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POLYMER-BASED CONTROLLED DRUG DELIVERY SYSTEMS: ADVANCES, APPLICATIONS, FUTURE PERSPECTIVES

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ABSTRACT

Polymer-based controlled drug delivery systems (CDDS) have surfaced as a groundbreaking solution to address the drawbacks of conventional drug administration, such as unpredictable plasma levels and low bioavailability. These systems employ natural, synthetic, and semi-synthetic polymers to facilitate sustained, targeted, and predictable release of medication. Mechanisms, including diffusion, dissolution, swelling, osmosis, and biodegradation, allow for customized delivery that meets therapeutic requirements. A variety of polymeric carriers, such as nanoparticles, micelles, hydrogels, liposomes, and dendrimers, enable precise targeting, improved stability, and reduced side effects. Their uses extend across oral, transdermal, ocular, pulmonary, and targeted drug delivery, thereby enhancing patient adherence and treatment effectiveness. Progress in biodegradable and stimuli-responsive polymers has broadened their significance in the biomedical field, making drug delivery responsive to both physiological and pathological signals. The combination of nanotechnology and polymer chemistry is continuously transforming personalized medicine, resulting in adaptive, biocompatible, and environmentally friendly drug delivery systems.

KEYWORDS: Controlled drug delivery systems, Conventional drug administration, Polymers, Mechanisms, Polymer chemistry.

INTRODUCTION

Controlled Delivery Systems (CDS): CDS are defined as a method that provides sustained drug action at a specific rate, ensuring a relatively stable and effective level of medication in

the body while simultaneously reducing unwanted side effects. This approach enables targeted drug delivery by strategically placing controlled-release systems near affected tissues or within diseased cells. The quantity and pace of drug release are guided by the body's physiological or therapeutic requirements. Typically, a controlled drug delivery system (DDS) is engineered to administer medication at a defined rate over an extended period. Safe and effective concentrations of the drug in the bloodstream are upheld as long as the system remains operational. The established rate of drug release is influenced by the target therapeutic level and the drug's pharmacokinetic properties.[1]

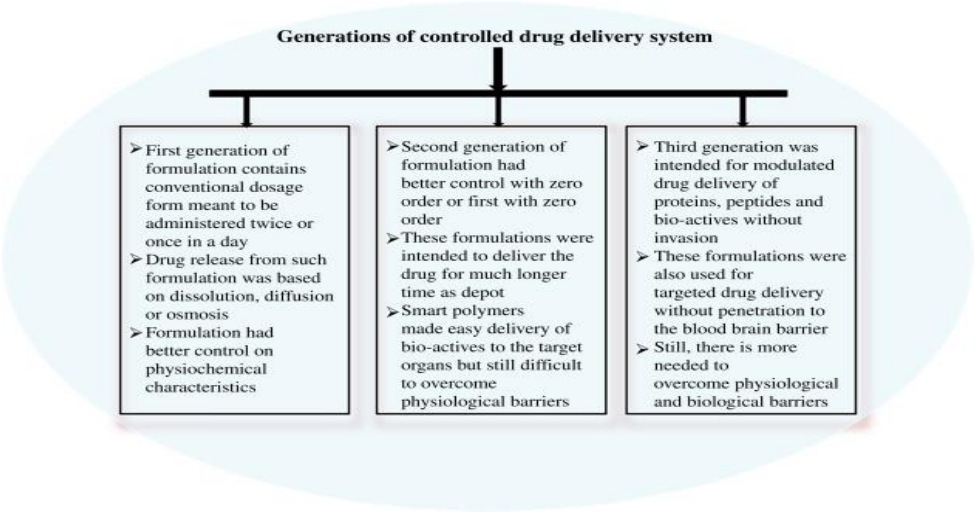


Figure 1: Diagrammatic representation of Generations of Controlled Drug Delivery Systems.[2]

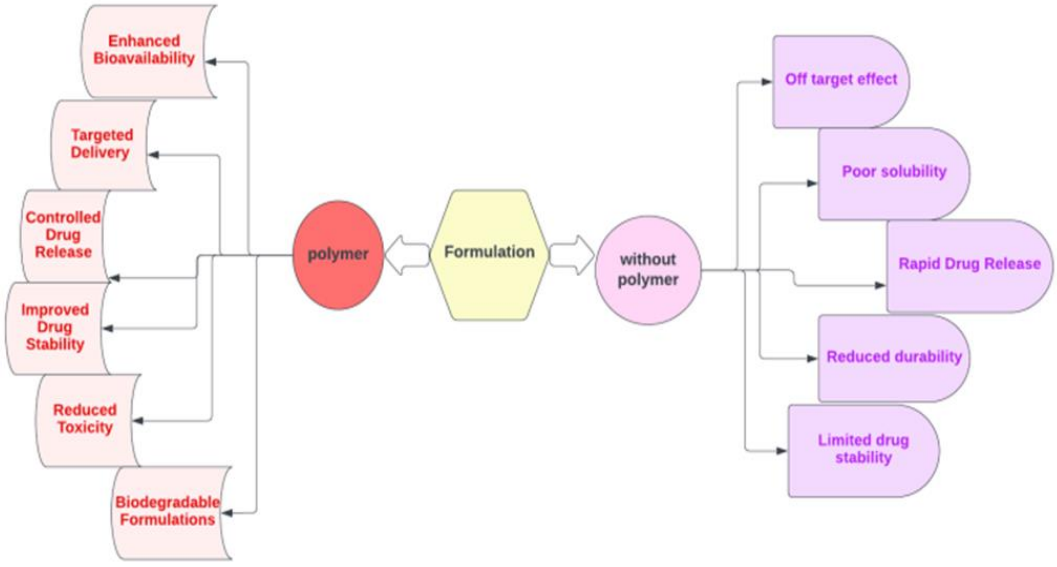
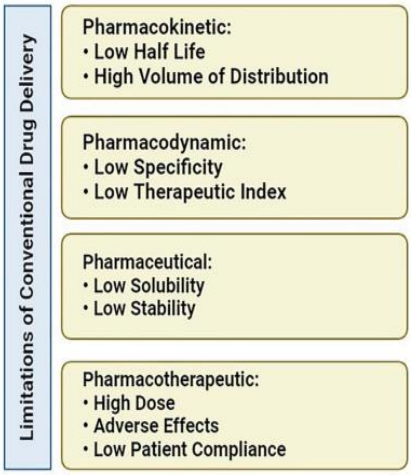


Figure 2: Diagrammatic representation of the Significance of Polymers.[3]



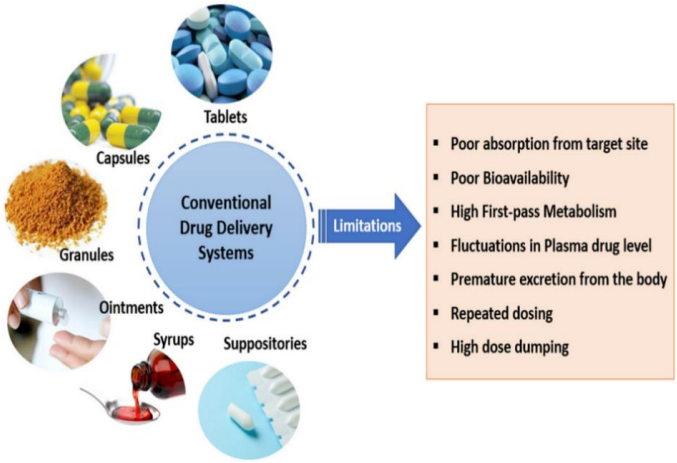


Figure 3: Schematic representation of Limitations of Conventional Drug Delivery.[4,5]

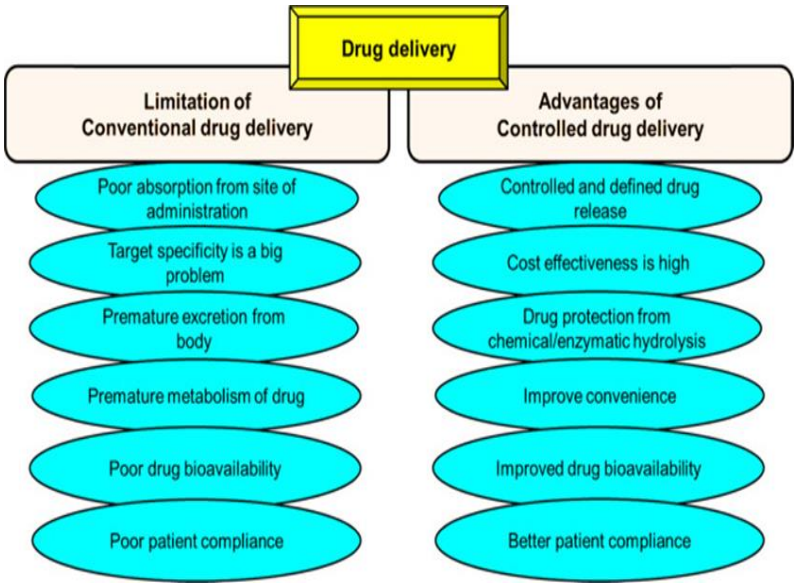


Figure 4: Diagrammatic representation of Limitations of the Conventional Drug Delivery System over the Controlled Drug Delivery System.[6]

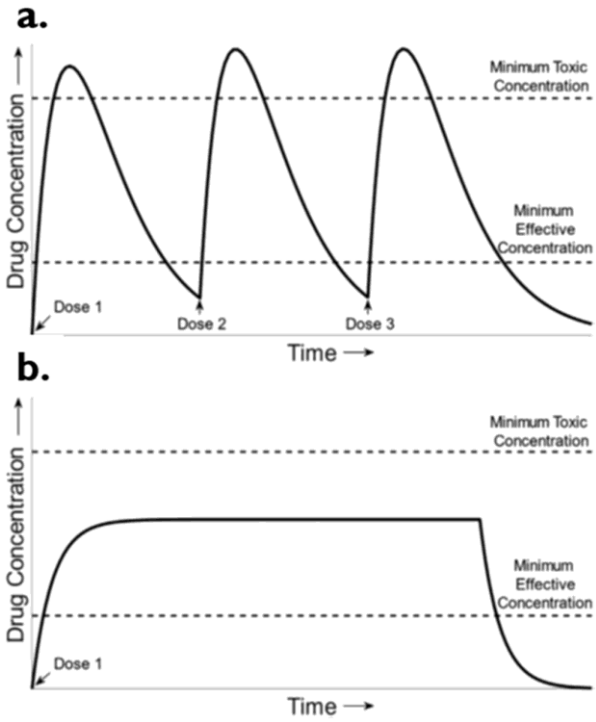


Figure 5: Diagrammatic representation of a typical bolus of a) Conventional Drug Delivery System versus b) Controlled Drug Delivery System.[7]

Polymer: A Polymer is defined as a material or substance characterized by its molecular structure, primarily composed of numerous similar or different units that are bonded together. The term "polymer" originates from ancient Greek, where "poly-" means "many" and "-mer" denotes "part," "segment," "units," or "particles," while "mono-" indicates "one" or "single." Monomers are the smaller molecules or particles that combine to create a long chain known as a polymer. As per Gooch (2007), there are five classifications of polymers: (1) entities made up of repeated structural units, either through a blend of chemical compounds formed via a polymerization process; (2) large molecular weight compounds resulting either from the addition of numerous smaller molecules, such as polyethylene, or from the condensation of smaller molecules with the release of water or alcohol, like nylon; (3) combinations of two or more polymeric substances; (4) products of polymerization; and (5) macromolecules. The definition accepted by IUPAC (1997), Jenkins et al. (2009), and ISO 472 (2013) states that a polymer is "a substance formed of molecules (either of the same or varying sizes, such as macro, nano, etc.) distinguished by the repeated presence of one or more types of atoms or atom groups (constitutional units) linked together in quantities sufficient to create new polymeric materials".[8] Examples include natural polymeric materials like shellac and natural rubber, which have been utilized for a long time. Biopolymers such as proteins and nucleic

acids are essential for various biological functions. Additional examples of natural polymers include cellulose, chitosan, and alginate. Synthetic polymers encompass a range of materials, including synthetic rubber, neoprene, nylon, PVC, polystyrene, polyethylene, polypropylene, silicone, and many others.[9]

HISTORY & DEVELOPMENT

Table 1: Historical Development of Polymers.[10]

Time Frame / Epoch	Significant Progressions	Notable Individuals & Innovations	Breakthroughs in Science	Social / Environmental Consequences
Precursor Period (Before the 1800s)	Utilization of natural polymers like cellulose, proteins, rubber, silk, and wool.	–	Limited grasp of polymer architecture; solely natural alterations.	Nature-based materials: limited industrial application.
Initial Industrial Period (1800–1850)	Initiation of the chemical modification processes for natural polymers.	Charles Goodyear developed the process of vulcanizing rubber in 1839; Christian Schönbein created nitrocellulose in 1846.	Identification of techniques to enhance the elasticity, durability, and stability of natural polymers.	Initial plastics started to take the place of natural materials such as ivory and horn.
Transitional Synthetic Era (1850–1900)	Creation of cellulose-derived materials and the advent of early synthetic fibers.	Alexander Parkes invented Parkesine in 1862; John Wesley Hyatt introduced celluloid in 1869; Chardonnet produced rayon in the 1890s.	Targeted modification of cellulose to create moldable and fibrous substances.	The commercial plastic industry emerged; alternatives for ivory, tortoiseshell, and silk were developed.
Era of Synthetic Polymers (1900–1930)	Emergence of completely synthetic polymers.	Leo Baekeland patented Bakelite in 1907;	Acknowledgment of polymers as elongated molecular structures; the	Accelerated industrial growth marked a significant turning point for

		Hermann Staudinger proposed macromolecular theory in 1920.	cornerstone of contemporary polymer science.	plastic manufacturing.
Growth of Industry (1930–1960)	Mass production of synthetic polymers for commercial purposes.	Wallace H. Carothers discovered nylon in 1935 and also contributed to the discovery of PVC, polyethylene, polystyrene, and polyester; Ziegler and Natta developed catalysts between 1953 and 1954.	Managed polymerization, stereoregularity, and synthesis driven by catalysts.	Extensive use during World War II and in post-war consumer products led to the ubiquity of plastics.
Advanced Polymer Science (1960–1990)	Expansion of different types of polymers and their applications.	Paul Flory researched polymer chain statistics and received the Nobel Prize in 1974.	Progress in polymer physics, the study of copolymers, and advanced materials.	Growth into sectors like electronics, healthcare, and construction raised initial concerns about waste.
Modern / Environmental Era (1990–Present)	Emphasis on recycling, biodegradability, and environmentally friendly materials.	There are research initiatives and Australian CRCs focused on sustainable polymers.	Innovation in green chemistry, bio-based polymers, and recycling methods.	A global transition towards sustainability and environmental accountability began.

CLASSIFICATION OF POLYMERS

Table 2: Classification of Polymers with their examples.[11]

Basis of Classification	Types	Examples
Source	Natural	Natural rubber, Cellulose
	Semi-synthetic	Cellulose nitrate, Methyl cellulose
	Synthetic	Sodium carboxymethyl cellulose, Hydroxypropyl methyl cellulose (HPMC)
Type of Polymerization	Addition	Polyethylene (PE), Polypropylene (PP)

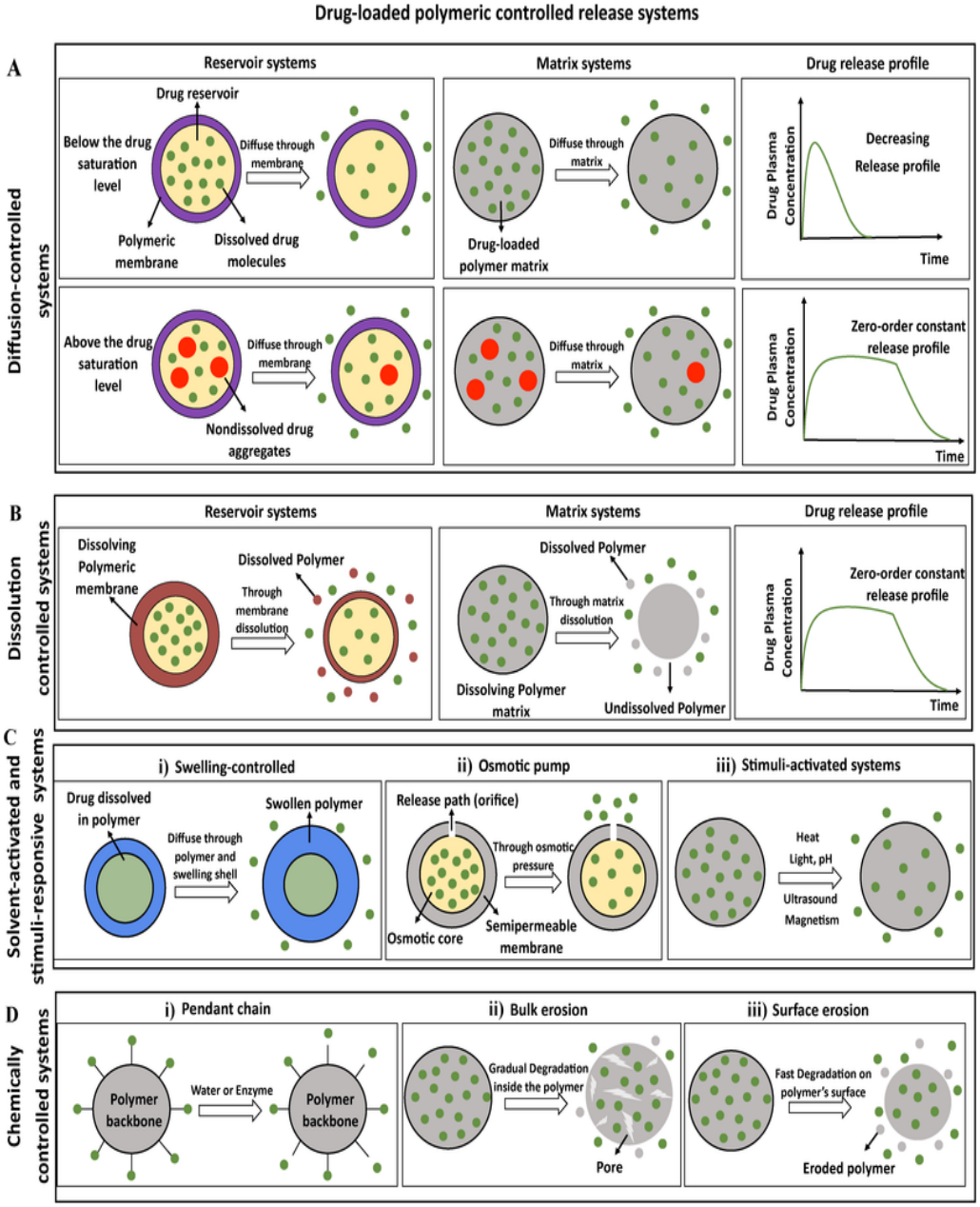
	Condensation	Nylon-6,6
Degradability	Non-biodegradable	Polyvinyl chloride (PVC), Polyethylene (PE)
	Biodegradable	Polylactic acid (PLA), Polycaprolactone (PCL)
Polymer-Water Interaction	Hydrophobic	Ethyl cellulose, Polydimethylsiloxane (PDMS)
	Hydrophilic	Hydroxypropyl methylcellulose (HPMC), Sodium alginate
	Hydrogel	Polyvinylpyrrolidone (PVP) hydrogel, Polyacrylamide
Structure	Linear	Polyethylene (PE), Nylon
	Branched	Glycogen, Amylopectin
	Cross-linked	Vulcanized rubber, Melamine-formaldehyde resin
Type of Monomers	Homopolymer	Polystyrene (PS), Polypropylene (PP)
	Random Heteropolymer	Poly (lactic-co-glycolic acid) (PLGA)
	Block Heteropolymer	Polyethylene glycol–Polylactic acid (PEG-PLA), Poloxamer (PEO–PPO–PEO)
Morphology	Crystalline	Polypropylene (PP), Nylon
	Amorphous	Polystyrene (PS), Polymethyl methacrylate (PMMA)
Thermal Behaviour	Thermoplastic	Polyvinyl chloride (PVC), Polypropylene (PP)
	Thermosetting	Bakelite (Phenol-formaldehyde resin), Melamine-formaldehyde resin
Tacticity	Isotactic	Polypropylene (PP), Polystyrene (PS)
	Syndiotactic	Polystyrene (PS), Polymethyl methacrylate (PMMA)
	Atactic	Polypropylene (PP), Polystyrene (PS)

IDEAL PROPERTIES:

Ideal properties of polymers.[12]

1. Polymers should be non-reactive and environmentally friendly.
2. They ought to be non-toxic and biologically inert.
3. They need to be easy to administer.
4. They should be simple to manufacture and cost-effective.
5. They must possess sufficient mechanical strength.
6. They should be compatible with a wide range of drugs.
7. They must not negatively influence the drug release rate.
8. They should not tend to accumulate in tissues and should be biodegradable.

MECHANISM OF POLYMER-BASED CONTROLLED-DRUG DELIVERY SYSTEM



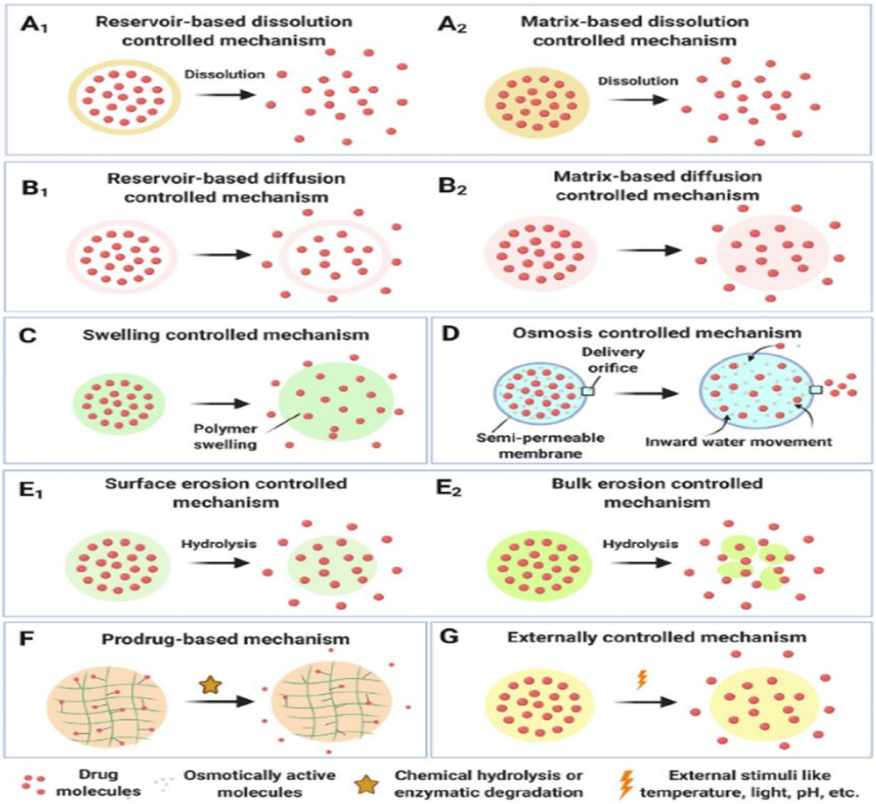


Figure 6: Diagrammatic representation of Mechanisms of Polymer-Based Controlled Drug Delivery Systems.[13,14]

Drug Release Mechanisms: The phrase "release mechanism" describes how active substances are liberated from a delivery medium into the adjacent environment.[15]

1. **Dissolution-Controlled Mechanism:** Dissolution-controlled drug delivery systems rely on disintegrating the polymer components within the microneedles to liberate the embedded medication.[16] The polymeric materials utilized in these systems are very soluble in water, such as hydroxypropyl methylcellulose, starch, natural gums, poly(vinyl alcohol), and poly(vinylpyrrolidone).[17]
2. **Diffusion-Controlled Mechanism:** Drug delivery systems based on diffusion utilize the movement of drugs through a polymeric matrix to control release, differing from dissolution-based systems, where polymers dissolve in water. Polymers such as ethyl cellulose, chitin, polyethylene, and polyurethane are typically employed in these systems, which can be categorized into reservoir or matrix-based configurations. Each of these can further be divided into nonporous and porous modules, with the former requiring drugs to diffuse through a solid barrier, while the latter allows initial drug diffusion into water-filled micropores before release. The release kinetics are influenced by factors such as

polymer thickness, pore size, porosity, and the properties and concentration of the drug.[14]

3. **Swelling-Controlled Mechanism:** Drug delivery systems that regulate swelling utilize polymeric materials with a significant capacity for water absorption. Typically, these polymers do not dissolve in water due to robust chemical or physical cross-linking among the polymer chains.[16] Examples of polymers employed in these systems are poly(vinyl alcohol), poly(methyl vinyl ether-co-maleic acid), and hyaluronic acid acrylate.[17]
4. **Osmosis-Controlled Mechanism:** Osmosis-based drug delivery systems leverage the concepts of osmosis to provide a controlled release of medications.[16] Osmosis refers to the process by which a solvent passes through a semi-permeable membrane in response to a solute concentration gradient. These systems consist of a semi-permeable membrane made from materials such as polycarbonate, polyurethane, cellulose acetate, or ethyl cellulose, alongside drug molecules that are osmotically active or a combination of an osmotically inert drug with an osmotically active compound like NaCl.[16,18]
5. **Biodegradation-/Erosion-Controlled Mechanism:** These drug delivery vehicles gradually release the medication into the surrounding area through biodegradation.[17] In contrast to dissolution-controlled systems, the polymer formulations utilized in these systems experience slow chemical or enzymatic hydrolysis. This process breaks down the matrix, allowing the drug to be released. The biodegradable polymers most frequently employed are poly(lactic acid), poly(glycolic acid), and poly(lactic-co-glycolic acid).[19]
6. **Pendant-Chain-/Prodrug-Based Mechanism:** In prodrug-based drug delivery systems, therapeutic agents are chemically linked to polymers,[20] allowing for their release via hydrolysis or enzymatic reactions. The release rate depends on the conjugation type and environmental conditions. A notable application involved PEGylated naltrexone prodrug microneedles, which demonstrated effective drug release into the skin of Yucatan miniature swine through ester bond hydrolysis.[21]
7. **Stimulus-Activated/-Modulated Mechanisms:** The final category of drug delivery systems utilizes an external trigger to initiate the release of medication. The presence of the external stimulus leads to physical or chemical alterations in the polymeric systems, which in turn facilitate the release of the drug.[17, 22]

TYPES OF POLYMER-BASED CONTROLLED DRUG DELIVERY SYSTEMS

1. Polymeric Films: Polymeric films serve as drug delivery mechanisms that stay in contact with the tissue where the drug is needed, providing a steady release of therapeutic

compounds. These systems enable prolonged drug interaction with the target area for topical applications and facilitate the regulated administration of medications.[23]

2. Polymeric Nanofibers: They are solid fibers with a diameter of less than 1 µm (1000 nm)[24], possessing inherent nanoscale characteristics along with unique functionalities (such as high surface area, high surface area-to-volume ratio, excellent mass transport, and interconnected nanoporosity).[25,26,27,28]

3. Polymeric Nanoparticles: Polymeric nanoparticles are solid particles made up of macromolecular polymers, with sizes varying from 10 to 1000 nanometers.[29]

Types

1. Nanospheres: They are systems of nanoparticles that consist of a solid core surrounded by a dense polymeric matrix. These particles typically range in size from 10 to 200 nm. Generally, nanospheres can be categorized into two types: magnetic nanospheres and immune nanospheres (Kim and Lee, 2001).[30]

2. Nanocapsules: They are vesicular structures that can encapsulate a variety of active ingredients, including pesticides, within their core-shell configuration. Biopolymeric materials, such as polyglycolic acid (PGA), polycaprolactone (PCL), polylactic acid (PLA), polyethylene glycol (PEG), poly lactic-co-glycolic acid (PLGA), and chitosan, are commonly utilized for the construction of the shell.[31]

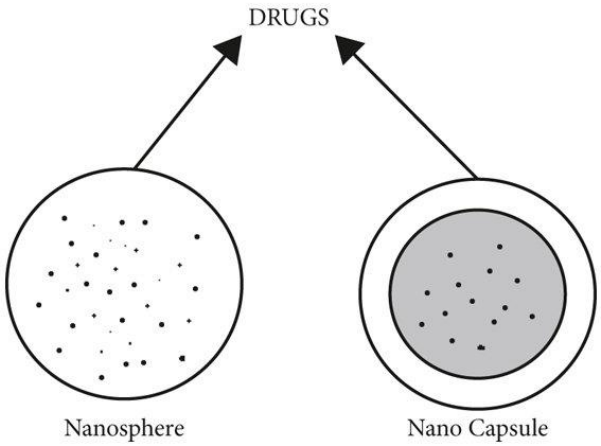


Figure 7: Diagrammatic representation of Nanosphere and Nano Capsule.[32]

4. Polymeric Micelles: They consist of colloidal structures made from block copolymers. The polymers utilized in their formation include PLA, poly(butyl methacrylate) (PBMA), polystyrene (PLS), or poly(ethylene oxide)–poly(propylene oxide) (PEO–PPO). They

spontaneously create a micellar structure once the critical micelle concentration and critical micellization temperature are exceeded.[33]

5. Polymeric Liposomes: The combination of liposomes and polymers results in a hybrid vesicle that possesses intermediate physicochemical properties and is responsive to various stimuli such as pH and temperature. The stability of liposomes regarding pH, the characteristics of the drug component, enzymatic activity, and immune reaction can be improved with the addition of polymers. By modifying liposomes with polymers, the pharmacokinetic and pharmacodynamic characteristics of the drug component are also enhanced.[34]

6. Polymeric Hydrogels: They are composed of polymers that form hydrophilic networks with crosslinks and are extensively utilized in drug delivery due to their capacity to retain significant quantities of water and biological fluids, as well as their ability to regulate drug release through their distinctive physicochemical characteristics and compatibility with biological systems.[35]

7. Polymeric Nanogel: They are three-dimensional hydrogel substances that exist at the nanoscale, created through crosslinked, swellable polymer networks capable of retaining significant amounts of water while remaining undissolved in the surrounding aqueous environment. These nanogels can be made from various natural and synthetic polymers or a blend of both. Their properties, including size, charge, porosity, amphiphilicity, softness, and degradability, can be adjusted by changing the chemical makeup of the nanogels.[36]

8. Polymeric Microspheres: They are tiny spherical particles ranging in size from 1 to 1000 μm. Sometimes, these microspheres are referred to as microparticles. They can be created from a variety of both natural and synthetic polymeric substances, as well as from inorganic materials. For instance, microspheres can be manufactured using commercially accessible polymers or ceramics.[37]

9. Polymeric Microcapsules: They contain particles sized between 1 and 100 μm, feature a separate capsule wall, typically made of polymer, which encases a biologically or chemically active core. These capsules are used for the regulated release of the active ingredient (a.i.), safeguarding it from the surrounding environment in which they are placed, or preventing the encapsulated material from interacting with other components in the formulation.[38]

10. Polymeric Implants: Polymers (with “poly” meaning many and “mer” meaning unit) consist of small molecules (mers) that are connected by primary covalent bonds in the main chain backbone, utilizing elements like carbon, nitrogen, oxygen, and silicon. A prime example of this is polyethylene, which is derived from ethylene (CH2=CH2); in this case,

carbon atoms bond with two hydrogen atoms and another carbon atom, resulting in the structure -CH2-(CH2-CH2)n-CH2-, where "n" represents the number of repeating units.[39]

11. Polymeric Patches: They typically consist of polymer films or materials based on electrospun fibers (in academic literature, the terms "film" and "patch" are frequently used as synonyms).[40]

12. Polymeric Vesicular Systems: Polymeric vesicles, known as polymersomes, are vesicular structures that can be easily created by the self-assembly of amphiphilic block copolymers in water-based solutions.[41]

13. Polymeric Dendrimer: They are uniquely structured nanoparticles formed through covalent assembly. Dendrimers have three main architectural features, which include:

• A central initiator core.

• Inner layers (generations) made up of repeated units that are radially connected to the central core.

• Outer terminal functionalities that are linked to the outermost layers of the interior generations.[42]

14. Polymer-Drug Conjugates: They are typically defined by a carefully engineered covalent linkage between a hydrophilic polymer and an active biological compound. They provide numerous important benefits compared to conventional small molecular and macromolecular therapies, including enhanced solubility and stability in water, regulated release, as well as modified pharmacokinetics and distribution within the body.[43]

15. Stimuli-responsive Polymers: They are characterized as polymers that experience significant and sudden physical or chemical alterations in response to minor external variations in environmental conditions. Various terms have been used to refer to 'stimuli-responsive' polymers, including stimuli-sensitive, intelligent, smart, and environmentally sensitive polymers.[44]

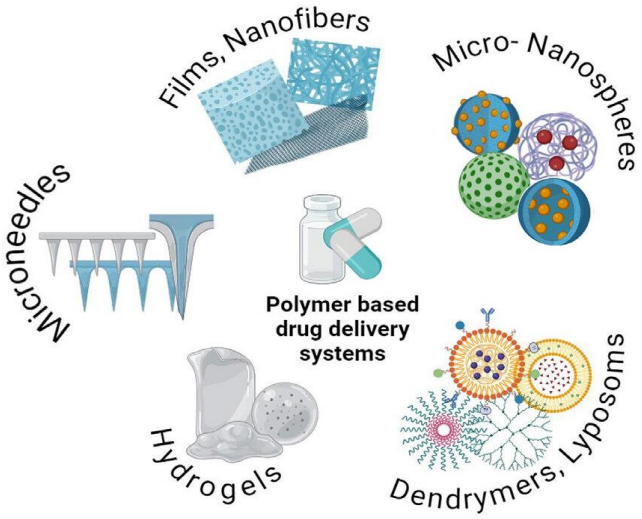


Figure 8: Diagrammatic representation of Polymer-Based Drug Delivery Systems.[45]

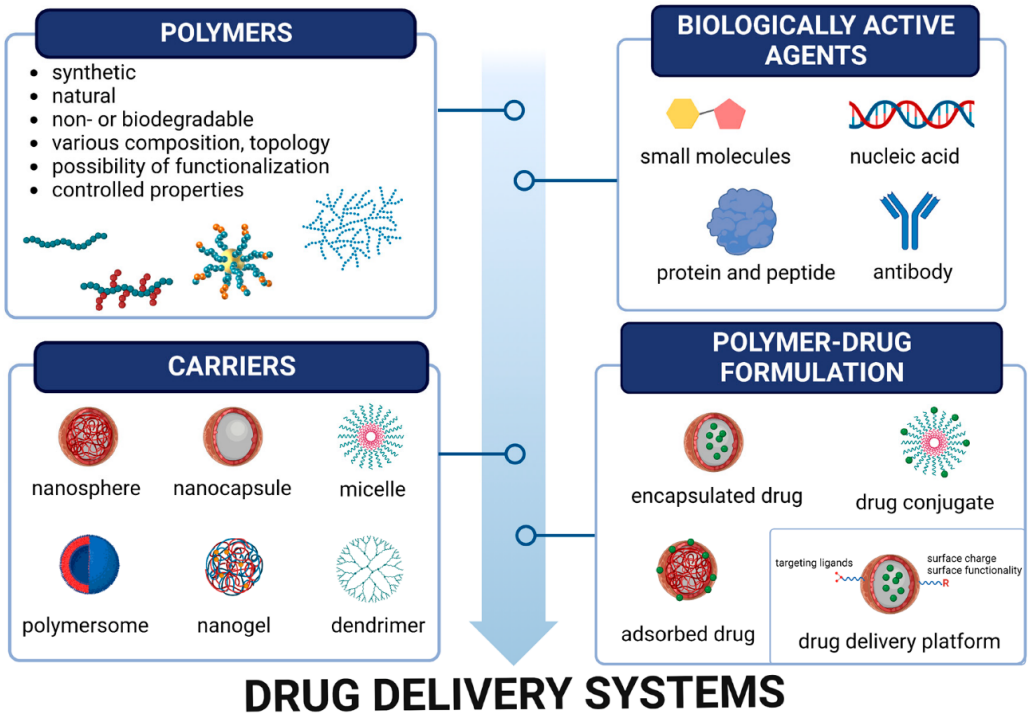


Figure 9: Diagrammatic representation of the formation of polymeric carriers for drug delivery systems.[46]

APPLICATION OF POLYMER-ENHANCED CONTROLLED RELEASE SYSTEMS:

1. Oral Drug Delivery

1. Extended-Release Tablets: Polymers can be used to formulate oral tablets that release medication gradually, reducing the frequency of dosing and sustaining therapeutic levels in the bloodstream.[47]

2. Oral Capsules: Polymeric coatings on controlled-release capsules assist in modulating medication release, improving patient adherence, and minimizing side effects.

3. Drug-Loaded Microspheres: For oral administration, microspheres encapsulated in polymer matrices facilitate sustained medication release.[48,49]

2. Transdermal Drug Delivery

1. Transdermal Patches: Constructed from polymers, transdermal patches release drugs steadily through the skin. This method is convenient and painless for administering treatments such as hormone therapy, nicotine replacement, and analgesics.

2. Microneedle Arrays: Drugs, vaccines, and biologics can be delivered subcutaneously in a controlled manner using microneedle arrays containing polymeric carriers.

3. PLGA Microspheres for Injectable Medication Delivery

Poly (lactic-co-glycolic acid) (PLGA) microspheres are extensively used as injectable long-acting drug depots, particularly for hormones, anticancer agents, and contraceptives [50]. These controlled release systems offer a versatile and innovative strategy for drug delivery, addressing diverse therapeutic needs. They can enhance therapeutic effectiveness across many medical and pharmaceutical applications by reducing side effects, improving patient adherence, and optimizing drug pharmacokinetics.[5, 51]

4. Ocular Drug Delivery

1. Contact Lens-Based Drug Delivery: Medications for eye conditions, such as glaucoma and dry eye, can be released through polymers incorporated in contact lenses, providing lasting comfort.

2. Ocular Implants: Introducing biodegradable polymeric implants into the eye allows for the gradual release of medication, decreasing the need for frequent eye drops.[52]

5. Targeted Drug Delivery

1. Polymer-Based Nanoparticles: Therapeutic agents can be embedded in polymer-based nanoparticles, which can be designed for precise drug delivery. They deliver medications directly to tumor sites while minimizing systemic exposure, especially in cancer treatment.

2. Antibody-Linked Polymer Transporters: Polymer carriers linked with antibodies or ligands that target specific receptors on cells can enhance the precision of drug delivery.[53]

6. Pulmonary Medication Delivery

Polymeric Inhalation Formulations: Polymers are utilized in inhalable drug formulations for conditions like asthma and chronic obstructive pulmonary disease (COPD) to allow controlled release in the lungs.

7. Intravaginal Drug Delivery

1. Polymeric Rings: Polymeric intravaginal rings can provide medication over an extended period, including antiviral agents and contraceptives.

2. Drug Delivery to the Central Nervous System: Biodegradable polymer implants and wafers can be inserted into the brain or spinal cord to deliver medication locally for neurological disorders.[54]

8. Periodontal Drug Delivery

Polymeric Gels and Films: In systems for periodontal drug delivery, polymers facilitate the regulated release of antimicrobial medications to combat gum disease.

9. Veterinary and Agricultural

Applications for polymer-based controlled release systems in veterinary medicine and agriculture include slow-release fertilizers, animal health products, and pest management. These systems offer a versatile and innovative method for drug delivery, addressing various therapeutic needs. They can improve therapeutic effectiveness in numerous medical and pharmaceutical contexts by reducing side effects, enhancing patient compliance, and optimizing drug pharmacokinetics.[5,51]

ADVANCES IN POLYMERS

Figure 10: Diagrammatic representation of the Advanced Polymers. [55]

FUTURE ASPECTS

The advancement of controlled drug delivery using polymers is heading towards the creation of intelligent, responsive, and biodegradable materials that can autonomously adjust drug release based on biological cues. Current studies are concentrating on hybrid nanopolymers, materials inspired by nature, and three-dimensional printed delivery systems to facilitate targeted therapies. The incorporation of artificial intelligence (AI) and biosensing technologies has the potential to further refine personalized treatment plans by anticipating drug behavior and fine-tuning dosage. Furthermore, environmentally friendly production methods and recycling of polymer materials will aid in achieving global sustainability objectives while ensuring biocompatibility and therapeutic effectiveness.

CONCLUSION

Polymer-based drug delivery systems with controlled release capabilities signify a significant advancement in contemporary pharmaceuticals, providing targeted, localized, and effective therapeutic results. Their adaptability across various classes of drugs and modes of delivery highlights their potential in clinical settings. Continuous progress in the fields of polymer science, nanotechnology, and biomaterials engineering is expected to address current issues such as toxicity, scalability, and meeting regulatory standards. In the end, these systems are set to become fundamental to the next generation of drug delivery, fostering precision medicine and enhancing the quality of life for patients.

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