REVIEW ARTICLE

Development of Grafted Copolymers from Plant Exudates and Their Application for Site-Specific Drug Delivery: A Systematic Review

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ABSTRACT

Grafted copolymers, extracted from plant exudates, have emerged as promising materials for their potential activity in site-specific drug delivery. These biopolymers, derived from natural sources, provide biocompatibility, biodegradability, and functional diversity. This review focuses on the methods of grafting copolymers onto plant exudates, the characterization of these novel materials, and their potential applications in drug delivery to specific targeted areas. We focus on specific grafted polymers such as *Tamarindus indica* acrylamide grafted polymer (TIAG), *Sterculia urens* acrylamide grafted polymer (SUAG), and *Eucalyptus obliqua* acrylamide grafted polymer (EOAG), among others, to investigate their advantageous characteristics in delivering potent molecules to the intended site of action, thereby enhancing crucial modalities such as the onset and duration of action. This review also highlights the mechanisms of drug release, targeting strategies, and the therapeutic benefits of using these biopolymers in medical applications.

Keywords: Grafted copolymers, Site-specific drug delivery, Biodegradability, Plant exudates.

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INTRODUCTION

The pharmaceutical industry continually strives for new compounds to be incorporated into the drug delivery systems that can provide controlled, targeted, and sustained release. Grafted copolymers derived from plant exudates have drawn attention due to their natural origin, ecological friendliness, and diverse chemical properties.[1] By grafting synthetic monomers like acrylamide onto these natural polysaccharides, researchers have been able to enhance their physicochemical properties, making them suitable for a variety of biomedical applications. This practice sets the stage for exploring the methods used to develop grafted copolymers, their characterization, and their potentiality in designing site-specific drug delivery systems, highlighting recent advancements and future directions.[2]

Plant Exudates and Their Grafting with Acrylamide

Tamarindus indica (TIAG)

T. indica, traditionally known as tamarind, produces a polysaccharide-rich exudate that is highly signified for its viscosity and stability. Grafting acrylamide onto tamarind polysaccharides improves their mechanical strength and responsiveness to environmental stimuli. The primary component of tamarind polysaccharides is xyloglucan, a high-molecular-weight polysaccharide composed of a β-1,4-linked glucan backbone with xylose, galactose, and other sugar residues as side chains. The structure can be summarized as follows:[3]

Glucan backbone

Comprised of β-(1→4)-linked D-glucose units.

Side chains

The side chains consist of α-D-xylose units linked to the 6-position of glucose residues. These xylose units can be further substituted with β-D-galactose and α-L-fucose.

Rationale for grafting acrylamide

The grafting of acrylamide onto tamarind polysaccharides is focused on improving certain key properties of the natural polymer such as:

- *Enhanced hydrophilicity*

Acrylamide, a water-soluble monomer, increases the hydrophilicity of the resulting grafted copolymer, which is found to be beneficial for drug loading and release, especially for hydrophobic drugs.

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- *Improved mechanical strength*

Grafting of polymers with acrylamide units enhances the mechanical strength and stability, making them suitable for film forming, hydrogels, or nanoparticles used in drug delivery systems.

- *Stimuli responsiveness*

Combining acrylamide with polymers introduces potential stimuli-responsive behavior, where the polymer can swell or shrink in response to environmental changes such as pH or temperature, aiding in controlled drug release.

Sterculia urens (SUAG):

S. urens, commonly known as gum karaya, yields a polysaccharide that is extensively used in pharmaceutical formulations. Acrylamide grafting onto it enhances its film-forming capabilities and bioadhesive properties, making it suitable for controlled drug release applications. The polysaccharides derived from SUAG are high-molecular-weight, water-soluble, and exhibit excellent viscosity with gel-forming properties. The polysaccharides in *S. urens* gum are primarily composed of galactose, rhamnose, and galacturonic acid. These monosaccharides are linked together in a specific arrangement that forms the backbone and side chains of the polysaccharide.[4]

- *Backbone*

The main chain of the polysaccharide is typically composed of repeating units of α-D-galacturonic acid and β-D-galactose, linked together through glycosidic bonds.

- *Side chains*

Rhamnose residues are often present as side chains or as part of the backbone, contributing to the branching and overall complexity of the structure.

Rationale

Enhanced drug loading and release

Acrylamide provides additional functional groups (e.g., amide groups) to the polysaccharide backbone, providing more sites for drug attachment.

Biocompatibility and biodegradability

By grafting with acrylamide, the biocompatibility and biodegradability of SUAG is retained while adding the desirable properties of synthetic polymers, making it suitable for use in drug delivery without significant risk of adverse reactions.

Versatility and functionalization

This versatile character of SUAG can be utilized for a wide range of applications, from drug delivery to the specific sites and wound healing to tissue engineering strategies.[5]

***Eucalyptus obliqua* (EOAG)**

E. obliqua, commonly known as messmate or stringybark, is a species of Eucalyptus tree that produces a natural exudate rich in polysaccharides. These polysaccharides have potential applications in various fields, including pharmaceuticals, due to their biocompatibility and biodegradability. To enhance their applications in diversified fields, acrylamide grafting is employed. The polysaccharides extracted from *E. obliqua* are typically composed of monosaccharides like glucose, galactose, mannose, arabinose, and xylose. These monosaccharides are linked together through glycosidic bonds, forming a branched and complex polymer.[6]

The general structure of *E. obliqua* polysaccharides can be described as follows:

- *Backbone*

The main chain of the polysaccharide is typically composed of repeating units of glucose, mannose, and xylose linked by glycosidic bonds.

Side chains

Galactose and arabinose are often present as side chains attached to the backbone, contributing to the overall branching of the polysaccharide.

Grafting techniques

The different techniques employed in grafting the polymers are as follows.

- *Free radical polymerization*

It is a widely used method for grafting synthetic polymers onto natural backbones. This technique involves the propagation of radical sites on the plant exudate, followed by the stimulation of synthetic monomers, resulting in graft copolymers with enhanced properties.[7] The steps involved in this method are:

Initiation

Free radical generation

The procedure of grafting begins with the generation of free radicals, which are highly reactive species with an unpaired electron. These radicals are typically generated by the decomposition of initiators such as azobisisobutyronitrile (AIBN) or benzoyl peroxide under heat or UV light.[8]

Activation of the backbone

The free radicals can be prepared to react with the existing polymer backbone, typically by abstracting a hydrogen atom from it. This step creates a radical site on the polymer chain, which is the active site for grafting**.**

Propagation

Monomer addition

Monomers (e.g., acrylamide) which were introduced into the system would react with the radical site on the backbone, stimulating the growth of a polymer chain from that point.

Chain growth

The newly formed free radical at the end of the growing chain reacts with additional monomer molecules, continuing the chain growth. As this process is repeated, the extension of the grafted polymer chain from the backbone is continued.[9]

Termination

Termination of radical sites

The polymerization process is expected to be terminated when two growing radical chains combine (coupling) or when a radical transfers its activity to another molecule (disproportionation). Termination results in the stabilization of the grafted chains and that could be the designated sign of completion of the graft copolymer structure.[10]

Graft copolymerization via chemical initiators

Chemical initiators such as ceric ammonium nitrate (CAN) and potassium persulfate (KPS) are employed to generate active sites on the plant exudate backbone. These initiators facilitate the attachment of monomers like acrylic acid, methacrylic acid, and vinyl acetate, forming graft copolymers with enhanced functionalities. The steps involved in this method are:[11]

Selection and preparation of the polymer backbone

The first step involves choosing the appropriate polymer backbone. This backbone should be typically a high molecular weight polymer that can provide the desired structural properties to the final graft copolymer. The polymer backbone must be capable of generating functional groups (e.g., -OH, $-NH_2$, -COOH) that can react with the initiators to generate active sites for grafting.

Initiation of active site

Chemical initiation of the active site is carried out due to the decomposition of the substances under specific conditions (such as heat, light, or chemical reaction) to generate free radicals, cations, or anions. The number of active sites on the backbone determines the density of grafted chains, influencing the final strength of the grafted copolymer. Chemicals like benzoyl peroxide (BPO), azobisisobutyronitrile (AIBN), potassium persulfate (KPS), ceric ammonium nitrate (CAN), aluminum chloride ($AlCl_3$), boron trifluoride (BF_3), butyllithium (BuLi) etc; are used for this purpose.

Propagation (Graft chain growth)

The monomer to be grafted (e.g., acrylamide, methyl methacrylate) is introduced into the system. The monomer molecules react with the active sites on the polymer backbone, propagating the growth of the grafted polymer chains.

- *Termination of the graft copolymerization reaction*

The graft copolymerization process is terminated when the reactive sites are deactivated by any of the mechanisms like disproportionation, combination with, Reaction with Inhibitors

- *Stabilization of structure*

After termination, the copolymer remains stabilized with grafted side chains of varying lengths and distributions, depending on the conditions of the reaction.

Enzymatic grafting

Enzymatic grafting utilizes enzymes such as laccases and peroxidases to initiate polymerization reactions. This method offers mild reaction conditions and specificity, making it suitable for sensitive bioactive molecules.

The enzymatic grafting process generally involves the following steps:[12]

- *Selection of the polymer backbone and monomer*

Enzymatic grafting begins with the appropriate selection of a polymer backbone, which may include natural polymers (e.g., polysaccharides like cellulose, starch, or chitosan) or synthetic polymers that have functional groups (e.g., hydroxyl, amino, or carboxyl groups) which interacts with the enzyme or the monomer. The monomer to be grafted is chosen based on the desired properties of the final graft copolymer.

- *Enzyme selection*

The choice of enzyme depends on the type of reaction required for grafting. Common enzymes used in grafting are laccases, peroxidases, and lipases.

- *Preparation of the reaction mixture*

The polymer backbone and the monomer are dispersed in an appropriate solvent or buffer system. The selected enzyme is added to the reaction mixture and allowed to stabilize.

- *Enzymatic activation*

Enzymes such as laccases and peroxidases catalyze the monomer, resulting in oxidation that generates reactive species such as phenoxy radicals or cationic intermediates. These reactive species combine with the polymer backbone to form a covalent bond, leading to grafting.

- *Propagation of the grafted chains*

Once the initial covalent bond is formed between the monomer and the polymer backbone, the grafted chain can continue growing through further enzymatic reactions according with the type of monomer and enzyme used.

- *Termination of the grafting reaction*

This process can be terminated by stopping the enzyme activity, usually by changing the temperature (e.g., heating) or adding enzyme inhibitors.

The pictorial representation of grafting techniques is shown in Figure 1.

Other forms of grafting techniques

Along with the above discussed methods, the grafting techniques can also be carried out by the following approaches.[14]

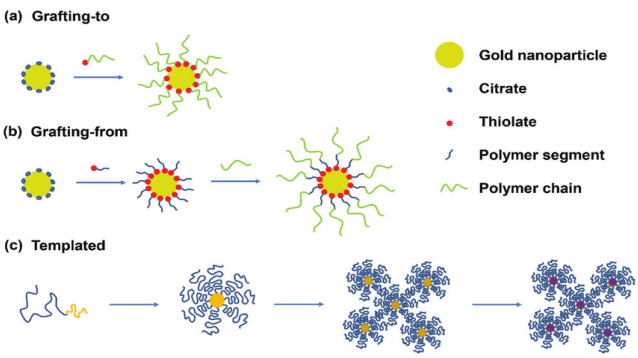

Figure 1: Diagrammatic representation of grafting techniques

- *Grafting "Onto" (Star-shaped systems)*

In this approach, pre-formed polymer chains (arms) are chemically linked to a central core. The preparation of star-shaped graft copolymers depends on the design and connection of these arms to the core.

Applications

- Precise control
- Controlled reaction rate.

Grafting "From" (Dendrimeric systems)

They are synthesized through a stepwise process, where monomers are added to reactive sites on a central core, leading to a highly branched structure. This method involves the growth of polymer chains directly from the active sites on the core molecule.

Applications:

- High surface functionality
- Enhanced drug loading capability.

Grafting "Through"

The macromolecular monomers containing polymerizable groups are assembled into a core, which results in graft formation. This technique allows for the integration of large, complex macromolecules into a single, highly functionalized polymeric system, which was illustrated in Figure 2.

Applications

- High degree of structural complexity.
- Enhanced functionality.

Purification of the graft copolymer

Purifying graft copolymers is a crucial step in ensuring that the final material is free from unreacted monomers, homopolymers, catalysts, initiators, and other impurities. Proper purification enhances the material's performance and reliability for its intended applications. The methods used for purification depend on the nature of the graft copolymer, the type of impurities present, and the solubility characteristics of the components involved. Here are some commonly used purification methods:[15]

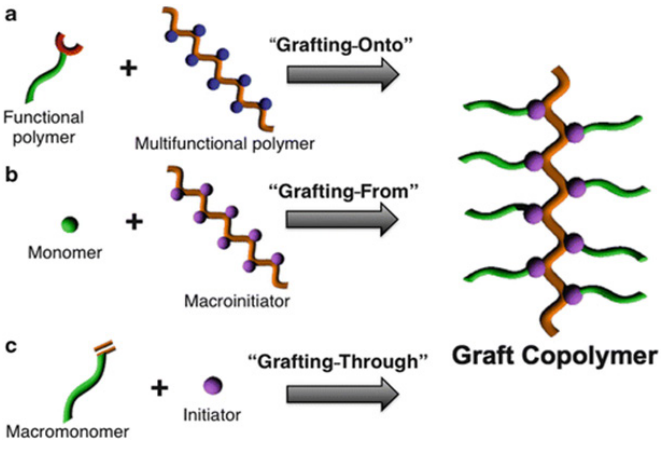

Figure 2: Grafting of monomers with polymers

- *Precipitation*

It involves dissolving the crude graft copolymer in a suitable solvent and then adding a non-solvent in which the copolymer is insoluble but the impurities are soluble. The graft copolymer precipitates out of the solution while impurities remain dissolved.

- *Dialysis*

Dialysis is a method that uses a semi-permeable membrane to separate small molecules (impurities) from larger graft copolymers based on their size. After sufficient dialysis, recover the purified graft copolymer from the bag.

- *Chromatography*

Chromatography involves passing the graft copolymer mixture through a column packed with a stationary phase, which separates components based on their size, charge, or affinity. Techniques like gel permeation chromatography, ion exchange chromatography and affinity chromatography are used for this purpose.

- *Solvent extraction*

Solvent extraction uses selective solvents to dissolve specific impurities, leaving the graft copolymer in the solid phase**.**

- *Ultrafiltration*

It is a pressure-driven separation process using membranes with specific pore sizes to separate graft copolymers from small impurities. The solution is passed through an ultrafiltration membrane, allowing small impurities to pass through while retaining the larger graft copolymer. Then the purified copolymer is recovered from the membrane surface or the retained solution.

Characterization Methods

Structural characterization

- *Fourier transform infrared spectroscopy (FTIR)*

The graft copolymer is exposed to infrared radiation, which causes molecular vibrations that are characteristic of specific chemical bonds. Key absorption bands in the FTIR spectrum can indicate the presence of functional groups such as hydroxyl (-OH), carbonyl (-C=O), amide (-$CONH_2$), and others. Comparison with spectra of the parent polymer and the monomer confirms successful grafting.

- *Nuclear magnetic resonance (NMR) spectroscopy*

The sample is subjected to a magnetic field, and the resonance frequencies of atomic nuclei (usually hydrogen or carbon) are measured. The chemical shifts in the NMR spectrum indicate the environment of the nuclei, allowing the identification of different structural units in the copolymer. This helps in determining the grafting ratio and the location of grafted chains.

- *X-ray diffraction (XRD)*

The sample is exposed to X-rays, and the diffraction pattern is recorded. Sharp peaks in the XRD pattern indicate crystalline regions, while broad halos suggest amorphous areas. Grafting

can disrupt the crystalline structure of natural polymers, leading to changes in the XRD pattern.

- *Scanning electron microscopy (SEM)*

The sample is bombarded with a focused beam of electrons, and the emitted electrons are detected to form an image. SEM images reveal the surface texture, porosity, and the presence of any grafted chains protruding from the surface. It can also show changes in morphology due to grafting.

- *Gel permeation chromatography (GPC)*

The copolymer is dissolved in a suitable solvent and passed through a column filled with porous beads. The time taken for molecules to elute from the column is related to their size. GPC provides information about the molecular weight (Mw), number average molecular weight (Mn), and polydispersity index (PDI) of the graft copolymer. The grafting process typically increases Mw and broadens the molecular weight distribution.

Thermal characterization

- *Thermogravimetric analysis (TGA)*

The sample is heated at a controlled rate, and the weight loss is recorded as a function of temperature. The temperature at which significant weight loss occurs (degradation temperature) indicates the thermal stability of the copolymer. TGA can also differentiate between the degradation of the backbone and the grafted chains.

- *Differential scanning calorimetry (DSC)*

The sample is subjected to a controlled heating/cooling cycle, and the heat flow associated with phase transitions is recorded. The Tg provides information about the polymer's flexibility and rigidity, while Tm and Tc indicate the crystalline properties. Grafting typically alters Tg, Tm, and Tc, reflecting changes in the molecular mobility and crystallinity of the copolymer.

- *Dynamic mechanical analysis (DMA)*

The sample is subjected to a small oscillatory force, and the resulting deformation is measured as the temperature is varied. The storage modulus (E'), loss modulus (E''), and damping factor (tan δ) are recorded, revealing the material's stiffness, energy dissipation, and glass transition. Grafting can influence the modulus and damping behaviour, reflecting changes in the material's mechanical properties.

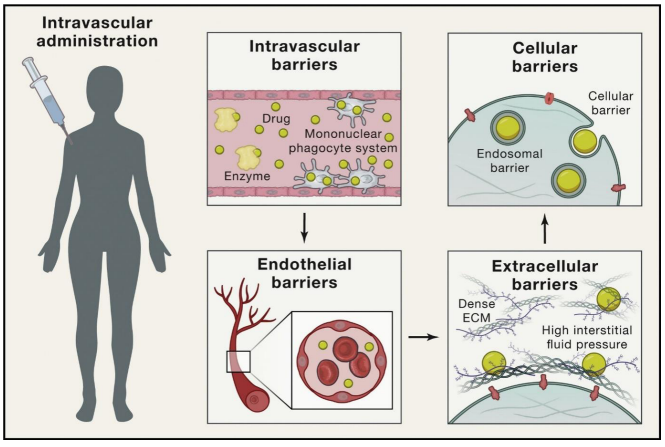

Figure 3: Applications of grafted polymers in site specific drug delivery

Applications in site-specific drug delivery

As shown in Figure 3 grafted copolymers are emerging as advanced materials for site-specific drug delivery due to their unique structural characteristics and the ability to tailor their properties for targeted therapeutic applications. These copolymers, formed by grafting monomers onto a polymer backbone, can be engineered to respond to specific stimuli, improve drug solubility, enhance stability, and control drug release profiles.[16]

Targeted drug delivery

- *Mechanism*

Grafted copolymers can be designed to selectively deliver drugs to specific tissues or cells. The grafted segments can be functionalized with ligands or antibodies that recognize and bind to specific receptors on target cells. This targeting can be passive (based on the enhanced permeability and retention (EPR) effect) or active (through ligand-receptor interactions).

Applications:

- *Cancer therapy*

Grafted copolymers can be engineered to target tumor cells by attaching ligands that bind to receptors overexpressed on cancer cells. For example, folic acid-grafted polymers target folate receptors, which are commonly overexpressed in certain types of cancer.

- *Cardiovascular diseases*

Targeted delivery to inflamed tissues or atherosclerotic plaques using grafted copolymers functionalized with peptides or antibodies that recognize specific markers on these tissues.

Stimuli-responsive drug delivery

- *Mechanism*

Grafted copolymers can be synthesized to respond to specific stimuli such as pH, temperature, enzymes, or redox conditions. These stimuli can trigger the release of the drug at the target site, ensuring that the drug is released only under specific conditions**.**

Applications

- *pH-sensitive drug delivery*

Grafted copolymers that are sensitive to pH changes can release drugs in the acidic environment of tumours or inflamed tissues. For instance, copolymers grafted with pH-responsive monomers like poly (acrylic acid) can release the drug when the pH drops in the target area.

- *Temperature-sensitive*

Drug Delivery: Copolymers grafted with thermoresponsive monomers, such as poly(N-isopropylacrylamide), can be used for drug release in response to local hyperthermia treatments in cancer therapy.

Table 1: List of some grafted polymers with specific approaches

Conducting polymer system	*Grafted/Attached system*	*Approach*
poly(3,4-ethylenedioxythiophene)	Poly (acrylic acid)	ATRP, followed by acid hydrolysis of tert-butyl acrylate
poly(o-methoxyaniline)	Polyacrylamide	Oxidative-radical coupling
Polyaniline	Xanthan gum	Oxidative polymerization
Polyaniline	Novolac	Oxidative polymerization
Polythiophene	Poly(ethylene oxide)	Combination of oxidative radical polymerization and click reactions
Polythiophene	Polyselenophene	KCTP followed by click reaction

- *Enzyme-sensitive drug delivery*

In diseases where specific enzymes are overexpressed, such as matrix metalloproteinases (MMPs) in cancer, grafted copolymers can be engineered to degrade and release the drug in response to these enzymes.

Controlled drug Release

- *Mechanism*

Grafted copolymers allow for the precise control of drug release rates. By adjusting the length and density of the grafted chains, the diffusion rate of the drug can be regulated, leading to sustained release over time**.**

Applications

- *Long-acting injectables*

Grafted copolymers are used in formulations that provide sustained drug release over weeks or months. This is beneficial in chronic conditions such as diabetes or schizophrenia, where consistent drug levels are needed.

Oral drug delivery

Grafted copolymers can protect the drug in the gastrointestinal tract and control its release, ensuring that the drug is released at the desired location, such as the colon.

Improved drug solubility and stability

- *Mechanism*

Hydrophobic drugs often suffer from poor solubility and stability, limiting their therapeutic efficacy. Grafted copolymers can improve the solubility and stability of these drugs by encapsulating them within the hydrophobic or hydrophilic segments of the copolymer.

Applications

- *Solubilization of hydrophobic drugs*

Grafted copolymers with hydrophilic backbones and hydrophobic grafts can solubilize poorly soluble drugs, making them more bioavailable.

- *Protection from degradation*

Drugs prone to degradation (e.g., peptides or nucleic acids) can be stabilized by grafted copolymers that protect them from enzymatic or chemical degradation.

Gene Delivery

Mechanism

Grafted copolymers can be used as non-viral vectors for gene delivery. They can encapsulate nucleic acids and protect them from degradation, facilitate their entry into cells, and release them in the intracellular environment.[17]

Applications

- *siRNA delivery*

Grafted copolymers are being explored for the delivery of small interfering RNA (siRNA), which can silence specific genes involved in disease processes. The copolymers protect the siRNA from nuclease degradation and ensure its delivery to the target cells.

- *DNA vaccines*

Grafted copolymers can enhance the delivery of DNA vaccines, ensuring that the genetic material is efficiently delivered to immune cells to stimulate an immune response.

Multifunctional Drug Delivery Systems:

Mechanism

Grafted copolymers can be designed to carry multiple drugs or therapeutic agents, enabling combination therapy in a single delivery system. This can be particularly effective in diseases like cancer, where multiple pathways need to be targeted simultaneously.[18]

Applications

- *Combination cancer therapy*

Grafted copolymers can co-deliver chemotherapeutic agents, targeted therapies, and imaging agents, allowing for simultaneous treatment, and monitoring of the disease.

- *Multimodal therapy*

Grafted copolymers can be engineered to release drugs in response to different stimuli, enabling a sequential or simultaneous treatment approaches.

CONCLUSION

Grafted copolymers from *T. indica*, *S. urens*, and *E. obliqua* represent a promising avenue for developing advanced site-specific drug delivery systems. Their biocompatibility,

biodegradability, and enhanced functional properties make them suitable for a wide range of therapeutic applications. Future research should focus on refining grafting techniques, improving drug loading and release profiles, and exploring new medical applications for these versatile biopolymers.

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