechanism	Examples (Natural & Synthetic)
pH-Responsive Polymers	Contain acidic or basic groups that accept or donate protons when pH changes, altering solubility or swelling.	**Natural:** Alginates, Hyaluronic acid, Chitosan **Synthetic:** Poly (acrylic acid) (PAAc), Poly (vinylphenyl boronic acid) (PVPBA), Poly (ethylene glycol acrylate phosphate) (PEGAP), Poly (vinyl sulfonic acid) (PVSA), PDMA, Poly(4-vinylpyridine) (P4VP), Poly(N-vinylimidazole) (PVI)
Ion-Responsive Polymers	Exhibit reversible physical/chemical changes (swelling or dehydration) when ionic strength or ion concentration varies.	Alginate (responsive to Ca^{2+}) and chitosan (responsive to Mg^{2+})
Redox-Responsive Polymers	Respond to intracellular redox potential, particularly high glutathione (GSH) levels, triggering drug release.	PAA-g-PEG micelles with disulphide bonds
Temperature-Responsive Polymers	Change solubility or other properties when exposed to temperature variations.	PNIPAAm, poloxamers, Prolastin
Magnetic Field-Responsive Polymers	Alter density, shape, or optical properties when exposed to a magnetic field due to embedded magnetic particles.	Polymers with Fe_3O_4 or γ-Fe_2O_3 combined with PEG, Dextran, PVA, and PEI
Ultrasound-Responsive Polymers	Respond to ultrasonic waves via thermal effects or cavitation, enabling triggered drug release.	Dodecyl isocyanate-modified PEG-g-PHEMA, Polyglycolides, Polylactides
Electric Field-Responsive Polymers	Show physical property changes when exposed to electrical stimulation, converting electrical to mechanical energy.	Polypyrrole (PPy), Polyaniline (PANI), PEDOT, Chitosan

3. Mechanism of Drug Release

Stimuli-responsive drug delivery systems (SRDDS) operate through a series of physicochemical and molecular interactions that convert environmental factors or externally applied triggers into detectable material responses that facilitate drug release. This process can be visualised as a succession of changes that begin with the expansion or contraction of polymers, followed by alterations in phase or bond cleavage reactions, and frequently culminating in the breakdown of nanocarriers or disruption of membranes, which ultimately results in the diffusion or release of the drug into the biological environment.

3.1 Expansion and Contraction of Polymers

The primary and frequently reversible response of polymer networks to an external trigger is either swelling or contraction. Hydrophilic polymers take up water, which causes an increase in their mesh size, facilitating the outward diffusion of drug molecules; conversely, hydrophobic transformations or ionic crosslinking can result in contraction, expelling the drug through convective flow. The equilibrium swelling degree (Q) is influenced by the balance between the osmotic pressure exerted by the solvent inside the gel and the elastic retractive forces of the network, according to the Flory–Rehner theory. For pH-sensitive polymers such as poly (acrylic acid) or chitosan derivatives, the ionisation of their acidic or basic functional groups alters the electrostatic repulsion, resulting in changes in volume [31,32]. Thermo-responsive polymers, such as poly(N-isopropylacrylamide) (PNIPAAm), undergo coil-to-globule transitions at their lower critical solution temperature (LCST, approximately 32 °C), where enhanced hydrophobic interactions cause shrinkage. In drug delivery systems, this adjustment of swelling and shrinking has a direct impact on the diffusion coefficients. An increase in swelling enlarges pore sizes, promoting sustained release, while shrinkage can trigger pulsatile “on-off” release patterns [33].

3.2 Phase Transitions in Responsive Materials

Phase transitions are defined by abrupt structural transformations triggered by external factors. These transitions may occur as sol-gel, micelle-unimer, or liquid–solid changes. In thermo-responsive systems, the polymer's lower critical solution temperature (LCST) or upper critical solution temperature (UCST) dictates its physical state: when the temperature falls below the LCST, the polymer chains remain hydrated and extended; when it exceeds the LCST, they contract due to the breakdown of hydrogen bonds with water. This mechanism leads to the rapid release of drugs as the matrix compacts. In the case of materials that respond to light or magnetic fields, the application of energy induces local heating or alters the conformation, triggering a phase transition that impacts permeability. For instance, gold nanorod-loaded PNIPAAm gels leverage plasmonic photothermal conversion, resulting in a swift increase in temperature and the collapse of the gel when exposed to near-infrared light, aiding the controlled release of anticancer drugs. Similarly, block copolymers like PEG–PLGA–PEG experience a sol–gel transition at body temperature, allowing injectable formulations that solidify in situ for extended release [34,35].

3.3 Bond Cleavage and Chemical Transformation

An essential feature of SRDDS is the inclusion of reactive chemical linkers between the drug and the carrier or within the polymer matrix that can be selectively broken by specific stimuli.

Typical labile bonds consist of:

- Hydrazone and acetal (which can be hydrolysed by acid and respond to lower pH levels)
- Disulphide and diselenide (which are reduced by intracellular glutathione)
- Boronic ester and thioketal (which get cleaved by reactive oxygen species)
- Photocleavable o-nitrobenzyl linkers (sensitive to UV/NIR light).

Upon cleavage, either the polymer loses its structural integrity or hydrophilicity, or the bond between the drug and the linker is severed, resulting in the release of the therapeutic agent. This mechanism provides .high chemical specificity, as the release occurs solely in the presence of the specific trigger. Recent studies from 2024–2025 have indicated the creation of multi-responsive polymers where drug release is governed by both pH and redox stimuli through the sequential cleavage of hydrazone and disulphide bonds, achieving accurate timing and location control in tumour microenvironments [36,37].

3.4 Disruption of Nanoparticles and Liposomes

At the supramolecular level, many sustained release drug delivery systems (SRDDS) employ self-assembled nanostructures, such as micelles, vesicles, liposomes, or polymersomes, that can be destabilised or disassembled in response to particular stimuli. In systems based on lipids, changes in pH or temperature can alter the arrangement of the bilayer, leading to the release of the encapsulated drug. The incorporation of protonatable lipids (such as DOPE and CHEMS) can trigger a transformation from lamellar to hexagonal phases in acidic pH, causing destabilisation of the membrane. For polymeric micelles, external triggers (like redox reactions or exposure to light) can disrupt the crosslinks in the hydrophobic core or the linkers in the hydrophilic corona, which prompts the breakdown of unimers and the release of medications. Similarly, magnetic nanoparticles encased in liposomes can generate localised heat when exposed to alternating magnetic fields, causing the formation of temporary pores and facilitating drug release [38].

3.5 Release of Drugs and Diffusion into the Surrounding Medium

After the previous transformations are finalised, the subsequent phase involves the physical relocation of drug molecules into the external environment, primarily driven by diffusion and convection. The transport mechanism is represented by numerical values: 0.5 indicates Fickian diffusion, 1 signifies case-II transport (governed by erosion or relaxation), and values in between represent anomalous transport. Consequently, the kinetics of the overall release result from a combination of stimulus-induced structural modifications (swelling, cleavage, disruption) and mass-transfer mechanisms (diffusion, erosion, convection) [39].

4. Multi-Route Applications of Stimuli-Responsive Drug-Delivery Systems

4.1 Oral delivery:

The oral route remains the most user-friendly option for patients, but it encounters numerous biological obstacles: harsh gastric acidity, digestive enzymes, mucus barriers, fluctuating transit times, and first-pass metabolism. As a result, stimuli-responsive oral systems are designed to protect the drug in the stomach while enabling targeted release in the small intestine or colon through signals from pH, enzymes, or microbiota. Conventional design approaches utilise enteric or acid-sensitive coatings, pH-responsive hydrogels that expand at intestinal pH levels to release the medication, and enzyme-degradable linkers that are disrupted by colonic microbiota [40].

4.2 Transdermal delivery (patches & microneedles):

The main challenge in transdermal delivery is the stratum corneum. Stimuli-responsive transdermal systems, such as microneedle (MN) arrays, stimuli-sensitive dissolving polymers, and wearable patches, enable a less invasive method to overcome the outer skin barrier, providing on-demand or feedback-regulated drug administration. Strategies include glucose-responsive MNs for insulin delivery (employing enzyme or phenylboronic acid detection), temperature- or ROS-responsive coatings that dissolve in inflamed skin areas, and electrically activated patches for accurate dosing [41].

4.3 Ocular delivery:

Implementing a drug delivery system for the eyes is recognised as a complex and challenging task due to the eye's isolation as an organ, making drug administration quite difficult. Antibiotic eye drops are among the most commonly employed topical treatments for various ocular infections. Nonetheless, conventional ophthalmic formulations require frequent application to sustain an effective concentration at the infection site, as the rapid turnover of tears and significant drug elimination via nasolacrimal drainage result in low bioavailability of eye drops. The process of delivering medication to the eye faces challenges like tear replacement, blinking, barriers posed by the cornea and sclera, and restricted access to the posterior segment as a result of the blood-retinal barrier. Stimuli-responsive ocular systems aim to extend the duration the drug remains in the precorneal area (such as thermo- or ion-triggered in situ gels) or to initiate localised drug release within deeper tissues using techniques such as light-responsive nanoparticles, ultrasound-assisted strategies, or enzyme-degradable delivery systems [42].

4.4 Nasal (nose-to-brain) delivery:

The nasal route for administration offers a rapid and, in certain instances, a direct means to transport substances from the nose to the brain via the olfactory and trigeminal nerve pathways, making it an attractive option for Central Nervous System (CNS) therapies. The main obstacles include mucociliary clearance and a limited duration of presence. Formulations that are responsive to stimuli in the nasal region often include thermo- or ion-sensitive in-situ gels that solidify upon contact with nasal mucus or nanoparticles that respond to reactive oxygen species/enzymes that are tailored to exploit specific oxidative/inflammatory conditions for targeted release [43].

4.5 Pulmonary / inhalation delivery:

The lungs possess a large surface area and a thin epithelial layer, making them suitable for rapid systemic absorption and focused treatment of respiratory issues. However, successful inhalation requires controlling the size of particles, ensuring stability during aerosol creation, and preventing clearance by macrophages. Inhalable carriers that are responsive to particular lung conditions (such as elevated ROS in inflamed regions) or that react to external triggers (like magnetic guidance) are currently under development [44].

5. Evaluation parameters for different routes:

5.1 Oral Drug Delivery:

- The pH-responsive swelling/deswelling ratio assesses the ability of the polymer to expand in the intestinal pH and remain contracted in the gastric pH, ensuring targeted release.
- The in-vitro release profile under gastrointestinal-mimicking conditions evaluates if the formulation

safeguards the drug in the acidic environment of the stomach and activates release in neutral or alkaline intestinal conditions.

- Mucoadhesion strength evaluates how well the formulation adheres to intestinal mucus, which indicates the potential residence time and enhancement of absorption [45, 46].

5.2 Transdermal drug delivery:

- Patch thickness: The thickness of a transdermal film is measured using a travelling microscope dial gauge, screw gauge, or micrometre at various locations on the film.
- Drug concentration: A defined area of the patch is dissolved in an appropriate solvent at a specific volume. Subsequently, the solution is filtered through a filter medium, and the drug content is analysed using suitable methods such as UV or HPLC techniques.
- Shear adhesion test: This evaluation is conducted to assess the cohesive strength of the adhesive polymer [47, 48].

5.3 Ocular drug delivery:

- Visual Appearance: The visual characteristics are influenced by particle size, the type and concentration of surfactants and oils. Transparency is assessed by measuring percentage transmittance (% T) with a UV Spectrophotometer at a wavelength of 520 nm.
- Ocular Retention: Retention in the eye is critical as it minimises dosing frequency and enhances drug bioavailability. The ocular retention primarily depends on the surface area of the nanosystem, since a larger surface area can prolong the residence time.
- Zeta Potential: Zeta potential (ZP) serves as an indicator of the physical stability of the created nanosystem. It is measured by observing the electrophoretic movement of particles in an electric field. Typically, a ZP around ±20 mV is suitable for electrostatic adhesion to the corneal surface [49, 50].

5.4 Nasal drug delivery:

- In vitro drug release assessments: For formulations intended for oral, ocular, or intranasal administration, drug release studies are conducted utilising a plastic dialysis cell.
- Texture evaluation: The firmness, consistency, and cohesiveness of the formulation can be assessed with a texture analyser, which primarily reflects the syringeability of the solution, ensuring that the formulation can be easily administered in vivo.
- In Vitro Mucoadhesion Strength: This refers to the force necessary to detach the nasal mucosa from the formulations. In vitro bioadhesion was quantified using a refined physical balance method [51, 52].

5.5 Pulmonary drug delivery:

- Particle Size Measurement: Particle size is measured using a cascade impactor or a light scattering decay technique, presented in micrometres (µm).
- Moisture Level: The moisture content can be assessed through the Karl-Fischer method or gas chromatography, expressed as a percentage [53].
- Clearance Dynamics: The rates of mucociliary clearance and macrophage uptake following deposition are evaluated to determine how long the drug remains in the lungs, which influences therapeutic duration and effectiveness [54].

CONCLUSION

A major step towards individualised, accurate, and flexible therapeutic interventions is the development of stimuli-responsive drug delivery systems. SRDDS offer spatially and temporally controlled drug release that is not possible with traditional formulations by utilising the biochemical and biophysical properties of diseased tissues or by incorporating externally controlled triggers. Targeted delivery within complex microenvironments, especially in cancer and inflammatory disorders, is made possible by the wide variety of endogenous stimuli, including pH gradients, enzyme overexpression, redox imbalances, and temperature variations. In a similar vein, exogenous triggers- such as light, magnetic fields, ultrasound, and electrical stimulation, offer extra levels of control that improve treatment efficacy and safety. The development of carriers that experience swelling, contraction, phase transitions, or selective bond cleavage has been made possible by

developments in polymer science, both natural and synthetic. These mechanisms underpin the high responsiveness and specificity observed in next-generation systems. Drug delivery systems that respond to stimuli are a big step towards individualised, accurate, and flexible therapeutic interventions. SRDDS offer spatially and temporally regulated drug release that is not possible with conventional formulations by utilising the biochemical and biophysical properties of diseased tissues or by incorporating externally controlled triggers. Targeted delivery within complex microenvironments is made possible by the wide variety of endogenous stimuli, including pH gradients, enzyme overexpression, redox imbalances, and temperature variations, especially in cancer and inflammatory disorders. Similar to this, exogenous triggers such as light, magnetic fields, ultrasound, and electrical stimulation, offer extra levels of control that improve treatment efficacy and safety. This development has been largely attributed to advances in polymer science, which have made it possible to design carriers that experience phase transitions, swelling, contraction, or selective bond cleavage.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

REFERENCE

1. Adepu S, Ramakrishna S. Controlled Drug Delivery Systems: Current Status and Future Directions. Curr Pharm Des. 2021;27(39):4334-56.
2. Li L, Jiang W, Qiu S. Nanomaterials in stimulus-responsive drug delivery systems facilitate precise therapy for haematologic diseases. J Mater Chem B. 2025 Jun 11. Doi:10.1039/d5tb00807g.
3. Liu D, et al. The Smart Drug Delivery System and Its Clinical Potential. Theranostics. 2016;6(9):1306-1323.
4. Das S, Ha DH, Lee ES, Park SY. Rational Design of Peptide-Based Smart Hydrogels for Biomedical Applications. Front Bioeng Biotechnol. 2021 Nov 15; 9:760569. Doi:10.3389/fbioe.2021.760569
5. Hua S. Current Trends and Challenges in the Clinical Translation of Nanoparticle-Based Nanomedicines—Critical Overview. Front Pharmacol. 2018 Jul 16; 9:744. Doi:10.3389/fphar.2018.00744
6. Zhuo, S.; Zhang, F.; Yu, J.; Zhang, X.; Yang, G.; Liu, X. pH-Sensitive Biomaterials for Drug Delivery. Molecules 2020, 25, 5649.
7. Rai, G.; Yadav, A.K.; Jain, N.K.; Agrawal, G.P. Eudragit-coated dextran microspheres of 5-fluorouracil for site-specific delivery to colon. Drug Deliv. 2016, 23, 328–337.
8. Deirram, N.; Zhang, C.; Kermaniyan, S.S.; Johnston, A.P.R.; Such, G.K. pH-Responsive Polymer Nanoparticles for Drug Delivery. Macromol. Rapid Commun. 2019, 40, 1800917.
9. Yang, Y.; Wang, Z.; Peng, Y.; Ding, J.; Zhou, W. A Smart pH-Sensitive Delivery System for Enhanced Anticancer Efficacy via Paclitaxel Endosomal Escape. Front. Pharmacol. 2019, 10, 10.
10. Shahriari, M.; Zahiri, M.; Abnous, K.; Taghdisi, S.M.; Ramezani, M.; Alibolandi, M. Enzyme responsive drug delivery systems in cancer treatment. J. Control. Release 2019, 308, 172–189
11. De La Rica R, Aili D, Stevens MM. Enzyme-responsive nanoparticles for drug release and diagnostics. Advanced Drug Delivery Reviews. 2012; 64:967-78
12. Monteiro, P.F.; Travanut, A.; Conte, C.; Alexander, C. Reduction-responsive polymers for drug delivery in cancer therapy—Is there anything new to discover? Wiley Interdiscip. Rev. Nanomed. Nanobiotechnology 2021, 13, e1678
13. Ghule RJ, Jadhav PN, Sanap YN, Pache MM, Darekar AB. Tumour-derived extracellular vesicles in chemotherapy resistance: molecular pathways, clinical implications and therapeutic opportunities. Asian J Res Pharm Sci. 2023;15(4):371-380.
14. Jain, K.; Vedarajan, R.; Watanabe, M.; Ishikiriyama, M.; Matsumi, N. Tunable LCST behavior of poly (N-isopropylacrylamide/ionic liquid) copolymers. Polym. Chem. 2015, 6, 6819–6825
15. Zhou T, Li Y, Zhou J, et al. All-In-One Second Near-Infrared Light-Responsive Drug Delivery System for Synergistic Chemo-Photothermal Therapy. ACS Appl Mater Interfaces. 2022 Jul

10;14(27):31188-31202. Doi:10.1021/acsami.2c06452
16. Ortner V, Kaspar C, Halter C, et al. Magnetic "eld-controlled gene Expression in encapsulated cells. J Control Release 2012; 158: 424-32
17. Cattaneo, M., Guerriero, G., Shakya, G. et al. Cyclic jetting enables microbubble-mediated drug delivery. Nat. Phys. 21, 590–598 (2025).
18. Rahim MA, Jan N, Khan S, Shah H, Madni A, Khan A, Jabar A, Khan S, Elhissi A, Hussain Z, et al. Recent Advancements in Stimuli Responsive Drug Delivery Platforms for Active and Passive Cancer Targeting. Cancers. 2021; 13(4):670.
19. López Ruiz A, Ramirez A, McEnnis K. Single and Multiple Stimuli-Responsive Polymer Particles for Controlled Drug Delivery. Pharmaceutics. 2022; 14(2):421.
20. Balcerak-Woźniak A, Dzwonkowska-Zarzycka M, Kabatc-Borcz J. A Comprehensive Review of Stimuli-Responsive Smart Polymer Materials—Recent Advances and Future Perspectives. Materials. 2024; 17(17):4255
21. Purohit, A.; Jain, S.; Nema, P.; Vishwakarma, H.; Jain, P.K. Intelligent or smart polymers: Advance in novel drug delivery. J. Drug Deliv. Ther. 2022, 12, 208–216.
22. Li, W.; Li, M.; Qi, J. Nano-Drug Design Based on the Physiological Properties of Glutathione. Molecules 2021, 26, 5567.
23. Smith, C.V.; Jones, D.P.; Guenthner, T.M.; Lash, L.H.; Lauterburg, B.H. Compartmentation of Glutathione: Implications for the Study of Toxicity and Disease. Toxicol. Appl. Pharmacol. 1996, 140, 1–12.
24. Sun, H.; Guo, B.; Li, X.; Cheng, R.; Meng, F.; Liu, H.; Meng, F.; Zhong, Z. Shell-Sheddable Micelles Based on Dextran-SS-Poly(ε-Caprolactone) Diblock Copolymer for Efficient Intracellular Release of Doxorubicin. Biomacromolecules 2010, 11, 848–854.
25. Shu, X. A review of thermoresponsive drug delivery systems based on LCST/UCST polymer nanofibers. J. Phys. Conf. Ser. 2023, 2539, 012032
26. Garcia, J.M.; Garcia, F.C.; Vallejos, S.; Trigo, M.; Reglero, J.A. Smart Polymers: Principles and Applications, 1st ed.; De Gruyter: Sotogrande, Spain, 2022.
27. Khizar, S.; Zine, N.; Errachid, A.; Elaissari, A. Introduction to stimuli-responsive materials and their biomedical applications. In Stimuli-Responsive Materials for Biomedical Applications; ACS Symposium Series; American Chemical Society: Washington, DC, USA, 2023; Volume 1436, pp. 1–30.
28. Manouras, T.; Vamvakaki, M. Field responsive materials: Photo-, electro-, magnetic-and ultrasound-sensitive polymers. Polym. Chem. 2017, 8, 74–96
29. Purohit, A.; Jain, S.; Nema, P.; Vishwakarma, H.; Jain, P.K. Intelligent or smart polymers: Advance in novel drug delivery. J. Drug Deliv. Ther. 2022, 12, 208–216.
30. Kanaan, A.F.; Piedade, A.P. Electro-responsive polymer-based platforms for electrostimulation of cells. Mater. Adv. 2022, 3, 2337–2353
31. Friesen S, Radulescu A, Wycisk P, Richtering W. Modified Flory–Rehner theory describes thermotropic volume phase transitions in copolymer microgels. Macromolecules. 2022 May 12;55(9):3455-3465. PMID: 35587318
32. Safari JB, Bapolisi AM, Krause RWM. Development of pH-Sensitive Chitosan-g-poly (acrylamide-co-acrylic acid) Hydrogel for Controlled Drug Delivery of Tenofovir Disoproxil Fumarate. Polymers. 2021; 13(20):3571
33. Ansari MJ, Rajendran RR, Mohanto S, Agarwal U, Panda K, Dhotre K, Manne R, Deepak A, Zafar A, Yasir M, et al. Poly(N-isopropylacrylamide)-Based Hydrogels for Biomedical Applications: A Review of the State-of-the-Art. Gels. 2022; 8(7):454.
34. Yoshida, Y., Takahashi, A., Kuzuya, A. et al. Instant preparation of a biodegradable injectable polymer formulation exhibiting a temperature-responsive sol–gel transition. Polym J 46, 632–635 (2014).
35. Dutta, K., Das, R., Ling, J., Monibas, R. M., Carballo-Jane, E., Kekec, A., ... & Liang, Y. (2020). In situ forming injectable thermoresponsive hydrogels for controlled delivery of biomacromolecules. ACS omega, 5(28), 17531-17542.
36. Wells CM, Harris M, Choi L, Murali VP, Guerra FD, Jennings JA. Stimuli-Responsive Drug

Release from Smart Polymers. Journal of Functional Biomaterials. 2019; 10(3):34.
37. Parshad, B., Arora, S., Singh, B. et al. Towards precision medicine using biochemically triggered cleavable conjugation. Commun Chem 8, 100 (2025)
38. Birhan YS, Darge HF, Hanurry EY, Andrgie AT, Mekonnen TW, Chou H-Y, Lai J-Y, Tsai H-C. Fabrication of Core Crosslinked Polymeric Micelles as Nanocarriers for Doxorubicin Delivery: Self-Assembly, In Situ Diselenide Metathesis and Redox-Responsive Drug Release. Pharmaceutics. 2020; 12(6):580
39. Fu, Y., & Kao, W. J. (2010). Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. Expert Opinion on Drug Delivery, 7(4), 429–444.
40. Amidon, S., Brown, J.E. & Dave, V.S. Colon-Targeted Oral Drug Delivery Systems: Design Trends and Approaches. AAPS PharmSciTech 16, 731–741 (2015).
41. Zhao, J., Xu, G., Yao, X. et al. Microneedle-based insulin transdermal delivery system: current status and translation challenges. Drug Deliv. And Transl. Res. 12, 2403–2427 (2022).
42. Abbas MN, Khan SA, Sadozai SK, Khalil IA, Anter A, Fouly ME, Osman AH, Kazi M. Nanoparticles Loaded Thermoresponsive In Situ Gel for Ocular Antibiotic Delivery against Bacterial Keratitis. Polymers. 2022; 14(6):1135.
43. Qian L, et al. In situ gels for nasal delivery: formulation, characterization and bioavailability studies. Adv Colloid Interface Sci. 2025; 325:103101.
44. Mohit Kumar, Ayah R. Hilles, Samah Hamed Almurisi, Amit Bhatia, Syed Mahmood, Micro and nano-carriers-based pulmonary drug delivery system: Their current updates, challenges, and limitations a review, JCIS Open, Volume 12,2023,100095.
45. Tulain UR, Ahmad M, Rashid A, Malik MZ, Iqbal FM. Fabrication of Ph-responsive hydrogel and its in vitro and in vivo evaluation. Advances in Polymer Technology. 2018 Feb;37(1):290-304.
46. Subramanian DA, Langer R, Traverso G. Mucus interaction to improve gastrointestinal retention and pharmacokinetics of orally administered nano-drug delivery systems. Journal of nanobiotechnology. 2022 Aug 6;20(1):362
47. Keleb E, Sharma RK, Mosa EB, Aljahwi A-AZ. Transdermal Drug Delivery System – Design and Evaluation. International Journal of Advances in Pharmaceutical Sciences. 2010; 1:201-211.
48. Rhaghuram RK, Muttalik S, Reddy S. Once – daily sustained-Release matrix tablets of nicorandil: formulation and invitro Evaluation. AAPS Pharm.SciTech. 2003; 4(4):480–488
49. Singh M, Bharadwaj S, Lee KE, Kang SG. Therapeutic nanoe-mulsions in ophthalmic drug administration: concept in formu-lations and characterization techniques for ocular drug delivery. J Control Release. 2020; 328:895-916.
50. Ahmed, S., Amin, M.M. & Sayed, S. Ocular Drug Delivery: a Comprehensive Review. AAPS Pharm SciTech 24, 66 (2023)
51. Chand P, Gnanarajan G, Kothiyal P. In situ gel: A Review. Indian J Pharm Biol Res (IJPBR). 2016;4(2):11–9
52. Xie H, Li L, Sun Y, Wang Y, Gao S, Tian Y, et al. An available Strategy for nasal brain transport of nanocomposite based on PAMAM dendrimers via in situ gel. Nanomaterials. 2019; 9(2)
53. Magramane S, Pápay Z, Turbucz B, Antal I. Formulation and characterization of pulmonary drug delivery systems. Acta Pharmaceutical Hungarica. 2019 Aug 1;89(2):63-83.
54. Fernández-García R, Fraguas-Sánchez AI. Nanomedicines for Pulmonary Drug Delivery: Overcoming Barriers in the Treatment of Respiratory Infections and Lung Cancer. Pharmaceutics. 2024; 16(12):1584.

HOW TO CITE: Ajinkya Kure*, Aishwarya Jadhav, Stimuli-Responsive Drug Delivery; Mechanism and Multi-Route Application: A Comprehensive Review, Int. J. Sci. R. Tech., 2025, 2 (12), 272-283. https://doi.org/10.5281/zenodo.17980253