# POLYMERS

- Introduction
- Classification
- Advantages
- Properties
- Applications of polymers in formulation of controlled release drug delivery systems

# Introduction to Polymers for CRDDS

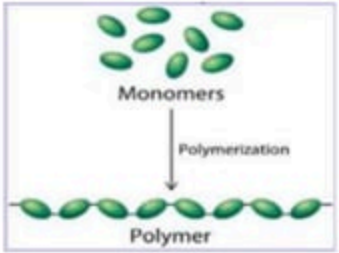
**Definition:** Polymers are compounds with high molecular masses formed by monomers. The word poly means 'many' and meros means 'units or parts' in Greek

Because of their unique properties polymers are used in pharmaceuticals
The new technology in polymer based drug release system offer possibilities in administration of drugs
Pharmaceutically these polymers are used as a binder in tablets, flow controlling agents in liquids, suspensions and emulsions, as film coating agents to mask unpleasant taste of drug, protective and stabilizing agents

Polymers for CRDDS
The polymers, being an integral part of drug delivery technology, play an important role in terms of giving controlled release to the therapeutic moieties for long periods

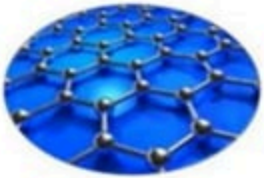
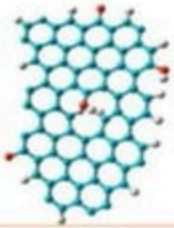
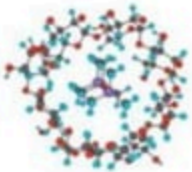
# Polymerization

It is a process of reacting monomer molecules together in a chemical reaction to form polymer chains or three-dimensional networks




**Types of polymerization**

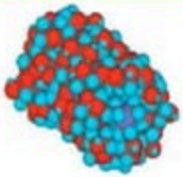
- Addition or chain growth polymerization
- Coordination polymerization
- Condensation or step growth polymerization
- Copolymerization

# Properties

**Characteristics of an ideal polymer**

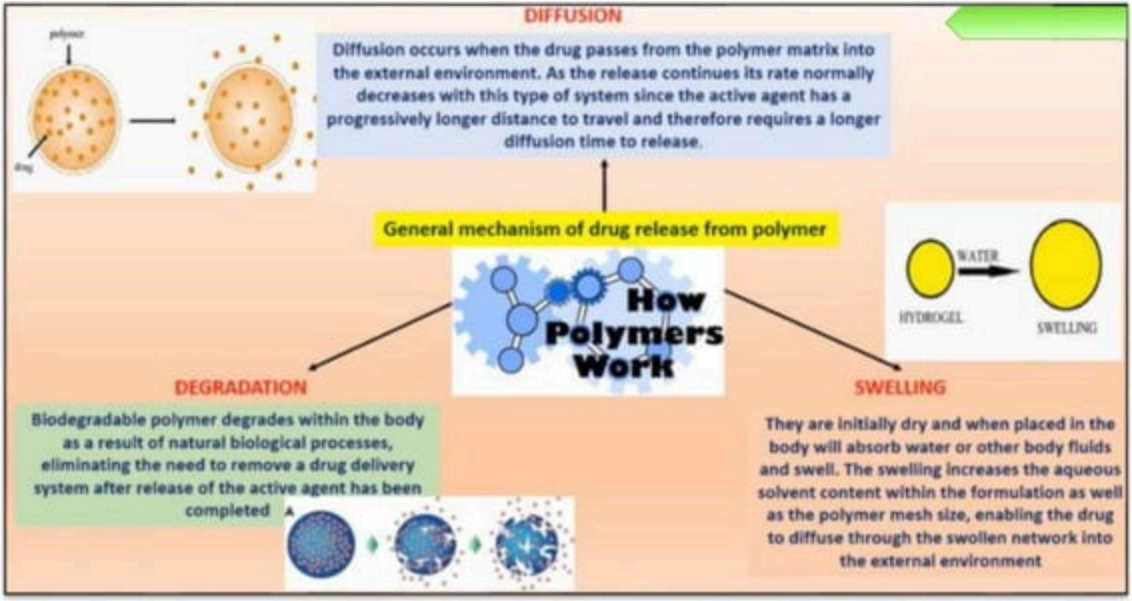
- ✓ It should be versatile and possess a wide range of mechanical, physical, chemical properties.
- ✓ It should be non-toxic and have good mechanical strength and should be easily administered.
- ✓ It should be inexpensive and easy to fabricate.
- ✓ It should be inert to host tissue and compatible with environment.



**Criteria followed in polymer selection**

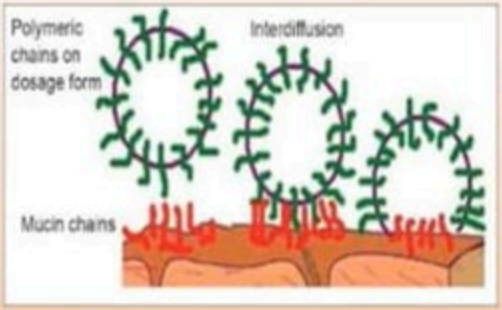
- ➢ The polymer should be soluble and easy to synthesis.
- ➢ It should have finite molecular weight.
- ➢ It should be compatible with biological environment.
- ➢ It should be biodegradable.
- ➢ It should provide good drug polymer linkage.

# Drug release from polymer



# Mucoadhesive Polymer

## NOVEL MUCOADHESIVE POLYMERS




Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time

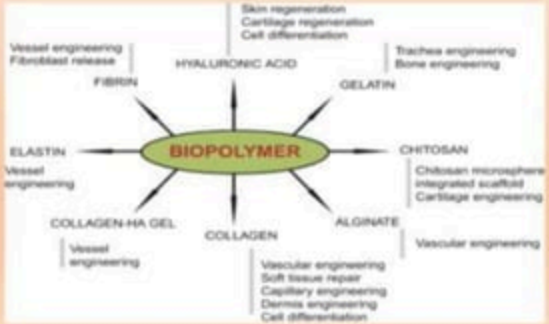
The use of a mucoadhesive polymer that attach to related tissue or to the surface coating of the tissue for the targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal etc

The various mucoadhesive polymers used for the development of buccal delivery systems include cyanoacrylates, polyacrylic acid, sodium carboxymethylcellulose, hyaluronic acid, hydroxypropylcellulose, polycarbophil, chitosan and gellan

# Different types of polymers in Pharmaceutical drug delivery system

## POLYMERS IN PHARMACEUTICAL DRUG DELIVERY SYSTEM

- Rosin
- Chitin and Chitosan
- Zein
- Collagen
- Starches
- Polycaprolactone
- Polyorthoesters




| Synthetic polymers | Natural polymers |
|---|---|
| Cellulose derivatives | Tragacanth |
| Polycarbophil | sodium alginate |
| Poly (ethylene oxide) | Karaya gum |
| Poly (vinyl pyrrolidone) | Guar gum |
| Poly (vinyl alcohol). | Gelatin |
| Poly (hydroxyethyl methylacrylate) | Chitosan |
| Hydroxyl propyl cellulose | Soluble starch |

## POLYMERIC PLANT-DERIVED EXCIPIENTS IN DRUG DELIVERY SYSTEM

- Cellulose
- Pectin
- Inulin
- Alginates
- Guar gum

# Synthetic polymers

## Different types of polymers to CRDDS: Uses and Properties

### Synthetic Polymers

Different types of synthetic polymers are being investigated for their performance in drug delivery. The synthetic polymers provide various advantages like

- Sustained action of the drug with the steady release
- drug stability
- Can be used as sutures, tissue adherent materials, hemostats, and drug delivery carriers
- The biodegradable polymers provide advantages like targeted drug delivery, controlled release, and stability of drug and stable release with time
- Localized delivery of drug : The product can be implanted directly at the site where drug action is needed and hence systemic exposure of the drug can be reduced. Especially for toxic drugs which are related to various systemic side effects
- Sustained delivery of drug : The drug encapsulated is released over extended period and hence eliminates the need for multiple injections. This feature can improve patient compliance especially for drugs for chronic indications, requiring frequent Injection
- Stabilization of the drug : The polymer can protect the drug from the physiological environment and hence improve its stability in vivo. This feature makes this technology attractive for the delivery of labile drugs like proteins

# Synthetic polymers: Types, Examples and Properties

| Types | Examples | Properties |
|---|---|---|
| **Biodegradable synthetic polymer** | Polylactic acid (PLA) | This polymer has different biomedical applications like in stunts, sutures, and various drug delivery devices |
| | Polyglycolic acid (PGA) | PGA is nontoxic and biodegradable |
| | Poly (lactide-*co*-glycolide), PLGA | It controls the degree of crystallinity of a polymer |
| | Polyhydroxybutyrate (PHB) | This polymer shows long-term drug delivery |
| **Phosphorous based derivatives** | Polyphosphazenes | Due to the chemical reactivity of phosphorus the manipulation of biodegradation rates of polymers is possible |
| | Polyorthoesters | These are degradable polymers used in orthopedic applications |
| | Poly (amino acids) | Low toxicity and good biodegradability |

# Natural Polymers

## Natural Polymers

- The natural polymers are widely used in drug delivery due to their abundant availability, good compatibility, and important role in deciding release rate of the dosage form

- These polymers can be modified chemically to alter the release properties. The various polymers like chitosan, alginate, and hyaluronic acid are commonly used in drug delivery systems

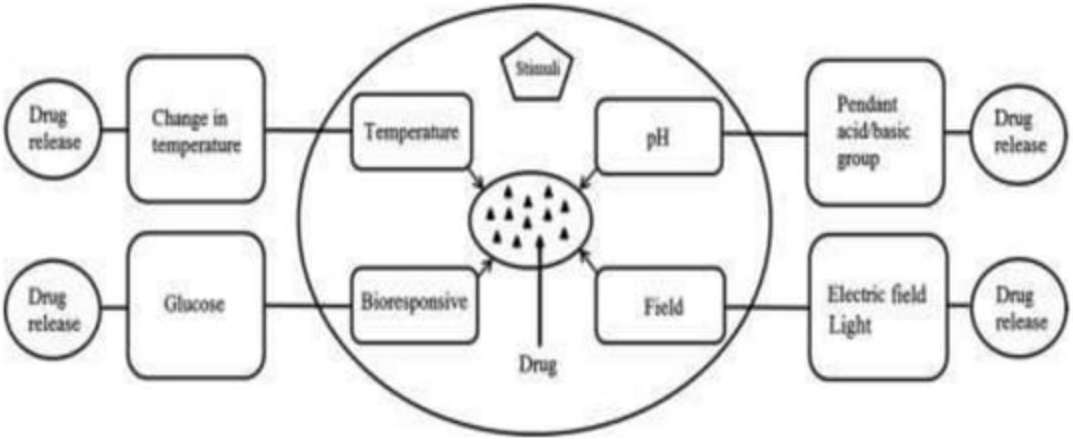
## Natural polymers: Types, Examples and Properties

| Types | Examples | Properties |
|---|---|---|
| **Polysaccharides** | Pectin | Nonstarch polysaccharides |
| | | Soluble in water, insoluble in ethanol and other organic solvents |
| | Alginates | The high acid content allows alginic acid to undergo spontaneous and mild gelling in the presence of divalent cations, such as calcium ions |
| | | Can form a polycation–polyanion complex results in an increment in the stability of microcapsules |
| | Chitosan | Cationic amino polysaccharide (p*K*a 6.5) copolymer of glucosamine and *N*-acetylglucosamine |
| | | Biodegradable, biocompatible, positively charged nontoxic mucoadhesive biopolymer |
| | | Contains primary amino groups in the main backbone that make the surfaces positively charged in biological fluids |
| | | It confers considerable antibacterial activity against a broad spectrum of bacteria |
| | Hyaluronic acid | Plays an important role in the organization and stabilization of the extracellular matrix (ECM), cell proliferation, and differentiation |
| | | Involves in morphogenesis, inflammation, and wound repair |

# Smart Polymers

**Smart Polymers**

- Smart polymers are the ones that show a change with the change in environmental factors
- The factors can include pH change, temperature, light, and pressure difference
- Designing of CRDDS using smart polymers leads to accurate and programmable delivery of a drug. These offer a drug delivery platform that can be utilized to deliver drugs at a controlled rate and in a stable and biologically active form




various stimuli responsible for controlling drug release from smart polymeric drug delivery systems

## smart polymer continue….

- A stimuli-sensitive or smart polymer undergoes an abrupt change in its physical properties in response to a small environmental stimulus
- These polymers are also called as **intelligent polymers** because small changes occurs in response to an external trigger until a critical point is reached, and they have the ability to return to their original shape after trigger is removed
- The exclusivity of these polymers lies in their nonlinear response triggered by a very small stimulus and which produces a noticeable macroscopic alterations in their structure
- These transitions are reversible and include changes in **physical state, shape and solubility, solvent interactions, hydrophilic and lipophilic balances and conductivity**
- The **driving forces** behind these transitions include neutralization of charged groups by the addition of oppositely charged polymers or by pH shift, and change in the hydrophilic/lipophilic balance or changes in hydrogen bonding due to increase or decrease in temperature
- The major benefits of smart polymer-based drug delivery systems includes reduced dosing frequency, ease of preparation, maintenance of desired therapeutic concentration with single dose, prolonged release of incorporated drug, reduced side effects and improved stability

## Stimuli

- These stimuli can be subsumed into discrete classifications of physical or chemical nature
- Physical stimuli (i.e., temperature, ultrasound, light, and magnetic and electrical fields) directly modulate the energy level of the polymer/solvent system and induce a polymer response at some critical energy level.
- Chemical stimuli (i.e., pH, redox potential, ionic strength, and chemical agents) induce a response by altering molecular interactions between polymer and solvent (adjusting hydrophobic/hydrophilic balance) or between polymer chains (influencing crosslink or backbone integrity, proclivity for hydrophobic association, or electrostatic repulsion)

## Various smart polymeric drug delivery systems

| Stimulus | Advantage | Limitation |
|---|---|---|
| Temperature | Ease of incorporation of active moieties | Injectability issues under application conditions. |
| | Simple manufacturing and formulation | Low mechanical strength, biocompatibility issues and instability of thermolablile drugs |
| pH | Suitable for thermolabile drugs | Lack of toxicity data |
| | | Low mechanical strength |
| Light | Ease of controlling the trigger mechanism | Low mechanical strength of gel, chance of leaching out of noncovalently attached chromophores |
| | Accurate control over the stimulus | Inconsistent responses to light |

## smart polymeric drug delivery systems continue.....

| Stimulus | Advantage | Limitation |
|---|---|---|
| Electric field | Pulsative release with changes in electric current | Surgical implantation required<br>Need of an additional equipment for external application of stimulus<br>Difficulty in optimising the magnitude of electric current |
| Ultrasound | Controllable protein release | Specialized equipment for controlling the release<br>Surgical implantation required for nonbiodegradable delivery system |
| Mechanical stress | Possibility to achieve the drug release | Difficulty in controlling the release profile |

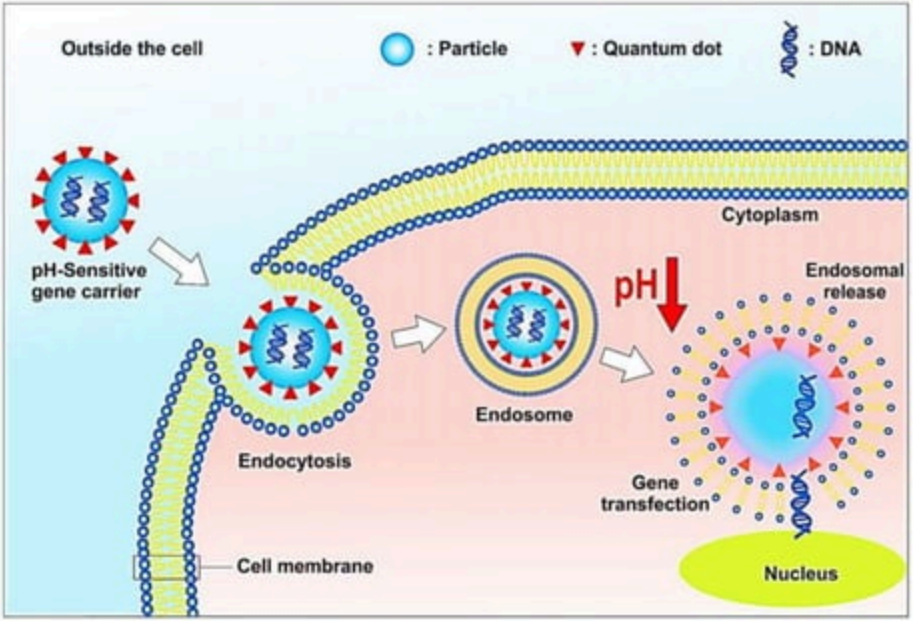
## pH-SENSITIVE POLYMERS

- These types of polymers have either an acidic or basic group in their architectural configuration, which in response to an **environmental change** accepts or donates a proton
- The pH-sensitive polymers have the ability to release the drug either in the intestine or stomach for therapeutic response generation
- Materials may swell, collapse or change depending on the pH of their environment due to the presence of functional groups in the polymer chain
- These polymers can be designed with many different architectures for different applications. Key uses of pH sensitive polymers are controlled drug delivery systems, biomimetics, micromechanical systems, separation processes, and surface functionalization
- pH sensitive polymers can be broken into two categories: those with acidic groups (such as -COOH and $-SO_3H$) and those with basic groups ($-NH_2$). The mechanism of response is the same for both, only the stimulus varies. The general form of the polymer is a backbone with functional "pendant groups" that hang off of it. When these functional groups become ionized in certain pH levels, they acquire a charge (+/-)

## PH-SENSITIVE POLYMERS- Examples

- **Eudragit E** is Food and Drug Administration (FDA) approved polymer with solubility under pH 5. The microspheres prepared by Eudragit E, of the drug donepezil, showed suppressed drug release in phosphate buffer at pH 7.4, which led to masking the bitter taste
- Eudragit E is also recognized for coating of tablets for taste masking, for example, atorvastatin
- Other polymers like Eudragit L, S, and F are responsive to intestinal high pH and can be used for colonic drug delivery and prevent degradation of the drug from the gastric region
- Beads of rabeprazole coated with Eudragit L are known to suppress the release of drug at low pH
- The pH-sensitive polymers like polypropylacrylic acid (PPAA) and polymethacrylic acid (PEAA) are used in carrying genes. The hemolytic performance of these polymers is increased when pH value is decreased ranging from **pH value 5 to 6** and does not show any hemolytic activity if pH is 7.4
- Another example of pH-sensitive polymer approach is the development of micelles with the help of copolymers PEG-poly(aspartame hydrazine doxorubicin) which helps in retaining the drug and genes at physiological pH and the drug is released at pH below 6

# Gene delivery through pH sensitive approach




Scheme of synthesis of a gene delivery through pH sensitive approach
Example: The polymer dimethyl aminoethyl methacrylate (DMAEMA) nanoparticles release DNA at low endosomal pH

## pH sensitive polymers: Examples and Properties

| Types | Examples | Properties |
|---|---|---|
| **Cationic polymers** | Aminoalkyl methacrylate copolymer (Eudragit E) | FDA approved |
| | | Responsive to low pH of the stomach |
| | | High solubility below pH 5 |
| | | Possess taste masking property |
| | Polyvinyl acetal diethylamino acetate | FDA approved |
| | | Responsive to low pH of the stomach |
| | | Insoluble above pH 5.8 |
| | Polyethyleneimine (PEI), Poly(L-histidine), Poly(amidoamine)s and Poly (propyl acrylic acid) | Can protonate at the acidic endo/lysosomal compartments, results in the responsiveness towards intracellular compartments |
| | Poly(L-histidine) | Possess pH-buffering capacity |

## pH sensitive polymers: Examples and Properties

| Types | Examples | Properties |
|---|---|---|
| **Anionic polymers** | Poly(methacrylic acid-*co*-methyl methacrylate) Eudragit L | Responsive to intestinal high pH<br>Carboxyl/ester group ratio 1:1<br>Soluble at pH 6 |
| | Poly(methacrylic acid-*co*-methyl methacrylate) Eudragit S | Responsive to intestinal high pH<br>Carboxyl/ester group ratio 1:2<br>Soluble at pH 7 |
| | Hydroxypropylmethylcellulose phthalate | Responsive to intestinal high pH<br>Soluble in the pH range 5–5.5 |
| | Hydroxypropylmethylcellulose acetate succinate (HPMC-AS) | Responsive to intestinal high pH<br>Soluble in the pH range 5.5–6.8 |
| | Poly(methacrylic acid-*co*-methyl methacrylate) Eudragit-F | Responsive to high pH of the colon<br>Soluble in pH above 7 |

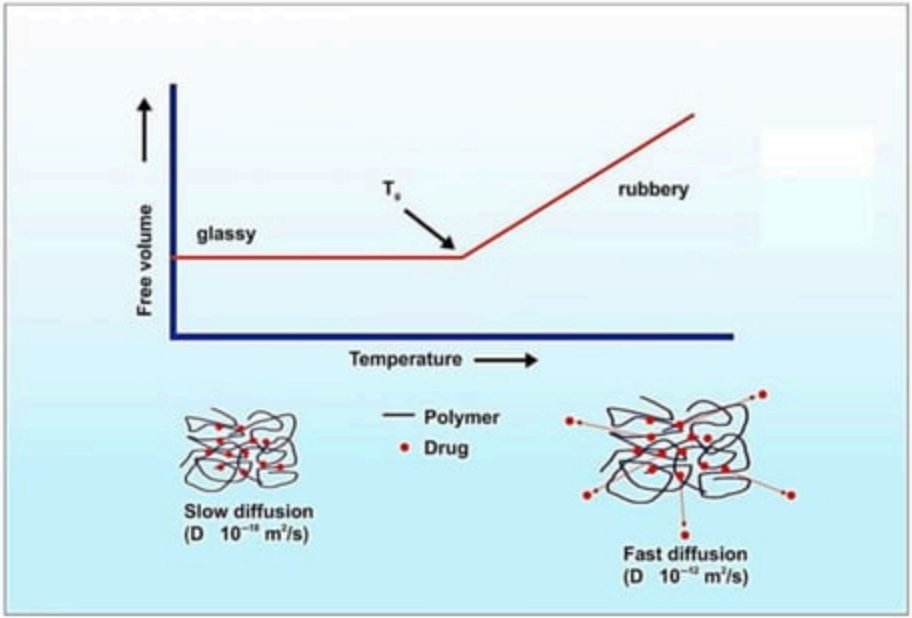
# pH sensitive polymers: Examples and Properties

| Types | Examples | Properties |
|---|---|---|
| **Polymers containing imidazole group** | Poly(L-histidine) (*P*(His)) | p*Ka* 6<br>Neutral at pH 7.4 but cationic in an acidic environment |
| **Poly (β-amino ester)** | PEG-b-poly (β-amino ester) | Undergoes micellization/demicellization transition in a slightly acidic environment (pH 6.4–6.8) |
| **Polymers containing hydrazone linkage** | *N*-(2 hydroxypropyl) methacrylamide (HPMA) | Faster hydrolytic rate at acidic pH relative to neutral physiological pH |
| **Polymers containing acetal, orthoester linkage** | Polyacetals [PEG-b-poly(ethyl glyoxylate)-b-PEG, Polyacetal-b-Pluronic] | Responsive to intracellular low pH<br>Produce biocompatible degradation products of alcohols and aldehydes |
| | Orthoesters (PEG-b-polymethacrylate diblock copolymer) | Responsive to intracellular low pH<br>Readily hydrolyzes in mildly acidic aqueous environments to form esters |
| **Cell-penetrating peptides** | N-terminus of the hemagglutinin HA2 | Unique property of pH dependent structural transformation |

## TEMPERATURE SENSITIVE POLYMERS

- The polymers that are sensitive to temperature change, that is, those whose properties are changed due to temperature, are referred to as temperature sensitive polymers
- There occurs a change in the internal adjustments of polymers, the main properties of which are their lower critical solution temperature (LCST), which can make them either insoluble or soluble. This property is also responsible for phase transition from an isotropic state to anisotropic state
- The polymers with **low LCST** are widely used in drug delivery systems because they show uniform mixing property and this helps in administering them to the human body via injection to the damaged area, where they form a gelled deposit. This makes the system deliver the drug in a controlled manner
- Poly (N-isopropyl acrylamide) is a type of synthetic temperature sensitive polymer that is mostly used in drug delivery systems and shows solubility in water at room temperature. The temperature sensitive polymers can also make some hydrophobic drugs soluble to produce a proper formulation with low soluble drugs

## Temperature sensitive phase transition takes place




**At a particular temperature, the phase transition takes place resulting in an alteration in polymer change and promotion in drug delivery**

## TEMPERATURE SENSITIVE POLYMERS- Examples

| Types | Examples | Properties |
|---|---|---|
| **Polymers with LCST (lower critical solution temperature)** | Poly(*N*-isopropylacrylamide) (PNIPAAm) | Presents an LCST at 32°C in water solution |
| | Poly(*N*,*N*'-diethyl acrylamide) | Exhibits an LCST in the range 26–35°C |
| | Poly(dimethylamino ethyl methacrylate) | LCST close to 50°C |
| | Poly(*N*-(L)-(1-hydroxymethyl) propylmethacrylamide) | LCST in the range of 26–35°C |
| **Polymers with amphiphilic balance** | Pluronics or poloxamers | Hydrophobic associations of PPO blocks lead to the formation of micelle structures above critical micelle temperature |
| | | Exhibit a sol-gel transition below or close to the physiological temperature, a gel–sol transition around 50°C |
| **Natural Polymers** | Gellan, gelatin, amylopectin, amylose, agarose | Exhibit temperature sensitivity by different gelation mechanisms that lead to the formation of helix conformations by physical crosslinks |
| | | These are *sol* at high temperatures and become a *gel* at lower temperatures by the formation of aggregation of double helices that act as crosslinking knots |

## ION EXCHANGE POLYMERS

- Ion exchange polymers possess a polystyrene backbone and side chains of ion-active precursors
- The ion exchange resins are promising candidates to form drug-resin complexes for drug delivery in the form of tablets, liquid orals, and beads
- These complexes release the drug into GIT and saliva due to the presence of activating ions. Also, ion exchange polymers are known to have taste masking properties
- Drug loading in ion exchange polymers is carried out with complexation and due to electrostatic interactions between drug and polymers. The drug release from the polymers is ruled by the equilibrium reaction that occurs in the presence of counter-ions when they come into contact with the solution
- For example, PEAA-base ion exchange polymer was used for taste masking of pseudoephedrine in chewable tablets to mask its bitter taste; due to low cation percentage in saliva than gastric fluids the drug release is minimized in saliva for masking the taste

# ION EXCHANGE POLYMERS- Examples

| Types | Examples | Properties |
|---|---|---|
| Ion exchange resins (Polystyrene backbone cross-linked with divinylbenzene and side chains of ion-active groups) | Polymethacrylic acid-based ion-exchange resin | Taste masking property |
| | A carboxylic acid-based ion-exchange resin | Sustained drug delivery |
| Cationic polymers | Poly(ethyl acrylate-methyl methacrylate–trimethyl aminoethyl methacrylate chloride) copolymers (Eudragit RS and RL) | Practically insoluble in water but can be hydrated with and swell in water |
| | | Responsive to the ions in saliva and stomach |
| Poly(*N*-isopropyl acrylamide) (PNI-PAM) | – | Exhibit lower critical solution temperature (LCST) transitions |
| Cellulose derivatives | | Responsive to the ions in saliva and stomach |
| Poly(vinyl ether) | | Colon delivery |
| Poly (*N*-vinyl caprolactam) | | |