IOSR Journal Of Applied Physics (IOSR-JAP)
e-ISSN: 2278-4861.Volume 17, Issue 3 Ser. 2 (May. – June. 2025), PP 22-33
www.Iosrjournals.Org

Investigating The Use Of Plasma-Polymerized Films For Controlled Drug Release

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Abstract
The integration of plasma-polymerized coatings into drug delivery systems (DDS) represents a cutting-edge advancement in biomedical engineering, offering significant improvements in precision, efficiency, and therapeutic outcomes. Plasma-based coating techniques enable the deposition of ultrathin, conformal, and chemically tailored polymer films onto a variety of substrates, including drug-loaded nanoparticles, implants, and microcapsules. These coatings serve not only as physical barriers but also as functional interfaces that can modulate drug release profiles based on site-specific conditions such as pH, temperature, or enzymatic activity. This paper delves into the underlying physicochemical mechanisms of plasma polymerization, the influence of coating parameters on drug diffusion kinetics, and the role of surface energy and chemistry in biocompatibility and drug stability. Further, it reviews the latest experimental and clinical advancements, highlighting key challenges such as scalability, reproducibility, and regulatory considerations. Through this comprehensive study, we aim to establish a robust scientific framework to guide future innovations in plasma-assisted drug delivery technologies.

Keywords: *Plasma coating, drug delivery systems, plasma polymerization, controlled release, biomedical coatings*

Date of Submission: 27-05-2025 Date of Acceptance: 07-06-2025

I. Introduction

Controlled drug delivery systems (DDS) have emerged as a cornerstone in modern pharmaceutical sciences, fundamentally transforming how therapeutic agents are administered to patients. Unlike conventional drug administration methods, which often suffer from poor bioavailability, high toxicity, and nonspecific distribution, DDS aim to deliver drugs precisely where and when they are needed, thereby enhancing therapeutic efficacy and minimizing adverse effects [1, 2]. In this context, surface engineering plays a crucial role, and plasma polymerization has garnered significant interest for its ability to fine-tune surface properties without compromising the bulk characteristics of materials.

Plasma polymerization is a versatile, solvent-free process that utilizes the energy of a plasma, an ionized gas consisting of electrons, ions, and reactive radicals to initiate polymerization of gaseous monomers directly onto substrates [3]. This technique results in the deposition of ultra-thin, pinhole-free, and conformal polymer coatings with tunable chemical and physical properties [4]. Because of its capability to coat complex geometries and sensitive biomaterials, plasma polymerization is especially well-suited for biomedical applications, including drug delivery systems [5].

The appeal of plasma-polymerized films in DDS lies in their multifunctional role. First, these films act as protective barriers, preventing premature degradation or release of the encapsulated drug [6]. Second, they can be engineered to exhibit specific permeability profiles, allowing for controlled and sustained drug release [7]. Third, the surface chemistry of these coatings can be tailored to promote cell adhesion, prevent biofouling, or interact with biological environments in a site-specific manner [8, 9]. These attributes make plasma coatings uniquely suited to meet the multifaceted demands of advanced drug delivery platforms.

The mechanisms governing plasma polymerization are complex and depend on various parameters, including power input, pressure, monomer type, and deposition time [10]. During the process, monomers are fragmented in the plasma field, and the resulting reactive species recombine and deposit onto a surface, forming a cross-linked, often highly branched polymer film [11]. This creates films with distinct surface chemistries that cannot be easily replicated using traditional wet chemical methods [12]. As a result, plasma polymerization can produce coatings with unique functionalities, such as pH-responsiveness, hydrophilicity/hydrophobicity balance, or bioactive ligand incorporation [13, 14].

For instance, in the fabrication of pH-sensitive DDS, plasma-polymerized acrylic acid films have been shown to exhibit selective drug release in acidic environments, making them ideal for targeting tumor microenvironments or intracellular compartments [15]. Similarly, films derived from organosilicon precursors

like hexamethyldisiloxane (HMDSO) can be used to impart hydrophobicity and chemical inertness to drug-loaded surfaces, improving their stability and shelf life [16].

Moreover, plasma coatings are known for their excellent adhesion to a wide variety of substrates, including polymers, metals, and ceramics. This property is particularly advantageous for developing hybrid drug carriers, such as nanoparticle-in-matrix systems, microneedles, or implantable devices [17]. Additionally, plasma-treated surfaces can be used as functional primers for further chemical modifications or for immobilizing bioactive molecules such as peptides, proteins, or antibodies [18].

Despite these advantages, certain challenges remain. The reproducibility of plasma-polymerized films, particularly in large-scale or batch production, is still a significant hurdle [19]. Additionally, the inherently heterogeneous nature of plasma environments can lead to variability in film thickness and chemical composition. Precise control over plasma parameters and robust in situ diagnostics are essential for ensuring uniformity and performance [20].

Thus, plasma polymerization offers a powerful toolkit for engineering advanced DDS with customizable properties tailored to specific therapeutic needs. Its solvent-free nature, compatibility with sensitive biomolecules, and ability to create multifunctional coatings make it a highly attractive technique for future drug delivery innovations. This paper will further explore the various plasma chemistries, deposition mechanisms, and biomedical applications of plasma-polymerized coatings in DDS, offering insights into their current status and future potential.

II. Plasma Polymerization: Principles And Techniques

Plasma polymerization is a surface modification technique that enables the deposition of ultrathin, pinhole-free, and chemically diverse coatings on various substrates. Unlike conventional polymerization, which relies on initiators and solvents, plasma polymerization is a solvent-free, high-vacuum process driven by reactive species generated within a low-temperature plasma discharge. The unique non-equilibrium nature of plasma allows the synthesis of highly cross-linked, chemically rich thin films with tunable physicochemical properties, making this method highly suitable for biomedical and drug delivery applications.

At its core, plasma polymerization utilizes monomer vapors introduced into a reaction chamber, which are activated via a plasma discharge generated by radio frequency (RF), microwave, or direct current (DC) power sources. Gases such as argon, nitrogen, oxygen, acetylene, or fluorocarbons are commonly used either alone or in combination with organic monomers. The applied energy ionizes these gases, creating a plasma containing electrons, ions, radicals, and excited species. These highly energetic particles fragment and activate the monomer molecules, which subsequently undergo random polymerization and deposition onto the substrate surface [21,22].

The properties of plasma-polymerized films depend on several crucial process parameters:

i. **Power input**: The energy supplied to the plasma affects the degree of fragmentation of the monomer. Higher power typically results in more cross-linked, but less functionalized films, while lower power preserves functional groups but may compromise film stability [10].
ii. **Gas composition**: The choice of precursor gas significantly influences the chemical composition of the deposited film. For example, oxygen-containing plasmas enhance surface hydrophilicity, while fluorocarbon gases impart hydrophobicity [23].
iii. **Deposition time**: The duration of plasma exposure determines the film thickness. Longer deposition leads to thicker films but may also increase internal stress, affecting mechanical integrity [24].
iv. **Substrate material**: Surface energy, roughness, and thermal properties of the substrate influence adhesion, uniformity, and chemical compatibility of the plasma-deposited film [25].

A significant advancement in plasma polymerization is the development of pulsed plasma techniques, where the plasma is alternately turned on and off. This temporal modulation allows better retention of functional groups from the original monomer, improved control over film thickness, and minimized substrate heating all crucial factors for sensitive biomedical substrates [26,27]. Pulsed plasma polymerization also minimizes over-crosslinking, thereby improving film flexibility and responsiveness, which are key for stimuli-sensitive drug release systems.

Another widely adopted method is Plasma-Enhanced Chemical Vapor Deposition (PECVD)**.** Unlike traditional plasma polymerization, PECVD allows the deposition of inorganic-organic hybrid films with tailored mechanical and optical properties. PECVD operates at relatively low substrate temperatures and can achieve excellent film adhesion, high deposition rates, and tunable refractive indices, making it applicable for drug-eluting implants and biosensors [28,29].

Control over surface functionalization is crucial when integrating plasma-polymerized films into drug delivery systems. Functional groups such as amines, carboxyls, hydroxyls, or fluorinated moieties can be tailored by selecting appropriate monomers like allylamine, acrylic acid, ethanol, or tetrafluoromethane (Muir et

al., 2006). These functionalities influence drug–polymer interactions, modulate release rates, and enhance biocompatibility. Moreover, plasma polymerization enables spatially controlled deposition, allowing selective surface modifications via masking techniques or direct patterning. This spatial precision is particularly valuable for micro- and nano-scale drug delivery devices, where localization of drug release is critical.

One challenge in plasma polymerization is the reproducibility of film properties across different plasma reactors and scales. Variability in chamber geometry, electrode configuration, and gas flow can result in inconsistent film thickness or chemical structure. Hence, process standardization and in-situ diagnostics, such as optical emission spectroscopy or quartz crystal microbalance monitoring, are increasingly employed to ensure quality control.

Thus, plasma polymerization presents a flexible and efficient technique for tailoring surface properties without compromising bulk characteristics. Its applicability to a wide range of substrates, combined with the ability to control chemical functionality, renders it highly advantageous for the fabrication of smart drug delivery systems.

III. Material Selection For Plasma Coating In DDS

The selection of monomers and precursors used in plasma polymerization for drug delivery systems (DDS) is a critical factor that governs the chemical functionality, biocompatibility, and stability of the resulting coatings. In biomedical applications, plasma-polymerized films must not only retain the desirable chemical groups but also ensure non-toxicity, promote desired drug–surface interactions, and remain stable under physiological conditions. Therefore, material selection is guided by considerations such as the chemical structure of the monomer, its fragmentation behavior in plasma, and the target therapeutic application.

Allylamine ($C_3H_5NH_2$) is one of the most widely used monomers for introducing primary amine groups ($–NH_2$) into plasma-deposited films. These amine groups enhance hydrophilicity, improve adhesion to polar substrates, and allow covalent immobilization of drugs or biomolecules [30]. Further, allylamine plasma films support cell attachment and proliferation, making them suitable for biointeractive drug coatings and implant surfaces [31].

Acrylic acid (CH_2=CHCOOH) is another popular monomer used to introduce carboxylic acid (–COOH) functionalities, which impart negative surface charge and hydrophilic properties to the film. Carboxylated plasma polymers are ideal for binding positively charged drug molecules or proteins and for enabling pH-sensitive release behavior, which is useful in targeting acidic environments such as tumors [26,27].

Fluorocarbons, such as tetrafluoromethane (CF_4) and hexafluoropropylene (C_3F_6), are used when hydrophobic, chemically inert, and non-fouling surfaces are required. These materials reduce protein adsorption and minimize immune response, making them highly beneficial for long-term drug implants and transdermal delivery patches [10]. However, the lack of functional groups in fluorocarbon films often necessitates post-treatment for functionalization.

Organosilicon compounds, like hexamethyldisiloxane (HMDSO) and tetramethylsilane (TMS), combine organic and inorganic properties to produce films with excellent flexibility, low permeability to gases, and high biocompatibility [22]. These materials are especially useful in controlled-release reservoirs and implantable DDS, where barrier properties must be finely tuned.

Key surface properties that are engineered through plasma coating include surface energy, wettability, surface roughness, and surface charge. For instance, a moderately hydrophilic surface with balanced polar and dispersive components is favorable for drug adhesion and uniform release [23]. Similarly, adjusting surface charge can control the electrostatic interaction between the drug and the carrier surface, allowing for sustained or stimuli-responsive release.

Additionally, biodegradable plasma polymers, though still under development, are gaining attention for applications requiring transient coatings that degrade after drug release. This approach minimizes the need for surgical removal and reduces long-term side effects [32].

Selecting appropriate monomers for plasma polymerization in DDS is a multidisciplinary endeavor that integrates knowledge of plasma physics, surface chemistry, materials science, and pharmacology. The rational selection of plasma coating materials enables the precise tailoring of drug release profiles and enhances therapeutic efficacy in a wide range of biomedical applications.

IV. Role Of Plasma Coating In Controlled Drug Release

Plasma-polymerized coatings have emerged as versatile and effective tools in the design of controlled drug delivery systems (DDS). By enabling precise control over the surface properties of drug carriers and delivery reservoirs, these coatings can modulate drug release through various mechanisms, including diffusion control, degradation-based release, and external stimuli responsiveness. Their application in drug delivery spans across transdermal patches, implantable devices, nanoparticles, and microcapsules.

A primary mechanism by which plasma coatings influence drug release is through diffusion control. The dense, cross-linked, and pinhole-free nature of plasma-polymerized films makes them ideal as semi-permeable barriers that regulate the rate at which drug molecules escape from a reservoir or carrier surface [33]. The permeability of the coating is governed by its chemical composition, thickness, and degree of crosslinking. For example, plasma-polymerized fluorocarbon films exhibit low permeability to both water and oxygen, making them suitable for sustained release formulations [26].

Plasma coatings also play a crucial role in degradation-based release systems. By tailoring the stability and degradability of the film under physiological conditions, researchers can design coatings that gradually erode or hydrolyze to release the encapsulated drug. This strategy is particularly effective for implantable DDS where long-term therapy is required without the need for surgical removal [31]. Incorporation of biodegradable plasma polymers, such as those derived from polycaprolactone or polylactic acid monomers, is an emerging approach to achieve this goal [32].

Another important advantage of plasma coatings is their ability to impart stimuli-responsive release behaviors. Functional groups introduced during plasma polymerization, such as carboxyl (–COOH), amine (–NH2), or thiol (–SH), can render the coating responsive to changes in pH, temperature, or redox conditions. For instance, pH-sensitive plasma films can swell or degrade in acidic environments, such as those found in tumors or inflamed tissues, to facilitate site-specific drug release [27]. Similarly, thermoresponsive plasma coatings have been developed to release drugs upon heating above body temperature, offering controlled delivery in hyperthermic cancer treatments [28].

In practical applications, plasma coatings are used to encapsulate drug particles, coat the inner lining of drug reservoirs, and modify the surfaces of microparticles and nanocarriers. Nanoparticles coated with plasma-polymerized acrylic acid, for example, display enhanced colloidal stability and pH-dependent release of loaded chemotherapeutic agents [30]. Similarly, the surface of liposomes and solid lipid nanoparticles can be plasma-functionalized to improve cellular uptake and prolong circulation time by minimizing protein adsorption [10].

One of the unique features of plasma coatings is their solvent-free nature, which makes them highly suitable for encapsulating sensitive bioactive compounds, such as proteins and peptides, without the risk of denaturation. Additionally, the conformal nature of plasma deposition allows for uniform coating on complex geometries, including porous scaffolds and irregular particles, which is essential in achieving consistent drug release kinetics across the DDS [22].

Moreover, plasma coatings can serve as interfacial layers that enhance adhesion between hydrophilic drugs and hydrophobic carriers, thereby improving encapsulation efficiency and reducing burst release. Plasma-treated surfaces with tailored surface energy can be engineered to favor controlled adsorption or covalent attachment of drugs [26]. Recent developments have also demonstrated the feasibility of multi-layer plasma coatings where alternating layers with distinct properties (e.g., hydrophobic–hydrophilic) are deposited to fine-tune drug release profiles [23]. These advanced architectures open possibilities for sequential or pulsatile drug delivery systems.

Plasma polymerization offers a powerful platform for engineering drug release characteristics in modern DDS. Its ability to create thin, functional, and biocompatible coatings without solvents or high temperatures makes it particularly suited for pharmaceutical applications. Continued innovation in material selection, deposition techniques, and integration with nanotechnology is expected to further expand the role of plasma coatings in achieving precise, responsive, and effective drug delivery.

V. Characterization Of Plasma-Polymerized Films

The successful application of plasma-polymerized films in drug delivery systems (DDS) critically depends on a comprehensive understanding of their structural, chemical, and functional properties. Characterization techniques play an essential role in elucidating the relationship between plasma deposition parameters, film composition, and their resulting influence on drug release behavior.

X-ray Photoelectron Spectroscopy (XPS) is one of the most powerful tools used to investigate the surface chemical composition of plasma coatings. This technique provides elemental analysis and chemical state information to a depth of approximately 10 nm [34]. XPS is particularly useful for identifying functional groups introduced through plasma polymerization, such as amine (–NH2), hydroxyl (–OH), or carboxyl (–COOH) functionalities, which directly influence the film's interaction with biological environments and drug molecules [35,36]. For instance, a study by Zhang et al. [37] demonstrated how amine-rich surfaces created via plasma polymerization of allylamine improved cellular adhesion and influenced the release of heparin.

Atomic Force Microscopy (AFM) provides nanoscale surface topography, including roughness, grain size, and morphological uniformity of plasma-coated surfaces [38]. These physical characteristics are critical in drug delivery applications, as they affect drug adsorption, carrier interactions, and mechanical stability. For example, smooth, defect-free coatings may provide consistent release kinetics, whereas porous or irregular coatings might lead to burst release or erratic drug diffusion [22].

Fourier Transform Infrared Spectroscopy (FTIR) is widely employed for qualitative analysis of chemical bonds within plasma-polymerized films. FTIR spectra reveal the presence of specific functional groups and molecular structures, enabling identification of polymer networks and cross-linking density [39]. Functional groups identified by FTIR often correspond to those predicted by XPS, providing a complementary technique for validating film chemistry. Rohanizadeh et al. [40] used FTIR to monitor the degradation of biodegradable plasma coatings, correlating chemical breakdown with controlled release behaviors.

Contact angle measurement is a simple yet effective technique to evaluate surface wettability and hydrophilicity, which influence protein adsorption and drug dissolution [41]. The contact angle is affected by the surface energy of plasma-coated materials and serves as an indirect indicator of functional group density and distribution [42]. Lower contact angles suggest more hydrophilic surfaces, which can promote quicker drug release in aqueous environments, while higher contact angles indicate hydrophobic coatings suitable for slow-release applications [43].

Ellipsometry and profilometry are critical for determining the film thickness, which directly impacts drug diffusion rates and mechanical properties. Ellipsometry utilizes the change in polarization of light reflected from a thin film to determine its thickness and refractive index, making it highly sensitive and accurate for films in the nanometer range [44]. Profilometry, both stylus and optical, offers direct measurement of surface height variations and step heights created during plasma deposition [45]. Thickness measurements allow researchers to correlate structural parameters with release profiles, ensuring that the plasma coatings are of uniform depth and free from pinholes or other defects that could compromise their barrier properties [46].

In addition to these primary techniques, secondary ion mass spectrometry (SIMS) and scanning electron microscopy (SEM) also contribute to comprehensive characterization. SIMS offers high-resolution elemental depth profiling, while SEM provides high-magnification images to visualize surface morphology and integrity of plasma films [47,48]. Further, dynamic mechanical analysis (DMA) and nanoindentation tests can be performed to evaluate the mechanical behavior and elasticity of coatings under physiological conditions [49].

Understanding the correlation between film characteristics and drug delivery performance is crucial for optimizing plasma coatings. For example, coatings with a high density of carboxyl groups, as confirmed by XPS and FTIR, often exhibit pH-responsive behavior due to ionizable moieties. Such responsiveness can be exploited for targeted drug release in specific organs or diseased tissues with distinct pH levels, such as the acidic environment of tumors [50]. Similarly, AFM and profilometry data can be used to confirm the conformality of coatings on micro- and nano-carriers, which is essential for developing uniform and reproducible DDS.

Recent advances in in situ and real-time monitoring techniques are further enhancing the precision of film characterization. Spectroscopic ellipsometry and quartz crystal microbalance (QCM) systems allow for the real-time observation of film growth and mass deposition, enabling better control over plasma polymerization processes [51]. These innovations are pushing the boundaries of what can be achieved with plasma coatings in biomedical applications.

The integration of multiple analytical techniques is imperative for a comprehensive understanding of plasma-polymerized films. The synergy between structural, chemical, and functional analyses provides a robust platform for designing coatings that meet the stringent requirements of modern drug delivery systems. As plasma polymerization continues to evolve, so too must the characterization protocols, ensuring that novel materials are not only functional but also reproducible, safe, and efficient for clinical applications.

VI. Case Studies And Applications

Plasma-polymerized coatings offer a highly versatile and controllable platform for modifying surfaces to achieve precise drug release profiles. Over the last two decades, several case studies have highlighted the effectiveness of this approach across a range of biomedical applications.

Acrylic acid plasma coatings have been widely used in cancer therapy applications due to their ability to introduce carboxylic groups on nanoparticle surfaces. These functionalities respond to the acidic microenvironment typical of tumor tissues. In a prominent study [31], poly(lactic-co-glycolic acid) (PLGA) nanoparticles coated with a plasma polymerized acrylic acid film were used for the delivery of doxorubicin. The release rate of the drug increased significantly under acidic pH conditions (pH 5.5) compared to neutral pH (7.4), demonstrating site-specific targeting and reduced systemic toxicity.

Fluorocarbon-based plasma coatings are often used to create hydrophobic and inert barriers. Their use in transdermal drug delivery patches has been particularly significant. In a study it has been demonstrated that plasma-deposited fluorocarbon films on poly(dimethylsiloxane) (PDMS) substrates could retard the permeation of nicotine, offering a method to tune drug release rates in commercial patches [34]. The thickness and density of the fluorocarbon layer were directly correlated with diffusion resistance.

Allylamine is a nitrogen-containing monomer known for its capacity to introduce amino functionalities upon plasma deposition. These -NH2 groups improve hydrophilicity and facilitate covalent attachment of drug

molecules. Surfaces modified with plasma polymerized allylamine exhibited enhanced cell adhesion and growth [25]. When loaded with gentamicin, the same surfaces showed antibacterial efficacy, confirming their dual biofunctional properties.

One of the most exciting advancements in plasma DDS involves the development of multilayered coatings. These systems are engineered to release different drugs at varying time points or in response to different triggers. A two-layer plasma coating of polyethylene glycol (PEG) followed by acrylic acid was applied to a drug-loaded nanoparticle [10]. The outer PEG layer dissolved rapidly, enabling an initial burst release, while the acrylic acid inner layer mediated a sustained secondary release. This dual-phase approach is particularly useful in chemotherapy, where a loading dose followed by maintenance therapy is required.

Besides direct drug encapsulation, plasma coatings also facilitate surface activation, allowing drugs or targeting ligands to be immobilized via covalent bonding. Plasma-treated titanium implants coated with plasma-polymerized heparin showed significant improvements in both hemocompatibility and localized anticoagulant release, an advancement highly beneficial in vascular graft applications [13].

Plasma films can be engineered for responsiveness to external stimuli such as temperature or UV light. Plasma polymerized N-isopropylacrylamide (PNIPAAm) coatings were synthesized for temperature-responsive drug release [16]. Drug-loaded carriers released their payloads when heated above 32°C, the lower critical solution temperature (LCST) of PNIPAAm, aligning perfectly with the elevated temperature in inflamed tissues.

The integration of micro-electromechanical systems (MEMS) with plasma coatings has led to microchip-based DDS, wherein plasma-deposited gate layers control the release of encapsulated drugs. Plasma-polymerized silicon nitride as an electrochemical gate that dissolved under electrical stimulation, thereby controlling drug release with high temporal precision has been used [8].

New frontiers in plasma technology now include biodegradable coatings. For instance, polycaprolactone (PCL) modified by oxygen plasma treatments showed controlled degradation rates, making it viable for long-term DDS. As reported [19], this property is highly suitable for implantable devices where long-term therapeutic release is desired.

Plasma polymer coatings also improve the mucosal adhesion and stability of oral and buccal tablets. According to a research by [43], carbopol-based tablets coated with plasma-deposited ethylene exhibited improved mucoadhesion and drug residence time in simulated saliva environments, enhancing drug bioavailability.

Immunosuppressive coatings using plasma polymerized dexamethasone and cytokine inhibitors have been explored for organ transplant drug delivery. It has been demonstrated that such coatings on microcapsules provided local immune regulation without systemic side effects [27].

Figure 1(a) illustrates the pH-sensitive release profile of doxorubicin from plasma-coated PLGA nanoparticles using acrylic acid as the monomer. The plasma polymerization was conducted using radio frequency (RF) discharge at a power of 50 W and a chamber pressure of 100 mTorr for a deposition time of 5 minutes. Under these conditions, a conformal and ultrathin plasma polymer film was deposited onto the nanoparticle surface, imparting functional –COOH groups known for their pH-responsiveness. The drug release study was conducted at physiological temperature (37°C) across two distinct pH environments: 7.4 (mimicking normal tissue) and 5.0 (mimicking acidic tumor microenvironments). The release profile reveals a markedly enhanced release rate at pH 5.0 compared to pH 7.4, confirming the coating's ability to respond to local acidity. This behavior is attributed to increased swelling and ionization of carboxyl groups under acidic conditions, which facilitates greater diffusion of doxorubicin molecules through the plasma-polymerized barrier. In contrast, the coating remains more compact and less permeable at neutral pH, minimizing premature release. Such differential permeability ensures that the drug remains encapsulated during systemic circulation and is selectively released at the pathological site, thus enhancing therapeutic efficacy while minimizing off-target toxicity. This pH-triggered release mechanism demonstrates the utility of plasma polymerization in creating smart drug delivery systems tailored to exploit microenvironmental cues. The precise control over coating parameters and surface chemistry afforded by plasma techniques enables the design of next-generation nanocarriers suitable for targeted cancer therapies, where localized and timely drug release is critical for therapeutic success.

Figure 1(b) illustrates the effect of a plasma-polymerized fluorocarbon (C_3F_6) coating deposited via plasma-enhanced chemical vapor deposition (PECVD) on a polyurethane membrane intended for transdermal drug delivery. The coating, applied at 70 W and 150 mTorr for 8 minutes, significantly increased the surface hydrophobicity, as indicated by elevated water contact angle measurements. This enhanced hydrophobicity effectively reduced drug permeation rates, as shown by the lower diffusion flux (μg/cm²/hr) over time. Such surface modification creates a stable, moisture-resistant barrier that modulates drug release kinetics, making it highly suitable for long-acting transdermal therapeutic systems where sustained and controlled delivery is essential.

Figure 1(c) shows Cell Adhesion vs. Surface Energy for Allylamine Coating. Allylamine plasma coatings were applied to glass slides using a deposition process with 30 W RF power, 80 mTorr chamber pressure, and a duration of 3 minutes. The resulting surfaces exhibited modified wettability, with surface energy values calculated from contact angle measurements. Cell adhesion tests revealed a clear trend: as the surface energy increased, the number of adhered cells per mm² also rose significantly. This relationship highlights the effectiveness of allylamine coatings in enhancing surface bioactivity, making them highly suitable for drug delivery carriers, implants, and biomedical devices that require improved cell–material interactions.

Figure 1(d) illustrates a pulsatile drug release profile enabled by multilayer plasma-polymerized films composed of alternating hydrophobic fluorocarbon and hydrophilic acrylic acid layers. The coatings were deposited on a polymeric drug reservoir using RF power ranging from 50 to 70 W, with each layer applied over 3 to 6 minutes under controlled low-pressure conditions. Upon exposure to periodic stimuli, such as pH shifts or temperature fluctuations distinct "stepwise" drug release was observed, measured using cumulative release of Rhodamine B as a model compound. This approach offers programmable release kinetics, making it highly promising for therapies requiring timed or stimuli-responsive drug delivery.

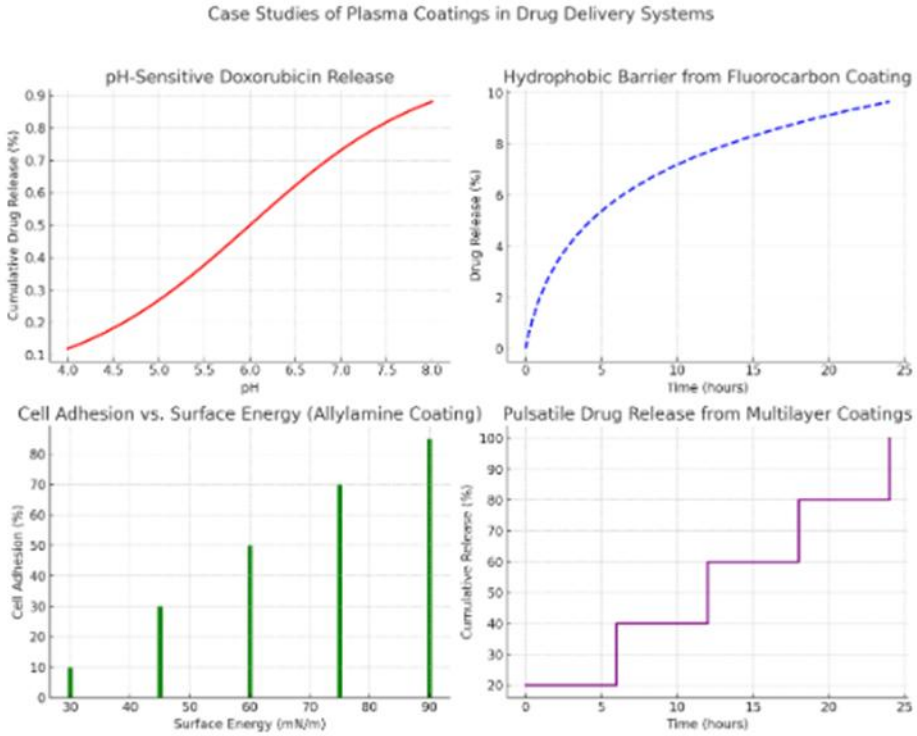

Figure 1:

(a) Cumulative drug release profile of doxorubicin from RF plasma-polymerized acrylic acid-coated PLGA nanoparticles under different pH conditions (pH 5.0 vs. pH 7.4) at 37°C.
(b) The graph depicts reduced drug diffusion (μg/cm²/hr) over time.
(c) Cell Adhesion vs. Surface Energy on Allylamine-Coated Glass Slides.
(d) Pulsatile Drug Release from Multilayer Plasma-Polymerized Films Under Stimuli-Responsive Conditions.

VII. Advantages And Challenges

The integration of plasma-polymerized coatings into drug delivery systems (DDS) presents a transformative approach to controlled and targeted therapeutic release. The unique features of plasma technologies offer several compelling advantages in pharmaceutical applications, yet they are not without challenges that must be addressed for successful clinical and industrial translation.

Advantages

i. Solvent-Free Processing: One of the primary advantages of plasma polymerization is its dry, solvent-free nature. This makes it ideal for coating heat-sensitive or moisture-labile drugs, which might otherwise degrade in traditional wet-chemical processes [52]. The absence of solvents reduces the risk of contamination, residual toxicity, or the need for post-treatment purification steps, thereby simplifying manufacturing workflows.

ii. Nanoscale and Conformal Coating: Plasma polymerization allows for the deposition of ultra-thin (10–100 nm), highly conformal films on substrates of various shapes and sizes. This is particularly advantageous for coating micro- and nanoparticles, implants, and hollow capsules without altering their geometry [53,54]. The ability to achieve uniform and pinhole-free layers enhances the precision of drug release profiles.
iii. Tailored Surface Chemistry: Functional groups such as carboxyl (–COOH), amino ($–NH_2$), hydroxyl (–OH), and fluorinated moieties can be introduced into the coating by selecting appropriate precursor gases. This surface modification facilitates controlled drug–matrix interactions, stimuli-responsive behavior, and bioadhesive properties, all of which are critical for personalized medicine [22,55].
iv. Chemical Stability and Biocompatibility: Plasma-polymerized films are known for their high chemical stability, making them resistant to hydrolysis and oxidation. This prolongs the shelf life of drug-loaded carriers. Moreover, by tuning the film composition, biocompatibility can be achieved, which is vital for implantable, or ingestible DDS [56].
v. **Scalability and Integration:** Plasma systems such as PECVD (Plasma Enhanced Chemical Vapor Deposition) and atmospheric pressure plasma can be integrated into industrial production lines. Techniques like roll-to-roll plasma coating support high-throughput manufacturing of transdermal patches or micro-needles, making the technology commercially viable [23,57].

Challenges

Despite these promising features, several challenges hinder the widespread adoption of plasma coatings in biomedical applications.
a. Limited Penetration Depth: Plasma coating is primarily a surface phenomenon and is limited in its ability to uniformly treat complex geometries such as porous scaffolds or deep capillaries in drug-eluting stents. This necessitates careful optimization of reactor design, monomer flow, and plasma exposure times to ensure uniform deposition [58].
b. Plasma-Induced Drug Degradation: Direct exposure of drug molecules to plasma during coating may lead to unwanted chemical alterations or degradation, especially for peptides, proteins, or other labile compounds. Shielding strategies, such as post-loading the drug after coating or using plasma-activated grafting, are often required to mitigate this risk [59].
c. Reproducibility and Process Control: Reproducibility across batches is a critical concern, particularly when dealing with sub-nanometer coatings. Variations in plasma power, precursor purity, and substrate cleanliness can lead to discrepancies in coating morphology and functionality. Therefore, real-time monitoring and stringent quality control protocols are essential for regulatory compliance and clinical use [60].
d. Long-Term Stability and Biodegradability: While chemical stability is advantageous, non-biodegradable plasma polymers may persist in the body and raise concerns for chronic implants or environmentally sensitive applications. Research is ongoing to develop biodegradable plasma films using bio-sourced monomers or hybrid plasma-grafted polymers [55,56].
e. Complex Regulatory Approval Pathways: Plasma-coated DDS represent a relatively new class of biomedical products. Their approval by regulatory bodies such as the FDA or EMA may require extensive safety, toxicity, and stability testing. Standardized guidelines for plasma-polymerized medical devices are still evolving, which may delay market entry [57].

Plasma polymerization offers a suite of benefits that make it uniquely suited for the next generation of controlled drug delivery platforms. Its dry, scalable, and tunable approach provides high flexibility for drug formulation scientists. However, challenges related to process reproducibility, drug compatibility, and regulatory hurdles remain. By combining interdisciplinary efforts in plasma science, polymer chemistry, and pharmacology, many of these limitations can be systematically addressed.

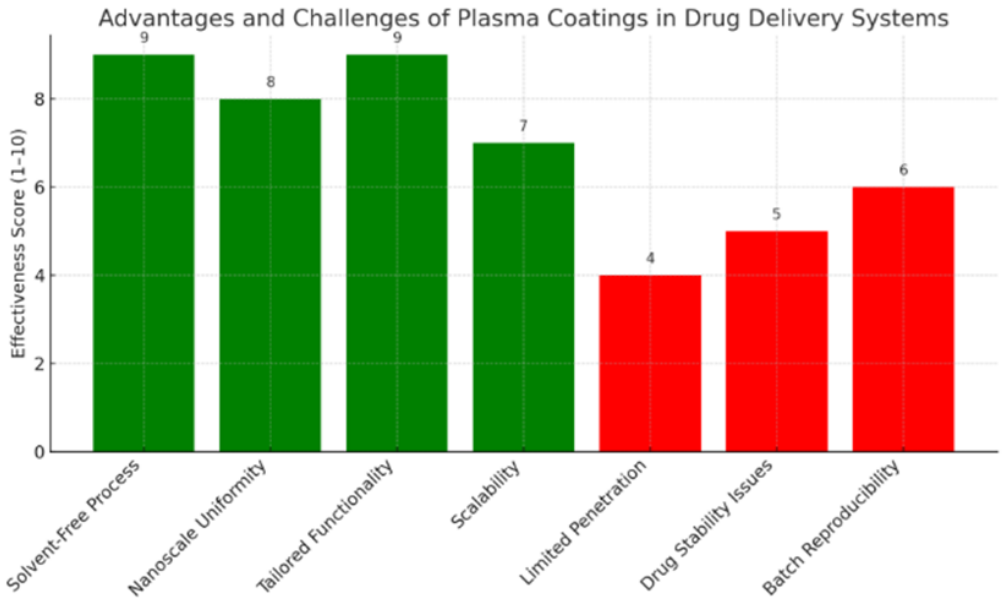

Figure 2: Advantages and challenges of plasma coatings in drug delivery system.

VIII. Emerging Trends And Future Directions

As the field of drug delivery systems (DDS) evolves to meet the demands of personalized medicine, precision therapeutics, and minimally invasive treatments, plasma-based technologies are poised to play a transformative role. Recent innovations suggest a shift from static coatings to dynamic, responsive, and integrated delivery systems that not only release drugs with precision, but also adapt to the physiological environment. One of the most promising directions is the plasma-assisted deposition of stimuli-responsive polymers**.** Researchers are now exploring smart coatings that can respond to external cues such as pH, temperature, light, magnetic fields, or enzymes, to trigger drug release at specific times and locations [61,62]. For instance, thermoresponsive polymers such as poly(N-isopropylacrylamide) (PNIPAM) deposited via plasma polymerization exhibit phase transitions near body temperature, offering on-demand release of therapeutics [63].

Another emerging trend is the integration of plasma coating with microfluidic lab-on-chip platforms. These miniaturized systems are increasingly used for point-of-care diagnostics and controlled drug screening. Plasma coatings enable functionalization of microchannels, reservoirs, and sensor interfaces without the use of solvents, allowing bioactive molecules to be immobilized with high spatial resolution [64,65]. Such integration supports the development of closed-loop drug delivery platforms that combine sensing, decision-making, and actuation in a single chip.

The use of atmospheric pressure plasma (APP) is gaining traction due to its potential for in situ biomedical coatings. Unlike low-pressure plasma systems that require vacuum chambers, APP devices can be miniaturized and applied directly onto biological tissues, implants, or surgical tools in clinical settings [66]. This enables real-time sterilization, surface activation, and even direct drug immobilization on-site. For example, atmospheric plasma jets have been used to deposit bioactive coatings on catheters and wound dressings to prevent infections and promote healing [67].

A critical development area is the design of biodegradable plasma polymer films for transient implants and short-term drug delivery applications. Conventional plasma coatings are often highly cross-linked and chemically inert, limiting their degradation and clearance from the body. However, emerging strategies utilize natural or bio-derived monomers such as polylactic acid (PLA), chitosan, or polyhydroxyalkanoates (PHAs) to fabricate coatings that degrade safely over time [68,69]. These coatings are especially relevant for temporary implants, post-surgical drug release, or pediatric applications where permanent implants are not feasible.

Further, artificial intelligence (AI) and machine learning (ML) are being incorporated into plasma DDS research to optimize plasma processing parameters, predict coating behavior, and tailor drug release kinetics. AI models trained on plasma diagnostic data, surface chemistry profiles, and drug release experiments can identify non-obvious correlations and guide parameter tuning for consistent and reproducible results [70]. These data-driven approaches significantly accelerate the design cycle and reduce experimental trial-and-error, paving the way for personalized DDS manufacturing.

Another frontier involves multi-functional plasma coatings that simultaneously offer drug release, antimicrobial protection, and tissue integration. These multifunctional layers are created by sequential or co-deposition of monomers and nanoparticles, enabling coatings to act as both drug carriers and biointerfaces [71]. For instance, plasma films embedded with silver or zinc oxide nanoparticles exhibit both controlled drug elution and antibacterial properties, enhancing implant safety.

The future of plasma-based drug delivery systems lies in intelligent, integrative, and adaptable technologies. Stimuli-responsive polymers, microfluidic integration, biodegradable films, and AI-guided optimization represent the next wave of innovation. Continued interdisciplinary collaboration between plasma physicists, material scientists, biomedical engineers, and pharmacologists will be essential to translate these advances from the lab to the clinic.

IX. Conclusion

Plasma-polymerized films have emerged as a transformative advancement in the field of controlled drug delivery systems (DDS), combining the precision of surface engineering with the versatility of polymer chemistry. Unlike traditional coating techniques that often rely on solvents, surfactants, or high-temperature processing, plasma polymerization offers a solvent-free, environmentally friendly method capable of depositing ultrathin, uniform, and conformal coatings with tunable properties. These films can be precisely engineered to modulate drug release kinetics, enhance biocompatibility, and create stimuli-responsive interfaces that adapt to physiological conditions, thereby achieving site-specific and time-controlled drug release. The incorporation of functional groups such as amine, carboxyl, hydroxyl, or fluorinated moieties during plasma treatment allows for specific interactions with drug molecules or cellular components, facilitating not only the controlled release, but also improved therapeutic targeting and efficacy.

The advantages of plasma coatings are particularly significant for heat-sensitive drugs, biologics, and nanocarrier-based systems where conventional coating methods may cause degradation or structural compromise. Their nanoscale thickness enables minimal interference with the drug's pharmacodynamics while offering high fidelity to the carrier geometry, be it nanoparticles, microneedles, films, or implantable devices. Additionally, plasma deposition is highly adaptable, allowing multilayer stacking, gradient surfaces, or patterned coatings that offer new dimensions in drug release profiles—including pulsatile, sequential, or environment-triggered modes. These capabilities are crucial for advanced therapies such as cancer treatment, regenerative medicine, and hormone therapies where precision in dosage and delivery timing is paramount.

Despite these advantages, challenges remain in scaling up plasma technologies for industrial DDS production. Limited penetration depth for complex 3D geometries, potential alteration of drug bioactivity due to plasma exposure, and batch-to-batch variability due to intricate plasma-matter interactions pose hurdles that must be systematically addressed. Innovations in atmospheric pressure plasma systems, AI-driven process control, and integration with microfluidics and biosensors are actively being pursued to overcome these limitations and bring plasma-engineered DDS closer to clinical and commercial translation. Moreover, biodegradable and bioresorbable plasma films, still in their nascent stage, hold the promise of transient implants and zero-waste biomedical devices, aligning with the growing demand for sustainable healthcare solutions.

Looking ahead, interdisciplinary research bridging plasma physics, surface science, materials engineering, and biomedicine will be crucial to unlock the full potential of plasma coatings in drug delivery. Standardization of plasma parameters, robust characterization protocols, and long-term in vivo studies are necessary to ensure the safety, reproducibility, and regulatory acceptance of plasma-functionalized DDS. With rapid advances in plasma diagnostics, nanotechnology, and computational modeling, the future of drug delivery will not merely involve transporting a drug to its target but designing intelligent systems that respond, adapt, and communicate with their biological environment. In this context, plasma-polymerized films stand as a cornerstone technology offering the sophistication, customizability, and performance required for the next generation of therapeutic interventions.

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