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A Review on Thermoresponsive Drug Delivery system on Localised Therapy

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ABSTRACT:-
Recently, there has been a lot of interest in thermoresponsive drug delivery systems (TR-DDS) as a new method for obtaining localized, controlled, and on-demand drug release. The main component of these systems is intelligent, or "smart," polymers, which are able to detect and react to temperature changes by going through reversible sol-gel transitions or conformational phase changes. including modified natural polymers like chitosan and gelatin, Pluronic® triblock copolymers, and poly(N-isopropylacrylamide*) (PNIPAM). Because of their adjustable LCST behavior, these materials provide a great platform for injectable formulations by remaining soluble at room temperature and forming gels or aggregates at body temperature. Furthermore, combining thermoresponsive behavior with other properties like enzymatic degradability, magnetic responsiveness, or pH sensitivity has improved the accuracy of drug release and therapeutic efficacy. These systems enable sustained and targeted drug release in response to temperature changes in pathological tissues, such as tumor regions or inflamed areas, where local temperature elevation naturally occurs. Injectable thermogels and nanocarrier-based formulations have further improved drug retention, bioavailability, and therapeutic outcomes. Even with great advancements, a number of issues still need to be resolved, such as limited biodegradability, burst release effects, and scalability for clinical translation. The development of biocompatible and biodegradable thermoresponsive polymers, the integration of several stimuli (temperature, pH, and redox) for precise control, and the use of sophisticated fabrication methods like 3D printing and Nano structuring are the main goals of current research. It is anticipated that next-generation thermoresponsive drug delivery systems will be made possible by the convergence of polymer chemistry, nanotechnology, and biomedical engineering. This will allow for patient-specific and precisely targeted localized therapies.

Keywords: smart polymers, LCST, PNIPAM, Pluronic, localized therapy, injectable hydrogels, temperature-sensitive release, nanotechnology, controlled drug release

I. INTRODUCTION

All essential biomolecules, including proteins, carbohydrates, and nucleic acids, are biopolymers that serve both structural and functional purposes in intricate cellular systems, making life itself intrinsically polymeric. Researchers have been motivated to imitate such cooperative behavior in synthetic materials by the remarkable nonlinearity, sensitivity, and coordinated interactions of biopolymers toward external stimuli. Over the past two to three decades, the demand for advanced, intelligent materials that meet modern industrial and biomedical requirements has driven immense scientific interest in the development of smart polymers. Smart or intelligent polymers are a collective term for stimuli-sensitive or environmentally responsive polymers. Dagani et al. coined the phrase “smart polymers” in 1995 to emphasize how similar they are to naturally occurring biopolymers. Synthetic analogs have been designed to mimic natural polymers through a variety of chemical and structural modifications thanks to advancements in polymer science and technology. These adaptive materials are frequently referred to in scientific literature by terms like “intelligent polymers,” “stimuli-responsive polymers,” and “environmentally sensitive polymers.” Smart polymers exhibit a remarkable capacity to react to even small environmental changes, such as chemical stimuli (pH, ionic strength, or reactive metabolites) . The macroscopic characteristics of the polymer, such as structure, shape, solubility, surface behavior, molecular organization, or phase transitions between sol and gel states, can be significantly altered by such responsiveness. Crucially, once the external stimulus is eliminated, the polymer can revert to its original state because these modifications are reversible. Bio-recognition components, sensory units, or other functional

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molecules can be incorporated into the framework of synthetic polymers using pre-polymerization or post-polymerization techniques These changes significantly increase the potential uses of smart polymers in a variety of domains, including biomimetic actuation, drug delivery, biomaterial separation, and biocatalysis. Higher temperatures or stronger ions can change the efficiency of hydrogen bonds, causing hydrogel collapse in networks of interpenetrating polymers. The main cause of these changes is the delicate equilibrium between hydrophilicity and hydrophobicity in the molecular makeup of the polymer. Although they can occasionally occur in other solvents and polymer blends close to transition conditions, these nonlinear responsive behaviors are most frequently seen in aqueous systems. (1)

II. FUNDAMENTALS OF THERMORESPONSIVE POLYMERS AND MATERIALS:-

• LOWER CRITICAL SOLUTION TEMPERATURE:-

In reaction to temperature changes, thermoresponsive polymers show reversible phase transitions. The polymer becomes insoluble in water when the temperature rises above the LCST . The hydrogen bonds between water and the polymer are broken at high temperatures when water molecules are driven out of the polymer chains. The polymer forms new hydrogen bonds, which alter the enthalpy of the system. As water molecules become more unrestricted, entropy rises concurrently. The Gibbs free energy equation ([\Delta G = \Delta H – T\Delta S]) states that when the temperature rises above the LCST, phase separation from a soluble to an insoluble state happens spontaneously due to the "hydrophobic effect." For instance, interactions between its amide side groups and water cause poly(N-isopropylacrylamide) (PNIPAM) to remain water-soluble below its LCST, leading to solvated, random coil conformations. Side chains preferentially interact with each other when heated, causing soluble coils to change into insoluble globules. A change from clear to opaque solution, typically when the solution transmittance falls to 50%, indicates the temperature at which this coil-to-globule transition occurs, known as the Turbidity point. Furthermore, by chemically altering the polymer structure through copolymerization, modifying end-group functionalities, altering molecular weight and architecture,, the LCST these polymers can be precisely adjusted for physiological relevance (usually within 35–40 °C). For biomedical applications involving temperature-triggered drug delivery, thermoresponsive polymers can be precisely optimized thanks to this tunability (2).

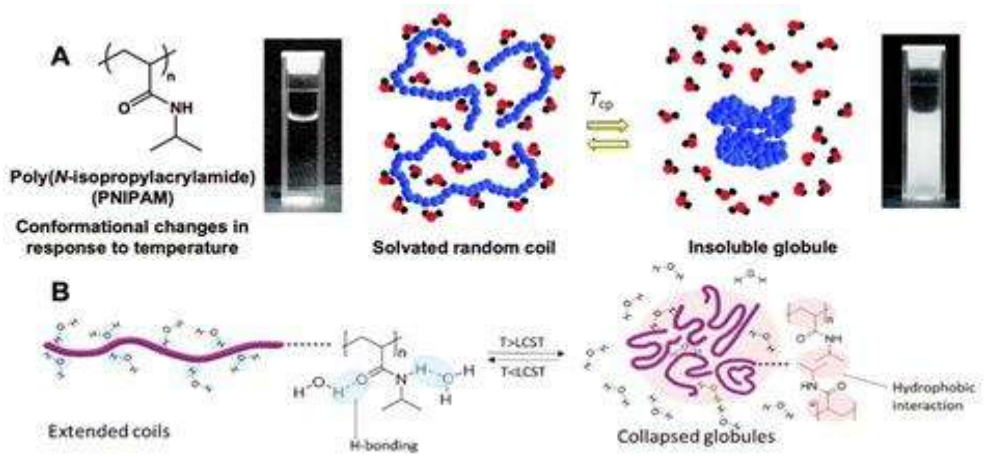

Fig.1 Illustration of PNIPAM Coil-to-Globule Transformation Across LCST

UPPER CRITICAL SOLUTION TEMERATURE:-

Because the interaction between these nonpolar groups and water is weaker than the hydrogen bonds that form between water molecules themselves, ordered cages of water molecules encircle the nonpolar segments of the polymer. As a result, water molecules often form stronger bonds with one another, encasing the polymer in a structured hydration shell. The solution

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characteristics of a non-ionic polymer known to display UCST behaviour .

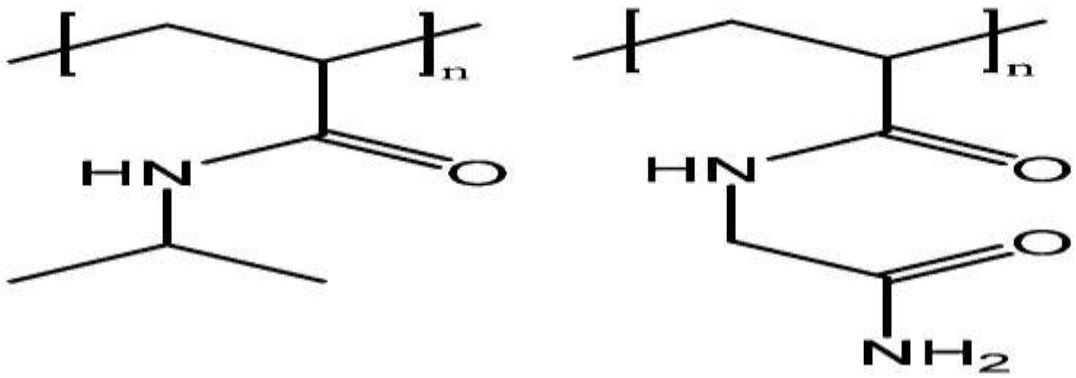

Fig 2. Depiction of PNIPAM structure (left) alongside PNAGA structure (right)

Strong supramolecular interactions, such as hydrogen bonding, as seen in poly(N-acryloylglycinamide) (PNAGA), or electrostatic interactions typical of zwitterionic polymers, are the main factors influencing the UCST behavior of polymers in water. Because of the hydrogen bonds that exist between its side groups. This demonstrates how important hydrogen bonding is to PNAGA and related polymers' thermoresponsive qualities.

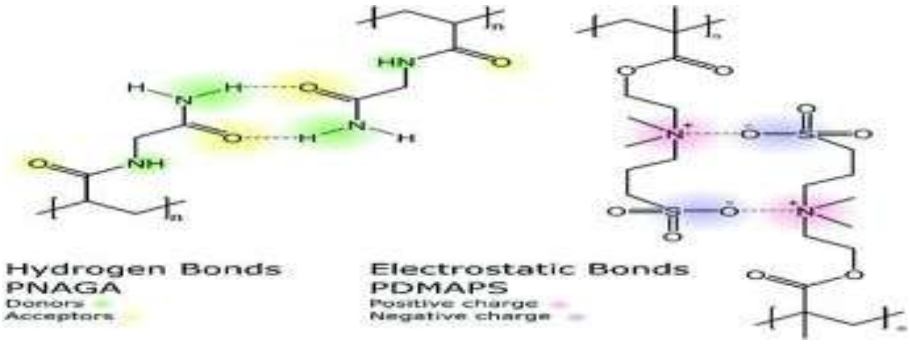

Fig 3. Schematic representation of hydrogen bonds between PNAGA side chains (left) and electrostatic bonds between zwitterionic groups in poly(N,N′-dimethyl(methacryloylethyl)ammonium propanesulfonate), PDMAPS, responsible for the thermoresponsive behavior of the respective polymers

When PNAGA dissolves in water, an endothermic reaction breaks the hydrogen bonds between its amine and carbonyl groups, and an exothermic reaction creates new hydrogen bonds with water molecules. Highly sensitive calorimetric measurements are needed to identify this dissolution process because the total enthalpy change is extremely small. In contrast, the phase transition enthalpy of PNAGA is approximately 90 J/mol (or 0.7 J/g), while that of PNIPAM, a well-known thermoresponsive polymer, is significantly higher at 4-6 kJ/mol. Compared to small molecules, polymer chains typically have a lower entropy of mixing, and as molecular weight increases, this entropy further decreases. This indicates that molecular weight has a significant impact on the cloud point temperature because polymer solubility becomes more vulnerable to other interactions. A polymer must have a negative Gibbs free energy of dissolution ([Δ Gm]) in order to dissolve. Phase separation occurs for UCST polymers below their cloud point when [ΔGm] becomes positive. The ratio of changes in enthalpy to entropy yields the cloud point temperature [T_{cp}].

$$Tcp = \Delta H/\Delta S$$

Indicating that the cloud point may be shifted by modifications in either enthalpy or entropy brought on by copolymerization or additional solutes. Therefore, UCST behavior can be induced or changed by external stimuli or additives. A thermoresponsive polymer with LCST behavior that has been extensively researched is

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poly(N-isopropylacrylamide) (PNIPAM). The polymer backbone's interaction with hydrophobic groups drives its phase separation, which is influenced by variables such as pressure and the distribution of polymer molecular weight. The observed cloud point is influenced by the rates of heating and cooling; in particular, polymer re-dissolution (rehydration) occurs more slowly than the initial coil. In addition to water forming a hydrated and swollen coil around nonpolar moieties, When it gets hotter These hydrogen bonds break above the phase transition, releasing water and allowing for intramolecular. Similarly, for LCST polymers, polymer dehydration causes the Phase separation results (3)

III. MECHANISMS OF DRUG RELEASE IN THERMORESPONSIVE SYSTEMS

Phase Transition materials:-

Thermo-responsive polymers' phase transition behavior is generally explained by the presence of both hydrophilic and hydrophobic functional groups. Temperature changes greatly affect how these groups interact with nearby water molecules in aqueous environments, changing the hydrophilic–hydrophobic balance of the polymer. As a result of this change, the polymer solution becomes a cloudy, two-phase (solid–liquid) system instead of a clear, homogeneous state. The temperature at which this transition occurs is known as the phase transition temperature of the polymer. Poly(N-isopropylacrylamide) (PNIPAM), which has hydrophobic isopropyl groups (-$CH(CH_3)_2$) and hydrophilic amide groups (-CO–NH–), is a prime example. Polymer chain collapse, aggregation, subsequent phase separation result from hydrophobic interactions taking precedence over hydrogen bonding when the temperature rises above the LCST (4).

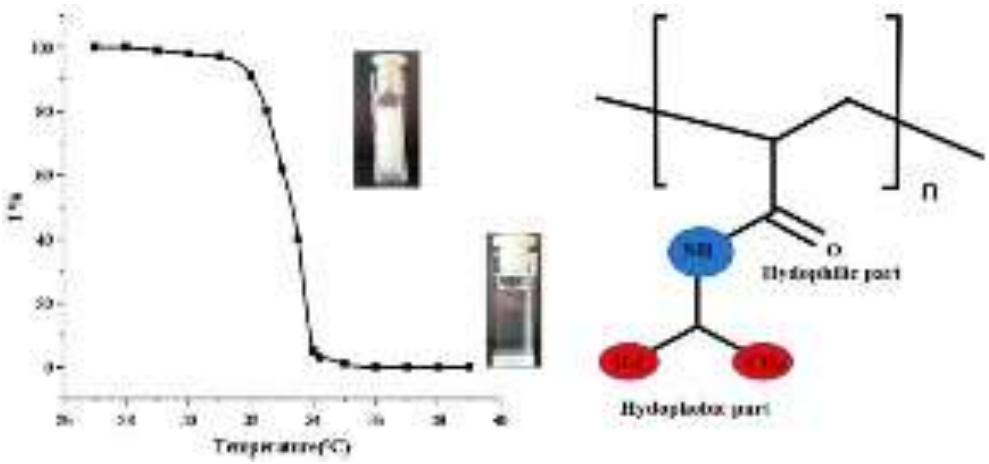

Fig 4. The structure of PNIPAM and its thermo-responsive phenomena.

The Flory–Huggins theory states that the change in free energy (ΔGm) of the polymer solution can be used to explain the phase transition behaviour of thermo-responsive polymers. The ΔGm value is negative when the temperature is either above the upper critical solution temperature (UCST) or below the lower critical solution temperature (LCST), meaning that the polymer is still dissolved. On the other hand, polymer precipitation results from ΔGm becoming positive when the temperature rises above the LCST or falls below the UCST. In order to create a thermodynamic map for thermo-responsive polymers in aqueous media, researchers created a coordinate system with enthalpy change (ΔHm) and entropy change (ΔSm) as perpendicular axes. In this illustration, the critical temperature (LCST or UCST) for that polymer system is represented by the slope (χΔHm/∂ΔSm) of a line that connects the origin to a particular point in the ΔHm–ΔSm plot. As a result, Tc = ΔHm / ΔSm is the mathematical expression for the critical temperature (Tc).

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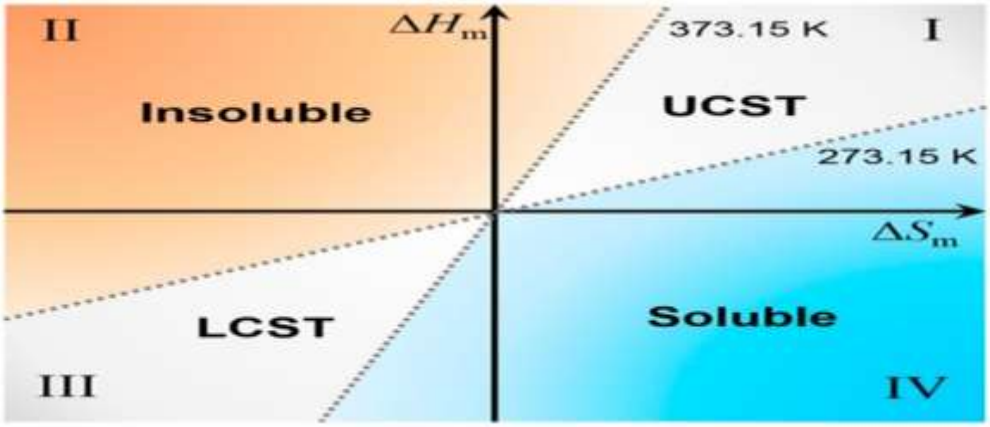

Fig 5. Map of thermodynamic parameters governing polymer behavior in aqueous environments

IV. DESIGN STRATEGIES FOR LOCALIZED THERAPY

- **Injectable In Situ Forming Systems:**

Injectable hydrogels reduce the need for invasive surgical procedures while allowing site-specific administration in the context of localized drug delivery. In which the hydrogel gelates upon injection into the tumor site to form a localized drug depot for sustained and controlled drug release, is usually used to achieve this injectability. In contrast to conventional hydrogels, in situ smart hydrogel systems can achieve both injectability and tunable drug release by dynamically changing their physicochemical characteristics, phase behaviour, swelling, or shrinkage, in response to internal or external stimuli, such as pH, temperature, light, enzymes, magnetic or electric fields. Promising options for localized cancer therapy because of their superior biocompatibility, low cytotoxicity, high drug-loading capacity, and controlled release performance (5).

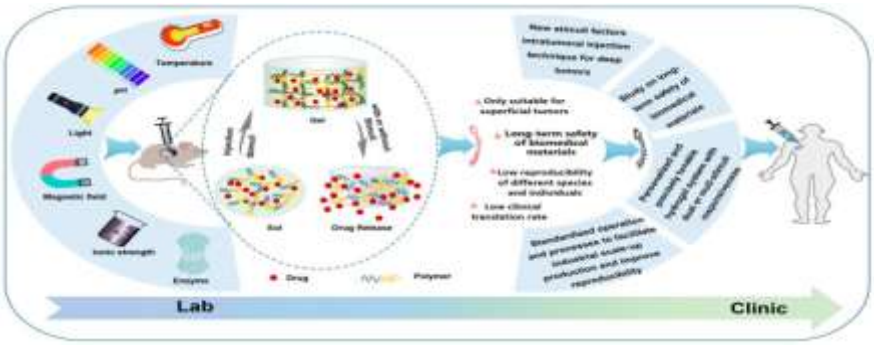

Fig 6. Overview of smart hydrogel generation and drug release pathways, along with current hurdles and future outlook

Implantable Devices and Depot Formulations :

Designed to release drugs directly into the bloodstream without the need for repeated needle insertions, implantable drug delivery systems (IDDSs) are inserted beneath the skin. . Surgical techniques, specialized implantation tools, or large-bore needles inserted into subcutaneous or intramuscular tissues are typically used for implantation. Because of their high fat content, which slows drug absorption, and their minimal innervation and good blood perfusion, which improve comfort and efficiency, these tissues are perfect for drug depot placement. IDDSs are especially useful for drugs that have inconsistent gastrointestinal absorption, cannot be taken orally, or benefit from localized delivery. Steroids, chemotherapeutic agents, antibiotics, analgesics, contraceptives, and biologics like insulin and heparin are common examples. (6)

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Formulation –

Implantable drug delivery systems (IDDSs) represent a significant area of advancement in modern medicine, aimed at providing controlled and sustained drug release within the body. These systems offer major benefits such as enhanced patient compliance, reduced dosing frequency, and minimized side effects. The formulation and development of IDDSs involve several critical steps:

•Drug Selection: The process begins with choosing an appropriate therapeutic agent based on factors like solubility, stability, and desired release profile.

•Polymer Selection: Biocompatible and biodegradable polymers—commonly PLGA (poly(lactic-co-glycolic acid))—are selected to encapsulate and protect the drug while regulating its release.

•Drug–Polymer Compatibility: Ensuring chemical and physical compatibility between the drug and polymer is essential to maintain drug stability and achieve predictable release behaviour.

•Formulation Design: The drug and polymer are combined using suitable methods such as solvent evaporation, hot-melt extrusion, or compression molding, depending on material properties.

•Controlled Release Mechanism: IDDSs can employ various release mechanisms, including diffusion-, erosion-, or osmotic-controlled systems, based on the therapeutic requirements.

•Biocompatibility and Safety Testing: Extensive testing ensures that the formulation is safe and does not provoke adverse biological reactions once implanted.

•Implantation Site Selection: The implantation site—subcutaneous, intramuscular, or intraocular—is chosen according to the drug's target and the desired therapeutic outcome.

• Release Kinetics Optimization: The drug release rate is fine-tuned by modifying polymer composition, implant size, or geometry to achieve the desired therapeutic effect.

• Quality Control and Manufacturing: Consistent production quality is maintained through strict quality assurance protocols to ensure safety and reproducibility.

• Regulatory Approval: Before clinical use, the system must undergo rigorous preclinical testing and meet regulatory standards set by health authorities.

• Post-Market Surveillance: Continuous monitoring after commercialization helps detect any long-term adverse effects or performance issues.(7)

• **Integration with Imaging and Theranostics-**

Noble metal nanoparticles have drawn a lot of attention lately; gold nanoparticles (Au NPs) stand out because of their useful applications in fields like drug delivery and imaging (Fig. 1). One of the earliest metals known to science, gold is naturally dense, bright yellow, and extremely malleable. Under normal circumstances, it remains solid. Its rarity, resistance to corrosion, and distinctive luster are all attributed to its low reactivity. Surface Plasmon Resonance (SPR) is one of AuNPs' most notable characteristics. This phenomenon happens when incoming light synchronizes with the oscillating frequency of surface electrons, creating a clear SPR band. The strong electromagnetic field that is created around the nanoparticles as a result of this interaction greatly improves their optical performance. The remarkable optical efficiency of AuNPs is demonstrated by the extinction coefficient linked to SPR, which can reach values as high as 10^{11} M^{-1} cm^{-1}, far exceeding that of most organic dyes. The anti-angiogenic activity of AuNPs is another notable characteristic that makes them potentially useful agents in cancer treatment. AuNPs contribute to the suppression of tumor growth and progression by obstructing the development of new blood vessels that supply tumors through mechanisms like extracellular matrix degradation and modulation of endothelial cell activation, proliferation, migration, and differentiation (8).

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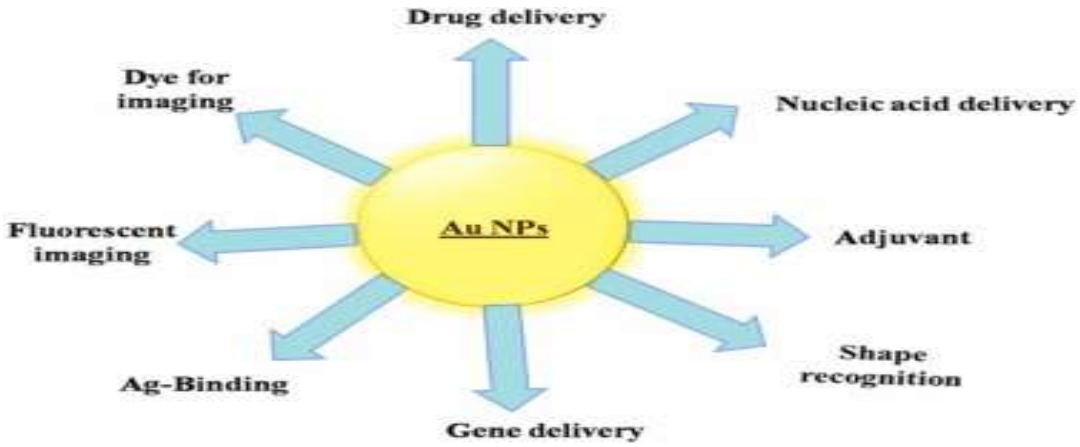

Fig. 7. Schematic showing the multifunctional roles of AuNPs in cancer management

V. PRECLINICAL AND CLINICAL APPLICATIONS-

• Oncology: Tumor targeted drug delivery system:

The ability of hyperthermia therapy to specifically kill cancerous cells with little damage to healthy tissue is one of its key advantages. Cancer cells are more susceptible to high temperatures because their dense, disorganized structures prevent them from dissipating heat. Because heating tumor cells above 42 °C makes them more vulnerable to radiation and chemotherapy, hyperthermia is a useful supplement to standard treatments. The therapy improves therapeutic drug delivery and penetration. However, in order to minimize side effects and maximize outcomes, the effectiveness of hyperthermia depends on variables like treatment temperature and exposure duration, which must be closely monitored. Treatments for hyperthermia fall into three categories: whole-body, regional, and localized. Regional hyperthermia targets larger or deeper tumors within particular organs or body regions [23], local hyperthermia targets accessible or surface-level tumors. Maintaining effective heat delivery while reducing energy loss is a significant challenge in this method. Ultrasound, infrared radiation, radiofrequency, and microwave energy are some of the current heat-generation techniques that can be used separately or in combination.

•Regenarative medicine and tissue engineering –

One promising method for creating functional tissues for biomedical applications is cell-sheet engineering. This technique uses hydrophobic materials like polystyrene dishes or elastomeric substrates to promote the formation of a continuous monolayer of cells. Functional tissue constructs can be made by separating these monolayers, also referred to as cell sheets, from the surface. Intact cell sheets can be recovered thanks to the precise control that thermoresponsive surfaces provide over cell adhesion and detachment. In 1990, a seminal study presented PNIPAAm-grafted culture substrates that react to temperature variations. PNIPAAm is hydrophobic and promotes cell adhesion at 37 °C (Figure 2A). Cell-cell junctions and cell-matrix interactions are harmed by conventional enzymatic methods of cell layer harvesting (Figure 2B). On the other hand, PNIPAAm becomes hydrophilic when the substrate is cooled to room temperature, causing cells to naturally separate without causing structural damage (Figure 2C). Cardiac, hepatic, skin, kidney, and corneal tissues have all been successfully engineered using cell sheets produced by this method.(9)

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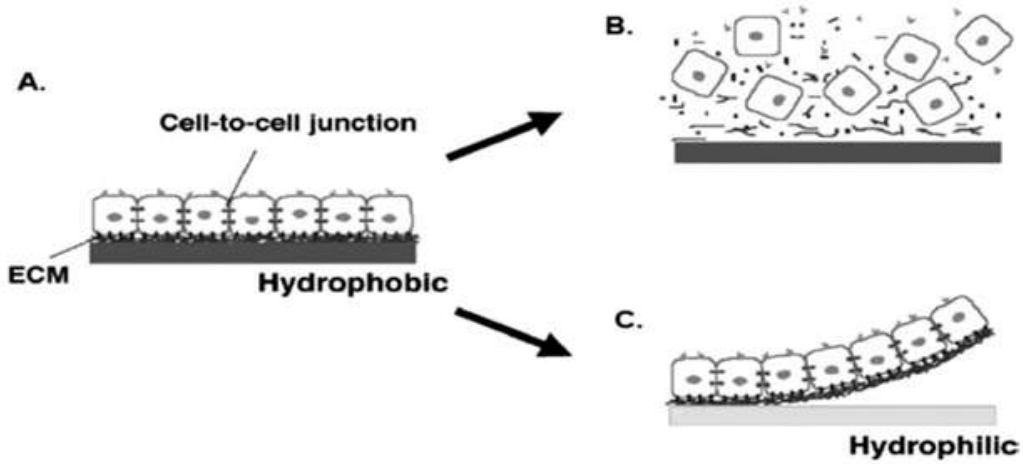

Fig. 8 Heat-controlled cell sheet adhesion and harvesting from 2-D surfaces

• Central nervous system and other sites specific therapies

• Cerebral neoplasms

Malignant glioma is the most malignant form of brain cancer in adults, known for its rapid progression and poor prognosis, with an average survival time of around 15 months . however, these approaches often fail to prevent tumour recurrence in nearby brain regions Furthermore, the lack of target specificity in conventional medications used in GBM therapy frequently leads to systemic toxicity and unfavorable side effects. In order to improve patient outcomes, alternative treatment methods have been investigated recently. Among these, thermoresponsive hydrogels have attracted a lot of attention because they can be injected directly into the surgical cavity after a tumor has been removed, enabling the localized and long-term delivery of therapeutic agents to the surrounding brain tissue.

• Spinal cord and brain injuries :

Furthermore, the lack of target specificity in conventional medications used in GBM therapy frequently leads to systemic toxicity and unfavorable side effects. In order to improve patient outcomes, alternative treatment methods have been investigated recently. Among these, thermoresponsive hydrogels have attracted a lot of attention because they can be injected directly into the surgical cavity after a tumour has been removed, enabling the localized and long-term delivery of therapeutic agents to the surrounding brain tissue. Dangerous and crippling condition, traumatic spinal cord injury (SCI) damages neural tissues, resulting in the loss of motor and sensory abilities . Decompression surgery, spinal stabilization, and rehabilitation are examples of current treatment approaches that frequently result in only modest neurological recovery, leaving many patients with permanent disabilities .Neural regeneration and functional restoration may be possible through strategies that deliver growth factors or encourage cell replacement at the site of injury . Traumatic brain injuries (TBI) can be treated using a similar approach.

• Neural degenerative disorders

Neurodegenerative disorders such as Alzheimer's dementia and Paralysis agitans are long-term, progressive conditions that impact millions of individuals globally . These diseases exhibit diverse pathological mechanisms and impaired movement and speech abilities all of which severely affect patients' quality of life. Current therapeutic approaches mainly focus on symptom management rather than disease reversal. However, drugs used to treat AD and PD often fail to achieve effective concentrations in the brain and require complex dosing schedules, resulting in poor patient compliance . In this regard, in situ thermoresponsive hydrogels hold great potential, as they can improve drug bioavailability at the targeted brain regions and reduce the frequency of administration, thereby addressing the limitations of conventional treatment methods.(10)

ADVANTAGES AND LIMITATIONS :

• CHALLENGES –

• SCALABILITY –

For instance, achieving nanoparticles with consistent size distribution and uniform drug-loading efficiency remains technically demanding and often depends on specialized equipment,

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including microfluidic systems and high-pressure homogenizers. Similarly, micro needle arrays face comparable difficulties, accurate microfabrication is both expensive challenging reproduce on a commercial scale without compromising product quality. Particularly when handling sensitive biological materials such as proteins or genetic payloads. Pharmaceutical manufacturers must also adhere to strict Good Manufacturing Practice (GMP) regulations to ensure product quality and consistency. To address these obstacles, researchers are developing innovative manufacturing approaches like continuous-flow synthesis and 3D printing, which offer the potential to enhance production efficiency, scalability, and cost-effectiveness.(11)

VI. CONCLUSION –

Thermoresponsive drug delivery systems offer a promising way to achieve precise and localized drug release using temperature-sensitive polymers. Their tunable behavior, biocompatibility, and ability to respond to multiple stimuli make them valuable for targeted therapies. While challenges such as biodegradability and clinical scalability remain, ongoing advances in polymer design and nanotechnology are steadily moving these systems toward more effective and personalized medical treatments.

REFERENCES :

[1]. Abuwatfa WH, Awad NS, Pitt WG, Husseini GA. Thermosensitive polymers and thermo-responsive liposomal drug delivery systems. Pharmaceutics. 2022;14(3):565.

[2]. Yuan Y, Raheja K, Milbrandt NB, Beilharz S, Tene S, Oshabaheebwa S, Gurkan UA, Samia ACS, Karayilan M. Thermoresponsive polymers with LCST transition: synthesis, characterization, and their impact on biomedical frontiers. RSC Adv. 2023;13(37):25481-25501.

[3]. Niskanen J, Tenhu H. How to manipulate the upper critical solution temperature (UCST)? Polym Chem. 2017;8:220-232. doi:10.1039/C6PY01612J.

[4]. Wang J, Liu L, Zhang S, Liao B, Zhao K, Li Y, Xu J, Chen L. Review of the perspectives and study of thermo-responsive polymer gels and applications in oil-based drilling fluids. Gels. 2023;9(12):969. doi:10.3390/gels9120969.

[5]. Zhao J, Wang L, Zhang H, Liao B, Li Y. Progress of research in in situ smart hydrogels for local antitumor therapy: a review. Pharmaceutics. 2022;14(10):2028. Doi:10.3390/pharmaceutics14102028.

[6]. E.M. Magill, A.T. Smith, Solid implantable devices for sustained drug delivery, Advanced Drug Delivery Reviews, 2023

[7]. Anusha A, Prameela K, Surya GV, Jaswanth B. Updated review on implantable drug delivery system. J EmergTechnolInnov Res. 2018;5(1):1-13.

[8]. Parthasarathy N, Karthikeyan L, Fabiola M, Vivek R. [Article title]. Next Nanotechnology. 2025;8:100212.

[9]. Yaramiri A, Abo Asalh R, Abo Asalh M, AlSawafatah N, Abuwatfa WH, Hussein GA. Moreira AF, editor. PMC (PubMed Central). PMID: 40806454.

[10]. Bellotti E, Schilling AL, Little SR, Decuzzi P. Journal of Controlled Release. 2021;329:16–35.

[11]. Pathak U, Vashishta V, Arora S. Novel drug delivery systems: advances & challenges. Int J Multidiscip Res. 2023;7(3):1–2.