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Review Article

PH-Dependent Polymer in Drug Delivery Systems

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ABSTRACT

pH-responsive polymers have emerged as a transformative class of smart materials in drug delivery systems due to their ability to undergo reversible physical and chemical changes in response to environmental pH variations. These polymers exhibit behaviours such as swelling, solubility modulation, and conformational transitions, enabling site-specific and controlled drug release. Their ionisable functional groups—typically weak acids or bases—allow for dynamic charge conversion, hydrophilic-hydrophobic balance shifts, and phase transitions that are crucial for targeting acidic microenvironments like tumours or intracellular compartments. Natural polymers such as alginate, chitosan, hyaluronic acid, and gelatine offer biocompatibility and biodegradability, while synthetic architectures like block copolymers, dendrimers, hydrogels, and micelles provide tenable responsiveness and structural versatility. Mechanisms such as PEG shielding/DE shielding, proton sponge effect, and acid-labile linker cleavage enhance cellular uptake, endosomal escape, and drug release. These systems are increasingly being engineered for dual stimuli-responsiveness, combining pH sensitivity with temperature, redox, or enzymatic triggers. Applications span from oral insulin delivery and cancer therapy to bio imaging and regenerative medicine. Despite promising in vitro results, clinical translation remains a challenge due to scalability, stability, and regulatory hurdles. Future research must focus on optimizing polymer architecture, enhancing biocompatibility, and integrating interdisciplinary approaches to fully realize the therapeutic potential of pH-sensitive polymer systems.

INTRODUCTION

Stimuli-responsive polymers exhibit a fast change in characteristics in response to a slight or modest change in external conditions, such as temperature, light, salt content, or pH. This behaviour can be used to create so-called' smart' medication delivery devices, which replicate biological response behavior to some extent. Stimulus-responsive

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materials in general, and pH-responsive polymers in particular, have grown in popularity during the previous two decades. Their unique properties, which stem from their ability to exhibit sharp and reversible changes in response to environmental pH conditions, have made them suitable for a wide range of applications, including drug delivery and specific body-site targeting, sensing and actuation, membrane functionalization, separation techniques, agriculture and food industry, and even chemical industries [1]

Polymers have the ability to undergo substantial physical or chemical changes in response to an external stimulus. Temperature and pH changes are frequently employed to cause behavioural changes, but additional stimuli, including as ultrasound, ionic strength, redox potential, electromagnetic radiation, and pharmacological or biological agents, can be utilized. These stimuli can be classified into separate physical or chemical categories [2]. Physical stimuli (such as temperature, ultrasound, light, magnetic and electrical fields) directly influence the energy level of the polymer/solvent system, causing a polymer response at a critical energy level. Chemical stimuli (such as pH, redox potential, ionic strength, and chemical agents) cause reaction by changing molecular interactions between polymer chains (affecting crosslink or backbone integrity, propensity for hydrophobic association, or electrostatic repulsion) or between polymer and solvent (modifying hydrophobic/hydrophilic balance) [2]. Changes in solubility, conformation, and the balance between hydrophilia and hydrophobia are examples of behavioural changes [3]. Numerous manifestations of these alterations include the swelling/DE swelling of covalently cross-linked hydrogels [5] and the coil-globule transition of polymer chains [4]. Sol-gel transition of physically cross linked hydrogels [6] and amphiphilic polymer self-assembly [7] (see color insert). In addition to reviewing current advancements in temperature and pH-responsive polymers, this part aims to provide light on the developing field of redox-responsive polymers for drug delivery systems. A brief overview of magnetically-triggered polymer Nano composites is also provided below. There are several top-notch reviews that cover these subjects in detail [2,3,8]

polymers is their capacity to react to an external stimulation by undergoing a significant physical or chemical change. In addition to the usual stimuli of temperature and pH changes, other stimuli that might cause behavioral changes include ultrasound, ionic strength, redox potential, electromagnetic radiation, and chemical or biological agents. Various physical or chemical categories can be used to categorize these stimuli [2]. At a certain critical energy level, physical stimuli (such as temperature, ultrasound, light, magnetic, and electrical fields) directly alter the energy level of the polymer/solvent system and cause a polymer reaction. pH, redox potential, ionic strength, and chemical agents are examples of chemical stimuli that cause a reaction by modifying the molecular interactions between polymer chains (affecting crosslink or backbone integrity, propensity for hydrophobic association, or electrostatic repulsion) or between polymer and solvent (changing hydrophobic/hydrophilic balance) [2]. Changes in solubility, hydrophilic-hydrophobic balance, and conformation are examples of behavioral change types [3]. Numerous manifestations of these alterations include the coil-globule transition of polymer chains [4], the swelling/DE swelling of hydrogels that are covalently cross-linked [5], the sol-gel transition of hydrogels that are physically cross linked [6], and the self-assembly of amphiphilic polymers [7], as shown in the color inset. In addition to reviewing current advancements in temperature and pH-responsive polymers, this part aims to provide

light on the developing field of redox-responsive polymers for drug delivery systems.

" Furthermore, a succinct overview of magnetically-triggered polymer Nano composites is provided below. A thorough examination of these subjects may be found in a number of outstanding reviews [2,3,8] It is feasible to make the medications release at a lower pH (lysosomal pH or the pH of the tumour microenvironment) and absorb them at physiological pH. [9] Body cavities' temperature, fluid pH, ionic concentration across the cellular membrane, tissue-specific enzymes, over-expression of particular receptors, and other characteristics give information about the body's distinct compartments, which enables the development of stimuli-specific polymers. The physical state and chemical structure of these polymers are significantly

Altered by changes in the ambient Ph [10,11]

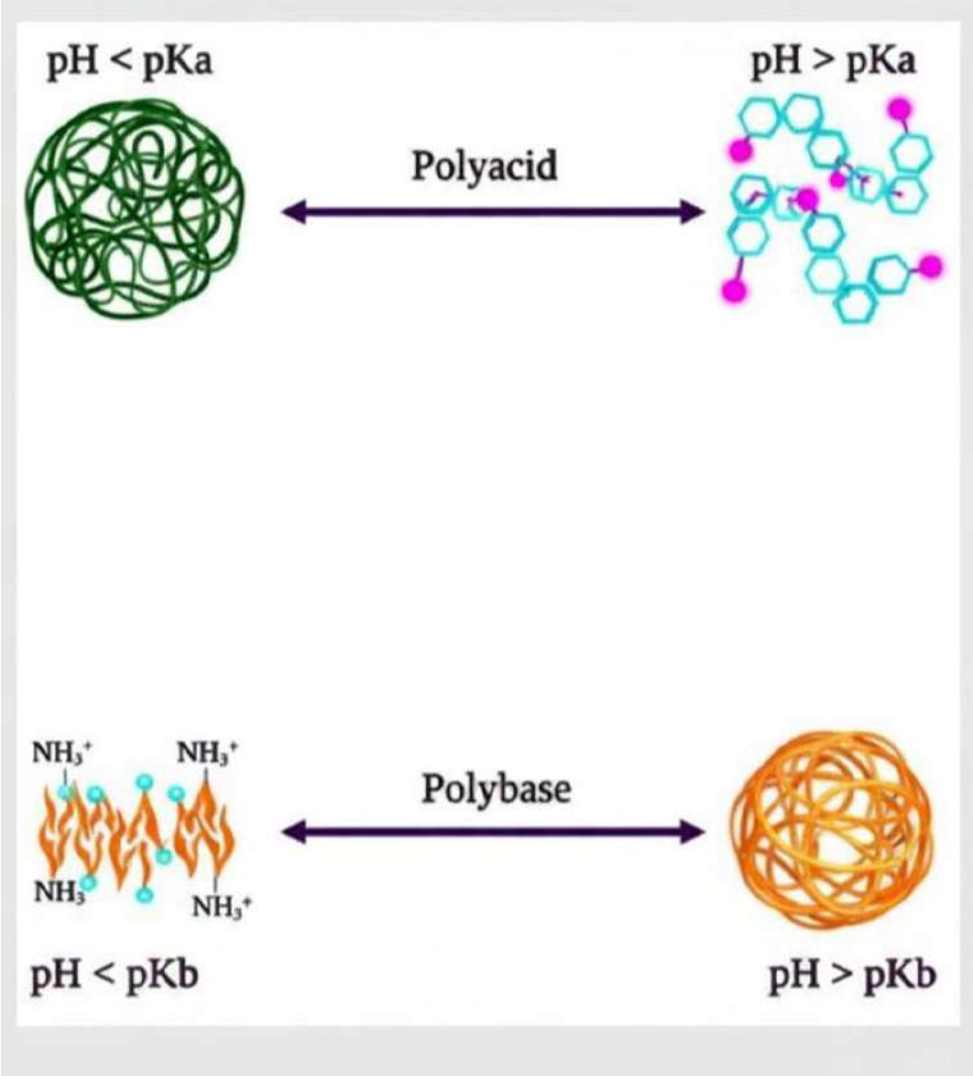
The Polymers Length Expand

pH < pKa

The Duration of Polymer Declines

pKa <pH

Figure: - Polymer Chain expansion Depends on pH and pka



Polyelectrolytes' structures contain either basic or acidic groups. At a certain pH, these polymers ionize, raising the surface charge of the polymeric chains. The solvent keeps the polymeric system from ionizing, which keeps the polymer chains folded and compact .In [12] The phase transition occurs when the polymer's functional groups ionize in response to a minor change in the surrounding pH (dissolution or swelling)

2. PROPERTIES:-

1. The Nature of Ionizability:- In pH-responsive polymers, protons can be donated or accepted by weakly basic (like -NH_2) or weakly acidic (like -COOH) functional groups, depending on the pH of the surrounding environment.

2. **pH-Controlled Ionisation**:- These polymers' degree of ionisation varies with the pH of the surrounding environment, changing their charge, conformation, and physical state.

3. **Reversible conformational change** :- Depending on whether they are protonated or deprotonated, these polymers have the ability to reversibly transition between expanded (swollen) and collapsed (compact) forms.

4. **Chain Expansion and Electrostatic Repulsion**: -The polymer chain expands and absorbs water (swelling) when it is ionized because the charged groups along its backbone resist one another.

5. **Hydrophobic Collapse in Unionized form:** - Hydrophobic interactions predominate in conditions that inhibit ionization (such as high pH for polybases or low pH for polyacids), causing the polymer to collapse into a compact or globular form.

6. **Solvent-Dependent Behaviours**:- The polymer's conformation is determined by the solvent's capacity to facilitate ionization; subpar solvents result in folding or precipitation.

7. **Controls Swelling Behaviours** :-When the pH rises, anionic polymers deprotonate, or swell. Protonation causes cationic polymers to expand at low pH.

8. **Reversibility of Swelling/Shrinking:** - Reversing the pH completely reverses the transition between swelled and collapsed states.

9. **Ionic Strength**: As ionic strength rises, the osmotic pressure differential between the gel and surrounding medium diminishes, causing pH-responsive hydrogels to expand less.

10. **Characteristic pKa or pKb** – The existence of a characteristic pKa or pKb indicates the pH range where ionization and conformational change take place. For example, PAA has a pKa of 4.25.

11. **Reversal Capability**: By varying the pH, the polymer's charge state may change from positive to neutral or negative and vice versa, allowing for dynamic charge management.

12. **Hydrophilicity/Hydrophobicity Balance**: In response to ionization, the polymer's hydrophilic or hydrophobic properties alter, impacting its solubility, water absorption, and interactions with biological molecules.

13. **Pressure Sensitivity:** The osmotic pressure differentials between the external solution and the polymer network caused by counter-ion distribution also contribute to swelling.

14. **Interfacial and Biological Responsiveness**: Variations in pH impact protein adsorption, cell attachment, and biocompatibility by changing the surface charge of polymers and their interactions with biomolecules.

15. **Capacity to generate pH-Responsive Hydrogels**: These polymers are appropriate for controlled drug delivery systems because they can generate hydrogels that swell or Deswell in response to pH.

16. **Environmentally Sensitive and Biocompatible**: They react to physiological pH changes (such as those in the stomach vs the intestine or the tumour microenvironment), which makes them perfect for biomedical applications

Example :-.

For instance, the carboxylic group in poly(acrylic acid) (PAA) becomes ionized at a certain pH (pK a 4.25), which is the dissociation constant (Fig. 3.2a). The chains experience electrostatic repulsion as a result, which can subsequently bond with water. to result in edema. Furthermore, the behavior of other polymers is inverse. [13,14]

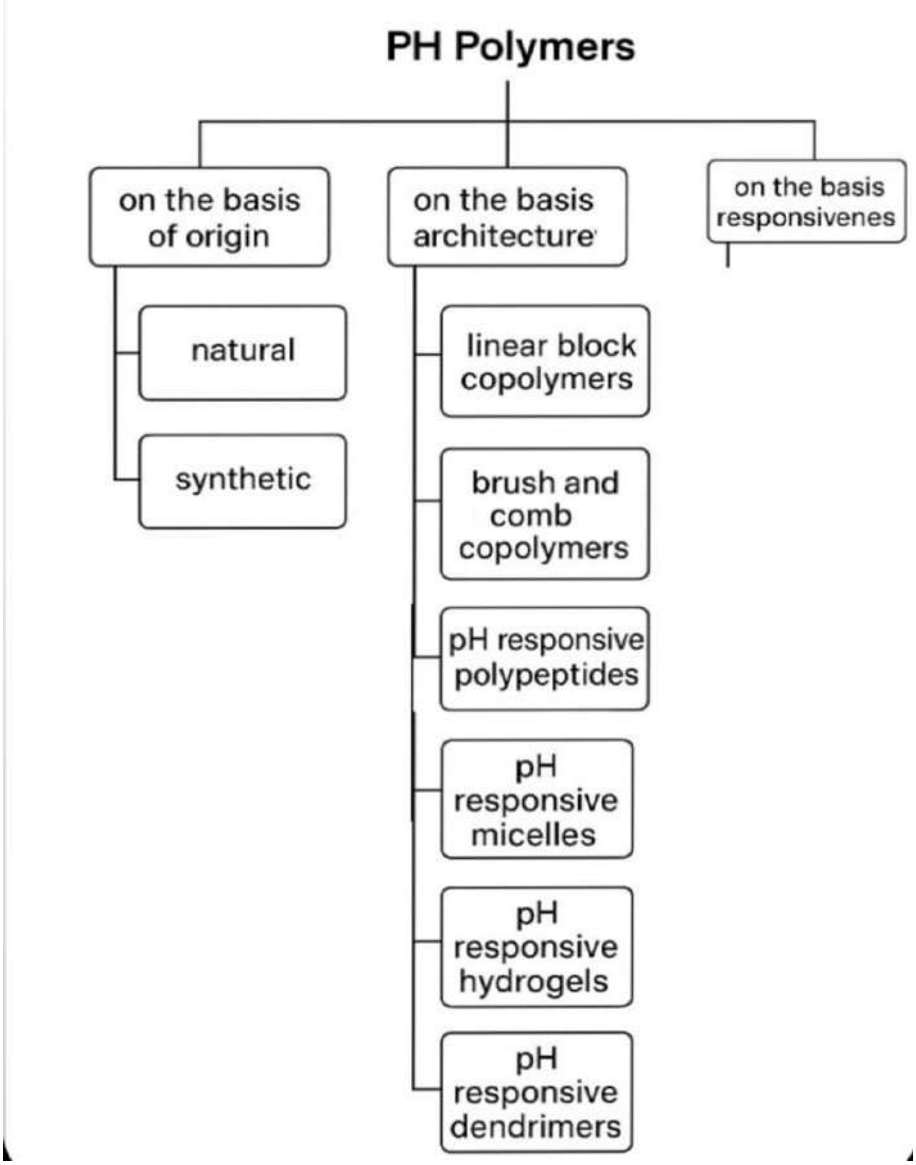
3.MECHANISMS :-

pH-Responsive Drug Delivery Mechanism Table

Phase / Location	Step in Cycle	Mechanism (Polymer Action)	Outcome	Reference
I. Surface Engagement	1. Charge Conversion	Surface Switch: The DDS surface flips from neutral/anionic to cationic as pH decreases toward 6.5.	Enhanced Cellular Uptake: Facilitates endocytosis by electrostatically attracting the negatively charged cell membrane.	[15]
II. Uncapping / Access	2. Shell Shedding / Nanovalves	Protective Layer Removal: Acidic environment cleaves the stabilizing polymer (e.g., PEG) linkers.	Exposure of Core: Increases lipophilicity for membrane interaction or uncaps drug release pores.	[16]
III. Intracellular Disassembly	3. Swelling / Solubility Change	Conformational Shift: Ionization causes polymer chain expansion (swelling) or rapid dissolution.	Pore Formation / Carrier Disintegration: Promotes faster diffusion and bulk drug release.	[17]
IV. Endosomal Escape	4. Proton Sponge Effect	Buffering Build-up: Proton accumulation inside the endosome triggers osmotic water influx.	Endosome Lysis: Ruptures the endosomal membrane, releasing the drug carrier into the cytoplasm.	[18]
V. Final Release	5. Acid-Labile	Covalent Breakage: Low pH hydrolyzes acid-	Terminal Drug Release: Active drug is released	[19]

	Linker Cleavage	labile bonds linking the drug or carrier components.	into the cytosol to reach its molecular target.	

4.CLASSIFICATION:-



4.1 ON THE BASIS OF ORIGIN: -

Both natural and manufactured polymers can react to pH. By copolymerizing natural monomers with acidic, basic, or hydrophobic groups, semisynthetic polymers with specific properties can be produced.

4.1.1 NATURAL POLYMERS

Since these polymers are easily chemically functionalized and can change their molecular weights and chain lengths, polymer scientists can produce derivatives of them that are better than the original ones. Because of their biocompatibility, low toxicity, biodegradability, and natural

abundance, they have proven to be the most effective pharmaceutical excipients. First

pH-responsive polymers can be natural or synthetic. Semisynthetic polymers with specified characteristics can be created by adding acidic, basic, or hydrophobic groups into monomers of natural origin and copolymerization among them.[20]

4.1.1.1 ALGINATE:-

One of the most often utilized polysaccharides is alginate, also known as sodium alginate. It comes from brown seaweed and is utilized in the food and medicine sectors. A block copolymer, alginate is composed of different combinations and ratios of (G)-D-mannuronic acid (M) and -L-glucuronic acid. It is an acidic polymer with carboxylic groups and a pKa of 3.2-2.22. Alginate is an excellent option for pharmaceutical applications due to its low cost, low toxicity, biocompatibility, and biodegradability. First (1)

A biopolymer called alginate is frequently used as a drug carrier; the pace at which medications are released from the polymer depends on how the pharmaceuticals interact with it. Sometimes the polymorphism character of the drug is changed by the chemical immobilization of the drug molecules to the backbone of the polymer. [21] There are several factors that affect how much alginate dissolves in water, including:
1. The medium's ionic strength affects the solution's characteristics, including viscosity, chain extension, and conformation solubility.
2. Because intermolecular hydrogen bonds prevent alginate from dissolving in any solvent when it is protonated, the solvent should have a pH higher than 3.0 to 3.5, where the carboxylic groups are ionized. As a result, the viscosity increases

3. Divalent ions (Ca2+ and Zn2+) are present in the solvent. [22]

4.1.1.2 CHITOSAN:-

Chitosan's chain has a large number of amino groups, which makes it a weak polybase that is sensitive to pH. Chitosan is rapidly dissolved at low pH values but insoluble at higher pH values. The optimal aqueous solution for dissolving chitosan is typically 1% glacial acid. [23]. When chitosan amine groups are protonated, the gel swells and undergoes proton, chain, and counter-ion diffusion with water. It has been demonstrated that chitosan improves the way medications pass through the mucosa of the mouth, nose, vagina, and gut. Chitosan microspheres have shown great promise in enhancing the oral or other mucosal distribution of bio-macromolecules such as proteins, peptides, plasmids, and oligonucleotides across biological surfaces. The degradation of chitosan in vivo has been shown to occur mostly due to enzymatic hydrolysis. A strong cytotoxic impact was produced by these microcapsules on the colorectal cancer cell lines HCT116 [24]. Site-specific pH-dependent drug delivery is being investigated using chitosan's physicochemical and biological properties, such as its low toxicity, biodegradability, superior film-forming ability, and biocompatibility. [25]

4.1.1.3 CARBOXYMETHYL CELLULOSE: -

Carbamethylcellulose (CMC) is an anionic cellulose derivative that is distinguished by the presence of carboxymethyl groups bound to the hydroxyl (OH) groups of the glucopyranose monomer. When CMC's carboxymethyl groups are ionized, the pKa is less than 4.3. CMC has hydrogel-forming properties and swells at a basic pH. Since the CMC-based hydrogel is non-toxic, biocompatible, and has good biodegradability, it also shows a dual response to pH and redox stimuli

through reversible sol–gel transitions. The development of matrix systems for medication delivery has been studied using CMC. It is possible to give cellulose a pH-responsive property by introducing carboxyl groups (COOH) into the polymer's structure by straightforward chemical changes. For example, the derivatives of cellulose phthalate are designed to manufacture desirable polymers with a pKa of 4.3 that include carboxyl groups. The hyaluronic acid D-glucuronic acid and N-acetyl-D-glucosamine monomer, which are coupled in (1–3) and (1–4), respectively, create the linear anionic polymer hyaluronic acid (HA). Glycoseaminoglycan (GAG) is a structurally non-sulfated molecule. Together with other GAGs, hyaluronic acid is thought to be necessary for cell growth and development as well as providing stability and shape to cells. HA has been used for drug delivery to cancerous cells that responds to two stimuli. [26] To increase the selectivity of nanoparticles made from HA copolymers, HA can be modified by additional moieties like glycyrrhetinic acid, specific ligands, and galactose. In comparison to conventional chemotherapy, this method massively improves drug accumulation in tumor cells while producing the least toxicity.[27] Han et al. developed a nanosystem by grafting HA with dodecylamine loaded with doxorubicin. This modified polymeric structure maintained its integrity in the alkaline systemic circulation, but an acidic tumor microenvironment stimulated drug release. Thus, the tissue-specific release of the drug was reported with lower off-target effects of doxorubicinHA, due to its unique chemical structure, has been crosslinked with various other polymers to produce dual stimuli-responsive systems for drug delivery at target sites.. The pH-responsive nanoparticles protected the insulin from the acidic environment of the stomach and mucoadhesive nature of nanoparticles aided the small intestinal absorption of insulin.[28] nonetheless, drug release was promoted by an acidic tumor microenvironment in the alkaline systemic circulation. As a result, tissue-specific drug release was documented with less off-target effects. Because of its distinct chemical structure, doxorubicin has been crosslinked with a number of other polymers to create dual stimuli-responsive systems for drug delivery at specific locations. The insulin was shielded from the stomach's acidic environment by the pH-responsive nanoparticles, and the mucoadhesive properties of the particles facilitated insulin absorption in the small intestine. [28]

4.1.1.4 GELATIN:-

A natural polymer called gelatin is utilized as a building block to create polymeric networks that will transport medications. [29] Gelatin's amphoteric nature allows it to mix with both cationic and anionic chemical compounds. [30]. The free amino and carboxyl groups, together with the side polymer chain, can regulate the chemically reactive behavior of gelatin. The physical and mechanical characteristics of the gels, as well as the viscosity of the solutions, are determined by the crosslinking of gelatin macromolecules. Collagenous tissues are exposed to acidic chemical agents such as hydrochloric acid, sulfuric acid, and others to produce type-A gelatin; colloidal tissues are exposed to alkaline solutions to produce type-B gelatin. [31] .Gelatin is regarded as a derived protein since it is not found naturally and is made from collagen protein by partially hydrolyzing animal corpses under controlled circumstances. A lot of people use it to make capsule shells. [32] Depending on whether gelatin is acidic or basic, gelatin hydrogel may swell at both basic and acidic pH values. Although gelatin is easily dissolved in water, it has a low fluid stability. This has led to the use of crosslinkers such as glutaraldehyde and epichlorohydrin for gelatin-based biomaterials.

Cross-linked gelatin's use may be prohibited in many pharmaceutical, biomedical, and main food product packaging applications due to its severe toxicity. Lai created hydrogels to transport medications to the eyes.

This formulation for the treatment of inflammatory bowel illness is said to protect curcumin from the gastrointestinal environment and guarantee colon-specific release. Furthermore, because gelatin has a great propensity to form films, hydrogel formulations have been investigated for use on the mucosal surfaces of bodily organs. Lai et al. developed gelatin-glutathione hydrogel drops filled with pilocarpine to treat glaucoma. Poly(N-isopropylacrylamide) was coupled with gelatin, and glutathione was then free-radical grafted.

4.1.1.5 XANTHUM: -

Xanthum gum is made by fermenting carbohydrates by the bacterium Xanthomonas campestris. The structure of xanthum is composed of D-glucose (linked by 1,4-glycosidic linkage), a trisaccharide branch on successive glucose units of the framework of D-glucose, D-mannose, and D-glucuronic acid in a 2:1:1 ratio, joined by 1,3-glycosidic connections. [32]. With a carboxyl group on one of the side chains of glucuronic acid, xanthan is an anionic polymer. Because the carboxylic groups on the side chains of xanthum completely ionize after a change in the ambient pH, it is pH-sensitive. These conjugates have properties including inertness, biocompatibility, effective solubility, and resistance to enzyme breakdown. In a simple setting, it exhibits notable swelling. [33].

The carboxylic acid group is neutral and unionized below its pKa value of 4.6, and ionized and negatively charged above it, which causes swelling. [26] Thus, it may be loaded with pharmaceuticals and employed as a pH-responsive hydrogel to target the gut (pH 7.4) for a controlled release of medications. [34] For example, xanthum-acrylic acid/MgO nanocomposite hydrogel loaded with methotrexate was developed by El-Sawy et al. Methotrexate is released at the right pH for the colon since it was found that the drug release mechanism is non-fickian at pH 7. [35]

4.1.2 pH-*RESPONSIVE SYNTHETIC POLYMERS* :-

Although natural polymers have garnered a lot of attention because of their accessibility, biocompatibility, degradability, and versatility, synthetic pH-responsive polymers are likewise accessible and have a range of applications. One of the most popular methods for creating these polyelectrolytes is atom transfer radical polymerization.

The third is emulsion polymerization. Polymerization by group transfer. regulated polymerization of radicals.[36]. The majority of pH-responsive polyelectrolytes are made using batch emulsion polymerization. This method uses water-soluble initiators such ammonium persulfate or potassium persulfate. In the industrial environment, the semi-batch emulsion polymerization technique has been used to create latexes with a high solid content. To create well-defined core-shell nanoparticles, seeded semi-batch emulsion polymerization under monomer-starved feeding circumstances can be used. For instance, copolymers have a propensity to self-assemble in solutions, forming aggregates or coacervates of various sizes and shapes. As the pH changes, the surface properties of hydrogels and microgels will also vary in size.

4.2 CLASSIFICATION ON THE BASIS OF ARCHITECTURE:-

Polyelectrolytes are capable of self-assembly. Exposure to a certain pH causes structural changes in them, including changes in surface activity, chain conformation, and solubility. Amphiphilic, linear homopolymers, and double hydrophilic block copolymers are the classifications for these polymers. [37] .Depending on the pH, they can produce Dendrimers, micelles or vesicles, polymer brushes, branched and hyper-branched polymers, Nano gels, stars, and hydrogels. For drug delivery, biocompatible polymeric materials with diameters less than 100 nm are considered to be beneficial. .[38]

4.2.1 *pH RESPONSIVE LINEAR BLOCK COPOLYMERS*

Biocompatible polymeric materials less than 100 nm in diameter are needed for biological applications. When self-assembled, block amphiphilic copolymers create micellar structures that resemble microspheres in solution and are sensitive to stimuli. [39] Amphiphilic block copolymer chains with various ionizable groups enable their regions to adjust to variations in the aquatic environment.
There are several self-assembly topologies that arise depending on the environmental conditions. [40]

4.2.2 *pH RESPONSIVE BRUSH AND COMB COPOLYMERS*

When polymeric chains—which resemble hair—are affixed to a surface or interface, the brushes and combs are said to be pH-responsive. [41] The most common method for attaching polymer brushes to substrate surfaces is covalent bonding. The degree of ionization is significantly influenced by the pKa values of the weakly acidic or basic groups found in these brushes. [42] Variations in osmotic pressure caused by mobile counter-ions cause a substantial shift in the total volume of polymer chains when the net charge of related functional groups varies quickly [43]. The brushes of Poly(2-(methacryloyloxy)-ethyl-trimethylammonium chloride) (PMAETMA) may be made for nanolithography and bio-mineralization by using Cl− as counter-ions. [44] The brushes of Poly(2-(methacryloyloxy)-ethyl-trimethylammonium chloride) (PMAETMA) may be made for nanolithography and bio-mineralization by using Cl− as counter-ions. [42] Brush copolymer drug conjugates were created by TT et al. utilizing the ring-opening metathesis copolymerization (ROMCP) technique for acid-triggered drug release. The accumulation of anticancer medications in the tumor microenvironment (acidic) can be enhanced by these systems through increased permeability and retention. [45]

4.2.3 pH RESPONSIVE HYDROGELS

Hydrogels are networks of polymeric fibers that do not dissolve in water at normal pH and temperature conditions. Acid-base-labile links or acidic/basic groups are found in pH-sensitive hydrogels. [40] These systems have the capacity to absorb water at rates ranging from 10% to 20% to hundreds of times their dry weight and volume. [46]
A chain's acidic groups deprotonate at high pH values, while its basic groups protonate at low pH values. This is what causes pH-induced swelling and de-swelling. pH-dependent swelling and de-swelling result from ionization, which creates a charge on polymer chains when water is drawn in or extended from the hydrogel network. Chitosan is a cationic hydrogel, whereas calcium alginate is an anionic hydrogel. [47] Xu et al. have provided a thorough analysis of pH-responsive hydrogels for more reading. [45] Since retention time is the main problem with ocular medication administration, making hydrogel contact lenses or films to improve drug interaction and corneal penetration

suits the goal. In order to treat dry eye condition, Eudragit S created 100 contact lenses that were filled with cyclosporine. . Being a derivative of methacrylate, Eudragit S 100 often has a transition pH over 7, which is comparable to the pH of lachrymal fluid. Using a quasi-emulsion solvent diffusion approach, the medication (cyclosporine) was put into Eudragit lenses after being encapsulated into nanoparticles. According to in vivo research conducted on rabbits, the contact lenses maintained the medication release for up to 14 days without showing any signs of cytotoxicity [48].

4.2.4 *pH - RESPONSIVE STAR COPOLYMERS*

Numerous linear chains are joined to a central core and interlocked in star polymers. Self-assembled micellar structures are formed when pH-responsive star polymers with block/arm topologies undergo fast phase transitions in response to changes in the surrounding pH. The star polymers created with these synthetic methods show significant limitations on the number of suitable monomers that can be integrated into the macromolecule due to the challenging synthetic experimental processes. [49] Consequently, their potential for usage in a variety of applications can be compromised. One of the easier and more popular methods for creating star copolymers is cationic and anionic copolymerization. [50] Branched polymers like dendrites, highly branched, hyper-branched, and multi-branched structures may also be seen in pH-responsive star polymers. When creating star copolymers, poly (acrylic acid) is the preferred polymer. [51]Adhesive polymers can be used to improve the arms of star copolymeric structures' adherence to tissues, improving medication targeting. To serve as a kind of perimeter for the cell-adhesive poly(ethylene oxide) (PEO) star polymer, GRGDS (Gly-Arg-Gly-Asp-Ser) segments were built. The cell-adhesive properties of star polymers were demonstrated by co-cultivating them with MC3T3.E1 cells. GRGDS's ligand-binding star polymers showed promise as a practical means of enhancing substrate-cell interactions. [52]

4.2.5 *pH -RESPONSIVE DENDRIMERS*

Because dendrimers have the unique dual characteristics of ultrasoft colloids and structured polymers, they might be used in a number of biological applications, including drug administration, gene therapy, and MRI imaging. [53]. The drug's penetration and retention qualities are enhanced by these substances. Using pH-responsive biodegradable linkers to directly conjugate the drug molecules to the dendritic backbone is another method for creating pH-responsive drug delivery systems. [53]. One of their primary characteristics that appeals to pH-responsive medication delivery is their capacity to dissolve in water. Certain dendrimers need to be modified to provide a variety of functionalities based on the needs. [54] Although dendrimers are very good, their widths of less than 15 nm make a number of application procedures challenging. Poly (propyleneimine) (PPI) and poly (amidoamine) (PAMAM) are pH-responsive polymers that have been thoroughly researched for their potential application as dendrimers.[55,56] .Zhang and colleagues synthesized partly acetylated PAMAM dendrimers coupled with doxorubicin-conjugated folic acid, along with an additional pH-sensitive cis-aconityl linker. In vitro tests on KB-LFAR and KB-HFAR cells verified that this acid-responsive nano system delivered the medication in an acidic tumor microenvironment. [57]

4.2.6 *pH - RESPONSIVE MICELLES*

Micelles are nanoscopic structures that consist of a core and a shell. Amphiphilic block copolymers self-assemble in aqueous circumstances above the critical micelle concentration (CMC) to create them. [58] Water solubility and steric stability are primarily the responsibility of the hydrophilic shell, whereas the hydrophobic domain serves as a reservoir and safeguards the medicinal substance. [59]

Micelles have limited practical applicability due to their structural instability. Ionic strength, temperature, pH, and dilution in bodily fluids are physiological conditions that might cause micelles to break down. [60].

4.2.7 *pH- RESPONSIVE POLYPEPTIDES*

In contrast to pH-sensitive small molecule electrolytes, polypeptides provide a broad platform for precise drug administration at the target region and structural changes. Whether cationic or anionic, these polypeptides are made from a particular sequence of amino acids that exhibit extremely abrupt pH-dependent changes when applied to biological fluids. [61]. Research has shown that these pH-responsive polypeptides are more biocompatible and biodegradable as medication carriers since they mimic the body's own proteinous backbone. In [62] These peptides engage in interactions with the target cells' membrane proteins, which helps endocytic processes internalize nanocarriers. For example, short histidine-rich peptides and histidine and aspartate dipeptides are frequently employed to transport drugs to the acidic microenvironment of cancer tissues in a pH-dependent manner. [63]In order to maximize the specific pH-responsive characteristics of polypeptides, they are often crosslinked with other polymers such as allyl glycidyl ether, polyethylene glycol, chitosan, and so on. Zheng et al. created chitosan nanoparticles loaded with 5-fluorouracil and poly-aspartic acid (PAsp) sodium salt using a mixing and absorption technique. Comparing the produced nanocarrier system to the PK characteristics of freely supplied 5-fluorouracil, the in vivo pharmacokinetic investigations showed that the medication was delivered to the target location in a sustained way while increasing the areas under the curve. [64] Nanocarriers have the potential to be employed as theranostics through the coupling of contrast agents with polypeptides. Because of their biocompatibility, these polypeptides allow contrast-imaging agents to penetrate with minimal harm and improve the image of deep-seated malignancies. [65]Yamei Liu and colleagues synthesized self-assembled peptide nanoparticles of genipin and diphenyl-alanine for nematode hyperspectral imaging. Enhanced dark-field hyperspectral imaging was used to identify the fluorescent signals produced by the peptides' self-functionalization processes inside the human tissues at acidic pH.[66]Sonaje and colleagues created a pH-responsive self-assembled poly (γ-glutamic acid) and chitosan loaded with Asp-Insulin for oral administration in order to analyze the biodistribution of the protein. The intestinal absorption and biodistribution was studied in rat using single-photon emission tandem computed tomography. The produced formulation showed a reasonable blood glucose lowering effect, and the pharmacokinetics and biodistribution of oral as well as subcutaneously injected asp-insulin were found to be similar [67]

4.2.8 *pH- RESPONSIVE VESICLES*

In the presence of water, amphiphilic building components self-assemble to form highly structured assemblies called vesicles. They are categorized as polymersomes, bilosomes, niosomes, and liposomes. [68] Particularly for poorly soluble medications, the phagocytic absorption of drug-loaded vesicular delivery systems enhances

bioavailability and decreases drug toxicity. [69]. Additionally, the use of vesicular medication delivery can lower therapeutic costs. A pH-responsive vesicular delays the elimination of rapidly bio-transformed medications by acting as a prolonged release mechanism. [70]. A popular method for creating the polymeric vesicle's shell is MPEG-b-PHIS. [71]

5.METHADOLOGY: -

5.1 EMULSION POLYMERIZATION: -

common synthesis pathways for producing vinyl-based pH-responsive polymers in advance, particularly microgel platforms Water, a water-soluble initiator, a surfactant (emulsifier), and one or more monomers make up the majority of emulsion polymerization systems. Solid particles can develop either before or after the polymerization reaction ends when phase separation occurs. One alternative method is surfactant-free emulsion polymerization, which is distinguished by the lack of additional emulsifier (Rao and Geckeler, 2011) [72]. Well-defined core-shell nanoparticles may be created using this type of emulsion polymerization. Initially, the PMMA core was created using a traditional seeded emulsion. polymerization, followed by the gradual introduction of pre-emulsified monomers and modest quantities of initiator under monomer-starved feeding conditions to develop the pH-responsive shell layer. Such latex is swellable at low pH because amino segments are protonated, unlike the PMAA or PAA system. Additionally, core-shell hybrid materials including an inorganic component have been created via emulsion core polymerization.

5.1.1.MINI- EMULSION POLYMERIZATION

The following ingredients are often employed in mini-emulsion polymerization: water, monomer mixture, co-stabilizer, surfactant, and initiator. The use of a low molecular mass substance as the co-stabilizer and a high-shear device are the two main distinctions between emulsion polymerization and mini-emulsion polymerization. With different combinations of initiators and co-stabilizers, versatile particles have been created (Baruch-Sharon and Margel, 2010)[73]. These combinations have a significant impact on the type and formation of the NPs that were employed. (Jiang and others, 2010) [74]. Kriwet and colleagues produced PAA NPs (Kriwet et al., Tween 80). The size of the particles depended on the type of radical initiator employed, and free radicals started the polymerization. Water-soluble initiators are used toMicroparticles were produced using a co-emulsifier system that contained a combination of Span 80 and between 80 and 150 nm when lipophilic radical initiators, including AIBN, were used. However, NPs were produced nearly predominantly with a diameter of 1998)[75].

5.1.2 MICRO -EMULSION POLYMERIZATION

In contrast to micro-emulsion polymerization, which only shows two reaction rate intervals, emulsion polymerization displays three. Micro-emulsion polymerization results in significantly smaller particles in terms of both size and average number of chains per particle. Usually soluble in water, an initiator is used in micro-emulsion polymerization.

is added to a thermodynamically stable micro-emulsion with inflated micelles in its aqueous phase. The polymerization process begins in this spontaneously generated, thermodynamically stable state and depends on large amounts of surfactant complexes, which have an interfacial tension near zero at the oil/water contact.

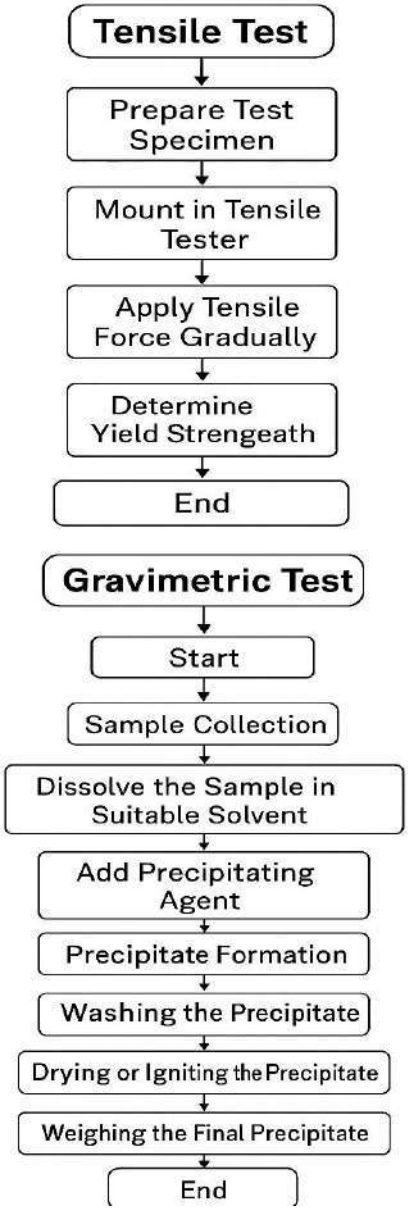
Additionally, a large amount of surfactant is used, which results in the particles being entirely covered in it. At first, only a small percentage of droplets form polymer chains since the initiation cannot be achieved simultaneously in all microdroplets. After a while, the chains' osmotic and elastic influence highlights the delicate micro-emulsions and usually causes secondary nucleation, empty micelle production, and a rise in particle size.

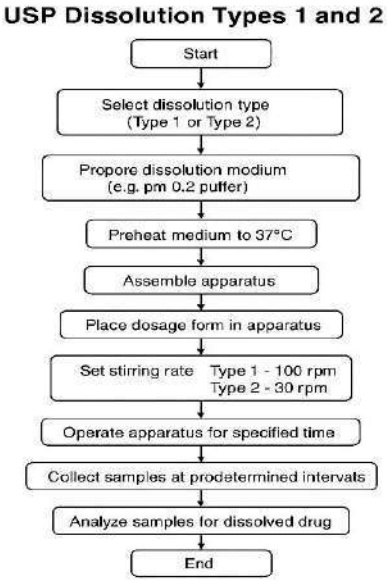
6.EVALUATION PARAMETER: -

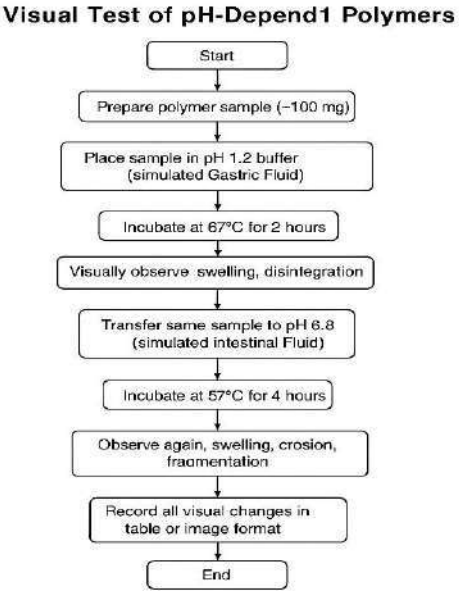
Polymer Characterization Parameters in Drug Delivery[77,78]

Serial number	Parameter	Purpose
01	Solubility	Determines polymer solubility at various pH (stomach, intestine, colon)
02	Drug Release Studies	Evaluates drug release pattern from dosage form
03	Swelling Index	Measures swelling behavior which affects drug diffusion
04	Mechanical Properties	Assesses film strength and flexibility
05	Mucoadhesion Studies	Measures polymer's ability to adhere to mucosal lining
06	Thermal Analysis	Determines thermal behavior and stability
07	FTIR/XRD/DSC Compatibility	Assesses interaction with drug, crystalline/amorphous nature
08	Morphology Study	Analyzes surface structure and porosity
09	Stability Testing	Evaluates long-term stability of formulation

6.1 FLOWCHART:-







7. APPLICATION: -

pH-responsive polymers and drug delivery systems: The human body is made to exhibit a wide range of pH values (table 4). This pH range can be used to tailor medications or treatments to a certain organ, bodily part, or location.

- pH readings from various tissues and cell compartments are shown in Table 4.

Cell / tissue compartment	pH
Tumor – extracellular medium	6.2 – 7.2
Golgi complex	6.4
Colon	7.0 – 7.5
Lysosome	4.5 – 5.0
Duodenum	4.8 – 4.2
Stomach	1.0 – 3.0
Blood	7.4 – 7.5

The best pharmaceutical systems, which are pH-sensitive polymers, use these circumstances to transport medications to certain organs, such as the colon [79]. Enteric polymers are frequently utilized because they hold up well in an acidic environment (the stomach's low pH) and release the medication in the intestine's alkaline medium through the production of salt. Numerous such polymers are

already made commercially and are in great demand, such as CAP from Wako Pure Chemicals Ltd., Eudragil-L and Eudragit-S from Rohm Pharma, GmBH (modification of methacrylic acid and methyl methacrylate), or CMEC from Freund Sangyo Co. Ltd., HP-50, and Shin-Etsu Chemical Co. Ltd.'s ASM (cellulose derivative). Numerous polysaccharides have also been investigated, and the findings are becoming more and more promising. Examples of polysaccharides that have been tested include cyclodextrin, chondroitin sulfate, dextran, amylose, guar gum, pectin, chitosan, and inulin [80,81]. Research and experimentation by Mishra [82,83] have shown that HPMC-AS and Eudragit-P4135 F can be made into nanoparticles that have an acidic resistance or enteric coating feature that guarantees drug delivery to a specific colon. Mishra attempted to formulate metoprolol succinate using HPMC-AS and Eudragit-P4135 F, which produced pH-sensitive nanoparticles that might be utilized as a colon-specific targeted drug delivery method. The use of pH-sensitive polymers in various formulations can help transport medications, proteins, peptides, etc. to a particular location. Different pH-responsive polymers can be used to create pharmaceutical compounds that are degraded or have very little absorption in the acidic environment of the stomach and intestines but are preferred by the mild conditions of the colon. These kinds of formulations may be helpful for systemic delivery and local colon diseases. Aside from the intended delivery, It has been demonstrated that pH-sensitive polymers, such as Thermocoat L30D55, may protect items against environmental elements including light, humidity, and temperature, extending their shelf life. Using Thermocoat L30D55, PH-regulated Tulsion microspheres that target medication delivery in the colon are created. The quasi-emulsion spherical crystallization process was used to create microspheres with a combined release mechanism. The two main contributing aspects to drug release were pH-dependent release and the polymer's particular biodegradability [82,84].

- **GENE CARRIER:-**

The use of pH-sensitive polymers as non-viral gene carriers is hopeful since naked DNA is difficult to incorporate into cells due to its negative charge and size under physiological circumstances. In order to transfer genes, DNA must condense into charge-balanced nanoparticles, which is made possible by gene delivery techniques that involve chemical assistance. There are two main varieties: polycation and liposome. According to Godbey and Mikos' review [80,84], poly (L-lysine) (PLL) and poly (ethylenimine) (PEI) are the best candidates for non-viral gene delivery. PEI is a highly polycationic (synthetic) polymer that creates complexes by condensing DNA in solution, which may be readily absorbed by a variety of cell types by endocytosis. Chitosan, a biocompatible and resorbable cationic amino polysaccharide, has also been widely employed as a DNAcarrier,previouslydescribed [85,86] . The molecular machinery of some viruses and pathogens has been the subject of amazing efforts by Hoffman's lab, which has also successfully obtained unique targeted structures to stimulate biomolecules to specific intracellular regions. The endosomal layer becomes unstable and more vulnerable to destruction when the molecular machine detects changes in the pH gradient of the endosomal area. Transport of the upgraded protein or DNA from intracellular locations, such as the endosome, to the cytoplasm is conducted out [87,88]using this method. A further easily accessible method is the grafting of a pH-responsive polymer (cationic) onto a lipidic double-layered system (liposome), which contains the DNA molecules as part of its internal system. DNA is compressed to

create nanoparticles with a diameter of around 100 nm while the balance of its negative charges is preserved by cationic polymers. In contrast to cationic polymers, anionic polymers increase the efficiency of DNA molecules by a different process. One hallmark of anionic polymers is their ability to change from a hydrophilic state to a hydrophobic or lipophilic state, which causes instability and rupture of the endosome layer [79,89]. The particle created by the physical or chemical combination of anionic polymers and DNA is joined by an extra cationic polymer to improve the condensation of the nucleic acid molecules. By entering the specific cells by endocytosis, the generated particles transform into a lipophilic condition, which ruptures the endosome layer and releases the content. Anionic polymers PEAA (polypropyl acrylic acid) and PPAA (polypropyl acrylic acid) combine to create nanoparticles that facilitate DNA transfection and improve formulation stability. The two types of polypropyl acrylic acid (PPAA) and polyethylene acrylic acid (PEAA) are the pH-sensitive polymers that transport genes. PPAA and PEAA have increased haemolytic activity at pH 7.4 but do not cause any blood cell abnormalities when the pH drops to a value between 5 and 6 [79,89,80]. In order to create a macromolecule and facilitate DNA condensation, they combine hydroxyproline (found in collagen, gelatin, and other peptides) with a biodegradable polycationic polyester polymer called poly (trans-4-hydroxy-L-proline ester) to enable gene transfection into mammal cells [79,90]. Combining doxorubicin with the copolymer poly (ethylene glycol)-poly (aspartame-hydrazine-doxorubicin) [(PEG-p (Asp-Hid-Dox)] resulted in pH-sensitive polymeric micelles. When the pH dropped below 6, the medication was released by this experimental formulation; nevertheless, drug and gene retention was noted at physiological

- GLUCOSE- RESPONSIVE POLYMER FOR DRUG DELIVERY

Creating an insulin delivery method or system to treat diabetic patients is a common use for pH-sensitive polymers . Insulin distribution is more challenging than that of other medications since it must be administered precisely when needed. A pharmaceutical approach for the administration of insulin was developed by studying the enzyme glucose oxidase and creating pH-responsive polymers that establish a covalent link with the enzyme [79,91]. The following is the mechanism in this pharmacological system that causes the release of insulin: A pH shift brought on by the oxidation of glucose by glucose oxidase results in the creation of glucuronic acid, which causes the pH-sensitive hydrogel to expand and releasing insulin. The process involves the use of pH-sensitive polycationic polymers, such as poly (2-diethylaminoethyl methacrylate) (PDEAEMA), which increase the permeability of the membrane and make it easier to administer insulin by lowering the medium's pH [79,92]. This increase in permeability is caused by ionization of the polymer in an acidic environment. did not release any drugs into the stomach because they were insoluble at acidic pH levels. The low molecular weight hydrophilic polymer beads showed a hump-like profile at normal body temperature and pH 7.4, which led to their dissolution in two hours (bead dissolution – controlled release mechanism). In contrast, the hydrophilic macromolecular polymeric beads expanded and sustainably delivered insulin for eight hours. Similar to the hydrogel-based PCO2 sensor, the use [93]of pH-sensitive hydrogel for the sensor may be extended by adding an intermediary phase where an analyte is converted into a material that fluctuates in pH. The CO2 gas released in this pharmacological system causes carbonic acid to develop in the water. As a result, the pH of the system fluctuates,

which in turn affects the volume of HGs that are sensitive to pH [94].

- **Chromatographic Studies:-**

In addition to medication delivery, purification and separation technologies can benefit from the use of pH-responsive polymers. Different compounds, such as proteins, enzymes, and peptides, can be separated using chromatographic devices. Because pH-responsive polymers have alkaline or acidic groups, such as amines and carboxylic acids, bonded to their hydrophobic backbone, changes in the pH of the surrounding environment can either protonate or deprotonate them. pH-sensitive polymers separate proteins by electrostatic interactions because they may easily interact with oppositely charged proteins through complexation, which leads to precipitation. The precipitated proteins can be recovered by altering the medium's pH. Materials for pH-responsive chromatography have been prepared using both basic and acidic polymers. PDMA, PVI, PDMAPAm, P4VP, PANMP, and other basic polymers are utilized, whereas PMAAc,

PAMPS, PAAc, PLL, and other acidic polymers are employed [95,96]

8 .Future Aspects:-

Researched in a variety of natural and synthetic polymeric systems. Most of these systems are only capable of in vitro screening because of several limitations that prevent them from having clinical significance. . Pharmaceutical firms are developing several intriguing technologies that are now in development andclinical evaluations. Peptides, hormones, and BCS class-IV medications—drugs with little oral bioavailability and no target specificity in traditional dose formulations—have been used in these cutting-edge technologies. . Several of these technologies that use pH-responsive 80 Smart Polymers and their uses Economic viability assurance to enable the production of these devices on a big commercial and population scale. creation of more regional medication distribution methodsTo create stimuli-responsive materials and their variety of uses, more interdisciplinary research combining the methods of chemical engineering, biology, and material science will be required in the future. particularly in the fields of regenerative medicine and cellular treatments. Applications for pH-responsive polymers might include medication delivery for medicinal treatments and cell manipulation, including stem and neural cells. In order to improve control over post-implantation processes, the next generation of biomaterials aims to create and apply smart materials in clinical settings. The substance may be controlled by the host site itself through specific molecular interactions, ionic strength, or local pH variations. To attain long-term structural stability, supramolecular assemblies of responsive polymers (such as shell or core cross-linking structures) can be employed. The detecting motifs that are more selective and sensitive The goal of developing and integrating responsive responses into responsive polymer matrices is to detect and distinguish minute variations in the gradients and concentrations of glucose, pH, temperature, bioactive small molecules, and other biorelevant macromolecular species. The creation of pH-responsive polymers is focused on systems that can selectively detect many analytes at once. It is still difficult to maximize material reactions and integrate them into medical devices so that these innovative smart materials may fulfill their potential for use in both in vitro and in vivo settings. . In vivo uses are becoming more thoroughly investigated, with encouraging efforts in targeted medicine delivery and illness therapy. Technologies that combine distinct qualities will be made possible by dual stimuli-responsive

materials, increasing the specificity and effectiveness of cells. medication delivery, cell receptivity, and targeting. The characteristics of smart materials may be modified to satisfy the requirements of particular applications by suitable copolymerization, cross-linking, and ligand attachment. As of right now, these innovative approaches to creating smart materials are offering fascinating new instruments for tissue engineering for regenerative medicine, medication delivery, and manipulation of neurons and other cells. Nevertheless, a large portion of the work completed thus far is entirely experimental and has minimal direct therapeutic value. Future developments must concentrate on maximizing these materials' unique and stringent specifications prior to their effective utilization in therapeutic treatments

" These cutting-edge approaches to creating smart materials are currently offering fascinating new instruments for tissue engineering for regenerative medicine, medication delivery, and manipulation of neurons and other cells. However, a large portion of the work completed thus far has only been exploratory in nature and has limited direct therapeutic value. Future developments must concentrate on maximizing these materials' unique and stringent specifications prior to their effective utilization in therapeutic treatments.[97,98]

9. Development:-

9.1 Recent Development:-

Recent advancements in tumours targeting technology have been led by the development of a Ph-sensitive polymer system that exhibits modulated properties and responds sharply to specific ph environments in solid terms and cells. These properties include triggered drug release at extra tumoral ph, exposure of ligands or cell penetrating peptides by shielding/DE shielding mechanisms or by pop-up mechanisms, poly(ethylene glycol) (PEG) shielding, and endosomal ph targeting. The

sensitive phase transition may be used to target intertumoral dependence, ph-induced drug tiggering, and bioimaging through a variety of processes that aid in the treatment of conventional chemotherapy. [99] Records of development

Title	Patent No.	Publication Date	Classification	Organization
Adriamycin prodrug anti-tumour preparation	CN115702902	17.02.2023	Drug-loaded albumin nanoparticles	Suzhou Yutan Pharmaceutical Technology Co., Ltd
pH-responsive silica metal–organic framework nanoparticles for biomolecule delivery	US20220177494	09.06.2022	Metal nanoparticles	Wisconsin Alumni Research Foundation
Effective intranasal delivery to the brain	US20220389160	08.12.2022	Polymer (per se)	Hanyang University, Massachusetts Institute of Technology
Responsive hydrogel drug delivery system, in addition to its preparation technique and use	CN114796502	29.07.2022	Hydrogel	West China Hospital, Sichuan University

CONCLUSION: -

pH-dependent polymers have emerged as a promising and versatile class of materials in the development of advanced drug delivery systems. Their ability to undergo structural or solubility changes in response to the physiological pH of specific body sites makes them particularly attractive for achieving site-specific, controlled, and sustained drug release. This approach not only enhances therapeutic efficacy but also minimizes systemic side effects, thereby improving patient compliance. For example, in oral drug delivery, pH-sensitive polymers enable the protection of acid-labile drugs from the gastric environment and facilitate their targeted release in the intestine or colon. Similarly, in cancer therapy, these polymers offer opportunities to exploit the acidic tumor microenvironment for selective drug release.

Despite these advantages, the clinical translation of pH-responsive polymer systems faces certain challenges. Issues such as incomplete pH sensitivity, variability of physiological pH in disease conditions, potential toxicity of synthetic polymers, and limited biodegradability remain critical hurdles. Furthermore, scaling up production with consistent quality, achieving regulatory approval, and ensuring stability during long-term storage are significant concerns that restrict their widespread application. Recent advances in natural polymer derivatives, hybrid polymer composites, and nanostructured formulations are helping to overcome some of these limitations, offering safer and more effective options for therapeutic use.

Looking forward, the integration of pH-sensitive polymers with other smart delivery strategies—such as stimuli-responsive nanoparticles, ligand-targeted systems, and biodegradable hydrogels—could significantly expand their scope in personalized and precision medicine. Advances in polymer chemistry, nanotechnology, and computational modeling are expected to enable the rational design of next-generation materials with enhanced sensitivity, selectivity, and biocompatibility. Interdisciplinary research and collaborative efforts between academia, industry, and regulatory bodies will be essential to accelerate the successful clinical translation of these systems.

Such systems have been particularly effective in oral formulations, where they protect acid-labile drugs from gastric degradation and facilitate targeted release in the intestine or colon. In addition, their utility in cancer therapy has been demonstrated by exploiting the acidic tumor microenvironment to achieve selective release of anticancer agents.

Nevertheless, several limitations hinder the broader clinical translation of pH-responsive polymer-based systems. Variability in physiological pH under pathological conditions, incomplete sensitivity, and potential toxicity of certain synthetic polymers pose significant challenges. Limited biodegradability and concerns regarding long-term safety further restrict their application. Moreover, reproducibility during large-scale production, regulatory approval, and stability during storage remain critical barriers to commercialization. These issues highlight the need for continued refinement in polymer design and formulation strategies.

Recent Advances, including the development of natural polymer derivatives, hybrid composites, and nanostructured systems, have shown promise in overcoming some of these obstacles. Integration of pH-sensitive polymers with other stimuli-responsive or targeted delivery strategies—such as nanoparticle-based carriers, hydrogels, and ligand-mediated approaches—offers potential to enhance therapeutic precision. Advances in polymer

chemistry and nanotechnology, combined with computational modeling, are likely to facilitate the rational design of next-generation materials with improved selectivity, sensitivity, and biocompatibility.

In conclusion, pH-dependent polymers hold immense potential as intelligent carriers for drug delivery, particularly in addressing site-specific therapeutic needs. While challenges remain, continuous innovation and refinement of these systems can pave the way for safer, more efficient, and patient-friendly drug delivery platforms that will transform modern healthcare in the years to come

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