RESEARCH PAPER

Ultrasonic Spray Coating for Drug-Loaded Medical Devices: A Review of Focused Beam Architectures, Process Control, and Future Directions

Hardikkumar Jayantibhai Lathiya [a], Pranav Heramb Kolapkar [b]
[a]Senior Manufacturing Engineer (Independent Researcher)
Email: lathiya3108@gmail.com
[b]Process Engineer (Independent Researcher)
Email: phkolapkar2@gmail.com

Abstract
Ultrasonic spray coating has emerged as a critical manufacturing technology for the deposition of drug-polymer coatings on implantable medical devices, including drug-eluting stents, coated balloons, and implantable delivery platforms. When compared to traditional coating methods such as dip coating and pneumatic spraying, ultrasonic atomization enables precise control of deposition on intricate, small-scale geometries, low-shear droplet generation, narrow droplet size distributions, and reduced overspray. This review offers a thorough and practical synthesis of the principles, equipment architectures, process parameters, and quality control techniques related to ultrasonic spray coating for drug-loaded medical devices. To identify key Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs), and to examine how these variables are managed using Design of Experiments (DOE), Quality-by-Design (QbD), and Statistical Process Control (SPC) methodologies, is presented. Practical manufacturing challenges, including coating defects, batch-to-batch variability, scale-up limitations, and transfer of ultrasonic coating processes from research and development, are discussed in the context of regulatory expectations for combination products. By integrating academic research with industrial manufacturing experience, this paper aims to provide a comprehensive review and practical reference for engineers, scientists, and regulators involved in the development, scale-up, and commercialization of ultrasonic spray-coated drug-eluting medical devices.

Keywords: Ultrasonic spray coating, Drug-eluting stent, Hypotube-Fed Focused Nozzle, Shroud-Based Focused Nozzle
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1. Introduction

For many implantable medical devices, especially drug-eluting stents (DES), where therapeutic efficacy and safety depend on exact control of coating weight, thickness, uniformity, and drug-release rate, drug-loaded coatings are essential to the device's operation [4]. Because it can produce micron-scale droplets without requiring high atomization pressures, ultrasonic spray coating has become one of the most popular coating methods [1], [2].

By enabling localized delivery of therapeutic agents at the site of implantation, the development of drug-coated and drug-eluting medical devices has revolutionized the treatment of many cardiovascular, peripheral vascular, and chronic disease conditions [5], [6]. These combination products combine pharmacological treatment with mechanical device functionality, resulting in special performance requirements that go beyond conventional medical device manufacturing [4], [12]. In this regard, surface coating technologies are essential for determining clinical efficacy and long-term patient safety in addition to device quality and reproducibility [4].

Precise control of coating characteristics, including drug dose, thickness uniformity, surface morphology, adhesion, and release kinetics, has become more important as drug-coated devices have developed [7], [8]. Any variation in these characteristics can have a direct impact on clinical results and therapeutic efficacy [6]. As a result, the coating process is widely acknowledged as one of the most important and crucial stages in the production of medical devices that release drugs [4]. Therefore, coating processes must be developed and validated using methodical, scientific approaches that show robustness, reproducibility, and traceability throughout the product lifecycle, according to regulatory agencies [11]-[13].

Because ultrasonic spray coating can produce uniformly sized, fine droplets under low shear conditions, allowing for controlled deposition on intricate and small-scale geometries, it has become one of the most widely used coating technologies [1], [2]. The use of focused ultrasonic spray systems is growing in both commercial manufacturing settings and research settings [24]. Despite its widespread use, the academic literature on ultrasonic spray coating is still dispersed, frequently concentrating on specific applications or laboratory-scale studies, with little integration of manufacturing considerations, quality-by-design frameworks, and regulatory expectations pertinent to the production of medical devices [2], [4].

This review's goal is to present a thorough and comprehensive analysis of ultrasonic spray coating as used on medication-loaded medical devices. In addition to discussing common manufacturing issues and new research directions, the paper summarizes basic atomization physics, equipment architectures, materials and formulation considerations, process parameters, and quality control techniques [1], [2], [7], [11], [23]. This review attempts to provide engineers, scientists, and regulators involved in the development, scaling up, and commercialization of ultrasonic spray-coated medical devices with a useful resource by bridging academic research and industrial practice.

Ultrasonic spray systems are widely used in medical device development and commercial production [24]. These systems allow for highly repeatable focused spray beams that can coat intricate, small-scale geometries [2]. Although ultrasonic spray coating is widely used in industry, there is still a dearth of publicly accessible literature that summarizes engineering practice, process control techniques, and potential future directions for this technology in regulated medical device manufacturing [4], [23]. This paper fills that void.

1.1 Clinical Context and Therapeutic Rationale for Drug-Coated Medical Devices

The management of numerous cardiovascular, peripheral vascular, and other chronic diseases now heavily relies on implantable and intravascular medical devices [5]. In many of these applications, the controlled local delivery of therapeutic agents meant to modify biological responses at the implant site also influences device performance in addition to mechanical or structural function. In order to overcome the shortcomings of early-generation bare-metal implants, where unfavorable biological reactions like inflammation, thrombosis, and pathological tissue proliferation hampered long-term clinical outcomes, drug-coated and drug-eluting medical devices were created [6].

The drug-eluting stent (DES), which was developed to reduce restenosis after percutaneous coronary intervention, is among the most well-known examples [5]. Vascular damage brought on by stent implantation causes neointimal hyperplasia and smooth muscle cell proliferation, which in turn causes restenosis. Dose-related toxicity and inadequate local concentration at the target site frequently limit the systemic administration of antiproliferative medications. These difficulties are addressed by drug-eluting devices, which maximize therapeutic efficacy while reducing systemic exposure by enabling localized, controlled drug delivery right at the tissue-device interface [21].

Drug-coated technologies have spread beyond coronary stents to include coated balloons, urological implants, neurovascular devices, peripheral vascular interventions, and new implantable platforms for localized therapy [21]. Delivering a specific drug dose over a predetermined time profile while preserving the device's mechanical integrity, biocompatibility, and long-term safety is the clinical goal in every situation. Because the coating acts as a drug reservoir, a release-rate controller, and an interface between the device and surrounding tissue, these requirements place strict demands on the coating that is applied to the device surface [7].

Coating properties, such as coating weight, thickness uniformity, surface morphology, adhesion, and microstructural integrity, have a significant impact on the clinical performance of drug-coated devices [20]. Clinically significant variations in drug release kinetics can be caused by slight variations in drug dose or coating uniformity, which may result in underdosing, a delayed therapeutic effect, or localized toxicity. Additionally, non-uniform coatings may present mechanical risks like flaking or delamination during deployment, which may result in inflammatory reactions or embolic events downstream [30]. The reproducibility, robustness, and traceability of coating processes used in the production of combination products are therefore highly valued by regulatory bodies and clinical stakeholders [23].

Because coating-related failures frequently appear only after device implantation, when corrective intervention is limited, they pose a serious risk from a clinical risk standpoint [6]. Patient safety may be seriously jeopardized by clinical events linked to coating defects, such as late thrombosis, restenosis recurrence, or inconsistent therapeutic response. Therefore, the ability to produce coatings with tightly controlled quality attributes across large production volumes is crucial to the translation of drug-coated device concepts from preclinical development to clinical practice [4].

These difficulties are made more difficult by the growing complexity of therapeutic approaches [21]. Several functional layers, polymer and drug combinations, or customized release profiles made to fit particular disease states or patient populations are all possible features of contemporary drug-coated devices. Devices must sometimes deliver medications for long periods of time while preserving the integrity of the coating under mechanical deformation, such as crimping, expansion, or repeated flexing [20]. Coating technologies that offer precise control over material deposition at the micro and nanoscale without sacrificing drug stability or device performance are necessary to meet these changing clinical requirements [7].

Coating technology is now a key factor in determining therapeutic success in this clinical setting rather than a secondary manufacturing step [4]. Clinical efficacy, long-term patient outcomes, device quality, and regulatory compliance are all directly impacted by the coating method selection. The need for sophisticated, controllable, and scalable coating processes has become a defining challenge in medical device manufacturing as drug-coated devices continue to expand into new therapeutic areas and incorporate increasingly complex payloads [23].

1.2 Limitations of Conventional Coating Technologies

Conventional coating methods like dip coating and pneumatic spray coating were the mainstay of early generations of drug-coated medical devices [4]. Although these techniques made it possible for drug-eluting technologies to be initially translated into clinical settings, as device designs, therapeutic approaches, and regulatory expectations have changed, their inherent limitations have become more obvious. When applied to intricate, small-scale medical devices, the need for more stringent control over coating uniformity, drug dose, and reproducibility has revealed serious flaws in conventional coating techniques [23].

One of the simplest and most popular coating techniques is dip coating, which entails submerging the device in a drug-polymer solution, then carefully removing it and letting the solvent evaporate [14]. Dip coating has limited control over coating thickness and uniformity, especially for devices with complex geometries like stents or scaffolds with fine strut structures, despite being appealing due to its conceptual simplicity and low equipment requirements. Non-uniform film thickness and pooling at geometric features can be caused by differences in withdrawal speed, solution viscosity, and solvent evaporation [14]. Small changes in coating thickness can result in clinically significant variations in drug dose and release kinetics, which makes these effects especially problematic for drug-eluting devices [20].

From a manufacturing standpoint, solution aging, solvent evaporation from open baths, and the gradual buildup of particulates or precipitates all have a significant impact on dip coating processes [23]. These elements complicate process control and increase batch-to-batch variability, especially when production is scaled up to high volumes. Furthermore, dip coating frequently produces comparatively thick coatings applied in a single step, which raises the possibility of mechanical damage, delamination, or cracking during subsequent device handling, crimping, or deployment [27]. The flexibility of dip coating for sophisticated, multi-layer drug delivery strategies is further limited by the inability to apply thin, incremental layers.

Pneumatic spray coating is more flexible than dip coating and has been used extensively to coat a range of pharmaceutical and medical products [14]. It does this by atomizing liquid formulations into droplets using compressed air. However, pneumatic atomization relies on high-velocity air streams and naturally produces a wide droplet size distribution, which can present a number of difficulties for drug-eluting medical devices [2]. Excessive droplet momentum can cause overspray, rebound, and poor deposition efficiency on small or complex substrates, while high shear forces during atomization may jeopardize the stability of delicate drug molecules or polymer systems [7].

For small-diameter devices like coronary stents, where precise spray material targeting is necessary, achieving uniform coatings with pneumatic spraying is particularly difficult [29]. Coating thickness can vary axially or circumferentially as a result of uneven deposition across the device surface caused by overspray and shadowing effects. It is challenging to identify these non-uniformities in real time, and they might only show up in downstream analytical testing or, in the worst situations, clinical performance variability [4]. Higher atomization pressures also result in increased solvent misting and environmental exposure, which raises issues with solvent management and operator safety [23].

Pneumatic spray coating and dip coating are both constrained by contemporary regulatory requirements for combination products [12], [13]. Manufacturers are under increasing pressure from regulatory bodies to use methodical development techniques like Quality-by-Design (QbD) to show how process parameters and important quality attributes are related [11], [12]. Defining robust design spaces and control strategies is challenging due to the multivariate, complex nature of conventional coating processes and their sensitivity to operator-dependent variables and environmental conditions [23]. Because of this, a lot of empirical testing and conservative process limits are frequently needed, which lengthens development times and raises manufacturing costs.

The limitations of traditional coating technologies become more restrictive as drug-eluting devices continue to advance toward thinner coatings, lower drug loads, and more complex release profiles [4]. Both innovation and manufacturing are hampered by the inability to precisely control droplet size, deposition rate, and wet film behavior at the micro-scale [2]. These difficulties have prompted the medical device industry to look for alternative coating technologies that are compatible with regulated manufacturing environments and provide increased precision, reproducibility, and scalability [2], [24].

1.3 Emergence of Ultrasonic Spray Coating as an Enabling Technology

The limitations of traditional dip coating and pneumatic spray coating methods have led to the creation and use of new coating technologies that can meet the growing needs of drug-eluting medical devices [4]. Ultrasonic spray coating has become a very effective solution because its unique atomization mechanism lets you control droplet formation, deposition rate, and coating uniformity very precisely at the micro-scale. In the last twenty years, ultrasonic spray coating has gone from being a lab-scale method to a widely used industrial process in the production of medical devices that are subject to strict regulations [2].

Ultrasonic spray coating, on the other hand, uses high-frequency mechanical vibration to make droplets directly from a liquid film at the nozzle tip [1]. This mechanism makes droplets that are all about the same size and needs very little atomizing air, which means that the shear forces are low and the droplet momentum is low. Because of this, ultrasonic spray coating gives better control over deposition efficiency and cuts down on overspray, rebound, and material waste [2]. These traits are especially helpful for coating small, complicated shapes like stents, where precise targeting of the coating material is necessary to ensure even drug distribution.

Another big benefit of ultrasonic spray coating is that it lets manufacturers apply coatings in thin, incremental layers [2]. Ultrasonic systems let manufacturers build up the desired coating weight through multiple controlled passes, with the solvent evaporating between layers. This is better than putting down one thick layer. This method of applying the coating layer by layer lets manufacturers fine-tune the thickness, shape, and drug distribution of the coating. It also lowers the risk of cracking, delamination, or mechanical damage during the next step of processing the device. This feature is very important for drug-eluting devices because it helps them keep their coating intact while crimping and deployment and get consistent drug-release profiles [20].

Hypotube-Fed Focused Nozzle and Shroud-Based Focused Nozzle are two examples of focused ultrasonic spray technologies that make ultrasonic coating even more useful for medical devices by adding spray shaping and beam control [24]. These systems use low-pressure air shaping or diffusion chambers to make narrow, very uniform spray profiles that can be lined up perfectly with the features of the device. When used with automated motion platforms, focused ultrasonic nozzles make it possible to precisely control where the coating goes on rotating and translating substrates. This makes it possible to deposit coatings in a repeatable way on complex three-dimensional structures [2].

Ultrasonic spray coating is in line with Quality-by-Design (QbD) principles from both a manufacturing and regulatory point of view [4]. The separation of droplet production from high-pressure air makes the process parameter space easier to understand and makes it easier to predict how the coating will turn out. Design of Experiments can be used to systematically test important process variables like flow rate, traverse speed, nozzle-to-substrate distance, and shaping air pressure. This makes it easier to create strong design spaces and control strategies. This level of understanding of the process meets regulatory requirements for reproducibility, traceability, and risk-based process validation [11].

Ultrasonic spray coating has gone from being a niche option to an enabling technology as the medical device industry moves toward more complex drug delivery methods, thinner coatings, and tighter tolerances on drug dose and release [4]. Ultrasonic spray coating is a key technology for current and future drug-coated medical devices because it can precisely deposit materials, be scaled up, and work with automated manufacturing systems [2], [24]. The next parts of this review build on this base by looking at the basic physics of ultrasonic atomization, the design of the equipment, the materials that need to be used, and the process control strategies that are needed for successful use in industrial settings.

2. Principles of ultrasonic spray coating

The basic physical mechanisms controlling atomization, droplet transport, wet film formation, and solvent evaporation must be taken into account for a thorough understanding of ultrasonic spray coating [1], [2]. Ultrasonic spray coating is controlled by microscale interfacial phenomena that directly relate formulation characteristics and operating parameters to coating results, in contrast to traditional coating methods that depend on macroscopic fluid breakup propelled by high-velocity gas streams. The improved controllability and reproducibility seen in ultrasonic coating processes used in the production of medical devices are based on these physical mechanisms.

A series of closely related phenomena determine how well ultrasonic spray coating works [1]. Liquid atomization starts at the vibrating nozzle surface, where ultrasonic energy creates capillary instabilities that produce droplets with distinctive sizes based on the liquid's characteristics and vibration frequency. After atomization, droplets are carried toward the substrate by a low-velocity gas environment, where their size, momentum, and evaporation state affect the spatial distribution and deposition efficiency. Surface energy, solvent volatility, substrate temperature, and deposition rate all influence how the droplets spread, combine, and create a temporary wet film upon impact. As the solvent evaporates and the polymer chains rearrange within the deposited film, the final coating morphology and microstructure are revealed [16], [18], [19].

These physical processes directly affect coating quality characteristics like thickness uniformity, surface morphology, adhesion, and drug distribution for drug-eluting medical devices [2]. Significant differences in coating performance can result from minor adjustments to drying dynamics or atomization behavior, especially for devices with intricate geometries or strict dose tolerances. Therefore, rational process development, scaling, and control within regulated manufacturing environments require a thorough understanding of the underlying physics [4].

Starting with the physics of ultrasonic atomization and capillary wave theory, this section goes over the basic concepts of ultrasonic spray coating [1], [26]. Droplet transport and wet film formation are examined in the following subsections, which are then contrasted with traditional pneumatic atomization mechanisms [16], [18]. These subjects collectively offer the scientific foundation for the manufacturing strategies, Quality-by-Design frameworks, and process parameter discussions covered in later sections of this review [4], [11].

2.1 Fundamentals of Ultrasonic Atomization Physics

Liquid atomization is the first and most important step in the ultrasonic spray coating process. It determines the size and stability of the droplets, as well as the starting conditions for transport, deposition, and film formation. In ultrasonic spray coating, high-frequency mechanical vibration is used to break up the liquid instead of high-speed gas flow. This is a very different way of breaking up the liquid than in regular pneumatic spraying. To make sure that process parameters, formulation properties, and coating quality attributes all work together in a predictable way, you need to understand this mechanism [1], [2].

2.1.1 Capillary Wave Theory and Droplet Generation

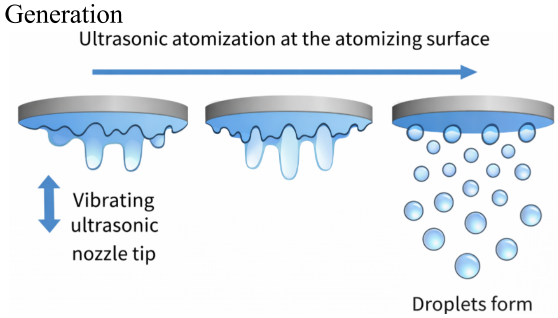

Figure 1 Schematic illustration of capillary wave formation and droplet ejection during ultrasonic atomization [2]

As shown in the Figure 1, ultrasonic atomization is driven by the formation of capillary waves on the surface of a thin liquid film supplied to a vibrating nozzle tip. When the nozzle oscillates at ultrasonic frequencies- typically between 20 and 120 kHz- mechanical energy is transferred into the liquid, generating standing waves at the liquid-air interface. As the vibration amplitude increases beyond a critical threshold, these capillary waves become unstable and eject droplets from their crests [1], [26]. The wavelength of the capillary waves is governed by a balance between inertial forces and surface tension forces within the liquid. Classical capillary wave theory describes this relationship as [1]:

$$\lambda = \left(\frac{2\pi\sigma}{\rho f^2}\right)^{1/3} \quad (1)$$

Where λ is the capillary wavelength, σ is the surface tension of the liquid, ρ is the liquid density, and f is the ultrasonic vibration frequency in equation (1).

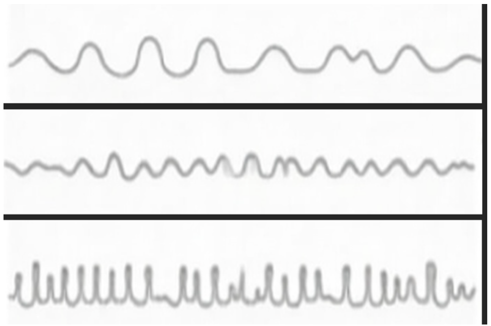

Figure 2 Representative relationship between ultrasonic frequency and mean droplet diameter [2]

Droplet formation occurs when the wave amplitude exceeds the stability limit, causing the wave crests to detach from the liquid surface. Because droplet size is closely linked to the capillary wavelength and frequency as shown in Figure 2, ultrasonic atomization inherently produces droplets with relatively narrow size distributions. This physical characteristic underpins the improved uniformity and reproducibility of ultrasonic spray coating processes compared with pneumatic atomization, particularly for precision medical device applications [1], [2].

2.1.2 Droplet Size Correlations and Engineering Interpretation

Building on capillary wave theory, Lang and subsequent researchers proposed empirical relationships linking ultrasonic frequency and liquid properties to the mean droplet diameter [1], [26]. A commonly used approximation for the Sauter mean droplet diameter (D_32) generated during ultrasonic atomization is given by:

$$D_{32} \approx 0.34\left(\frac{8\pi\sigma}{\rho f^2}\right)^{1/3} \quad (2)$$

Where σ is the surface tension of the liquid, ρis the liquid density, and f is the ultrasonic vibration frequency in equation (2) [1].

This expression provides several critical insights for ultrasonic spray coating process development:

- **Frequency dependence:** Droplet diameter scales inversely with the two-thirds power of ultrasonic frequency. Increasing frequency is therefore an effective means of reducing droplet size.
- **Surface tension dependence:** Higher surface tension liquids generate larger droplets, necessitating either higher operating frequencies or formulation adjustments to achieve fine atomization.
- **Density dependence:** Liquid density has a secondary but non-negligible influence, particularly when comparing solvent systems with substantially different densities.

Practical use of droplet size equations

In the real world, this correlation is more of a guide than a sure way to tell what the size of a droplet will be. Engineers can use it to choose the right ultrasonic nozzle frequencies based on the size of the droplets they want to create and the thickness of the coating they need, to test changes to the formulation like replacing solvents or changing the concentration of polymers to see how they affect atomization behavior, and to help with process transfer and scale-up by giving a physics-based reason for changing parameters when moving between different ultrasonic platforms. The equation doesn't explicitly take into account the effects of flow rate or viscous dissipation, but it is still a useful starting point for figuring out possible operating windows during the early stages of process development [2].

2.1.3 Role of Liquid Viscosity in Ultrasonic Atomization

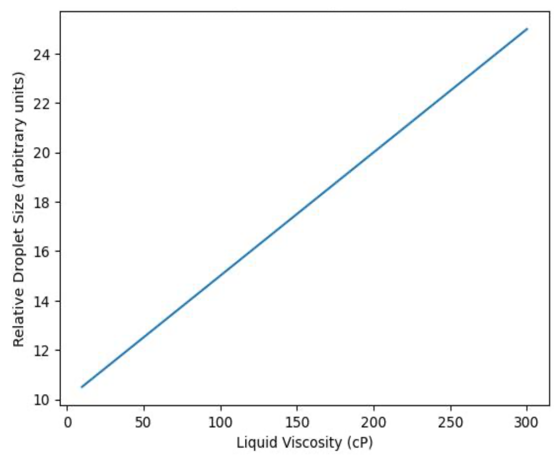

Figure 3 Liquid Viscosity vs Relative Droplet Size

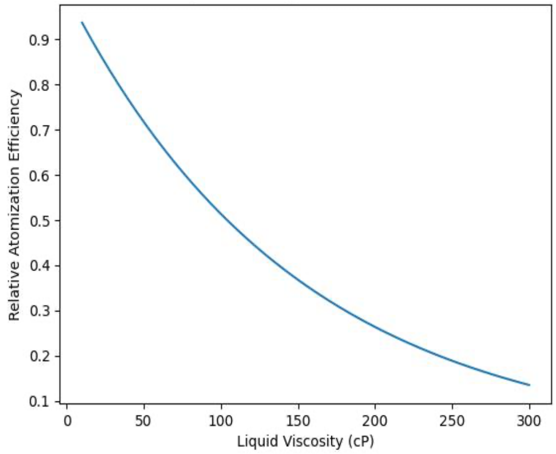

Figure 4 Liquid Viscosity vs Relative Atomization Efficiency

Viscosity plays a crucial role in ultrasonic atomization by damping capillary wave growth, even though it is not explicitly mentioned in classical capillary wavelength formulations [28]. Figures 3 and 4 demonstrate that when liquid viscosity rises, the droplet size grows linearly and, in contrast, the atomization efficiency falls because more of the supplied ultrasonic energy is internally dissipated, which lowers wave amplitude and prevents droplet ejection. Viscosity in drug-polymer coating solutions is determined by temperature, solvent composition, solids concentration, and polymer molecular weight. Increases in viscosity are typically linked to decreased atomization efficiency, unstable spray behavior, larger droplet sizes with wider size distributions, and increased sensitivity to flow rate and nozzle wetting conditions [2]. Therefore, solutions with viscosities below about 100-200 cP (100-200 mPa·s) are typically the most stable for ultrasonic spray coating processes, though the precise upper limit depends on nozzle design and operating frequency. Therefore, a crucial formulation and process control factor in the production of drug-eluting medical devices is keeping viscosity within a compatible range.

2.1.4 Interdependence of Frequency, Surface Tension, and Viscosity

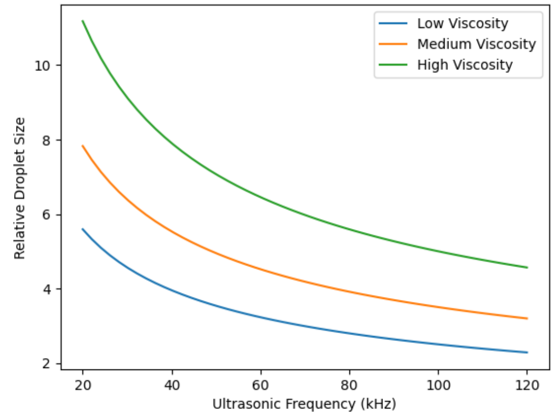

Figure 5 Independence of Frequency and Viscosity on Droplet Size

In reality, frequency, surface tension, and viscosity all work together to influence ultrasonic atomization behavior rather than any one factor alone [1]. Increasing frequency decreases both the maximum viscosity that can be efficiently atomized and droplet size, as seen in Figure 5. Although it may have a negative impact on wetting behavior, film spreading, or coating adhesion, lowering surface tension can allow for finer droplets at lower frequencies.

In order to find stable atomization regimes, this multidimensional parameter space requires systematic development approaches, most frequently through Design of Experiments (DOE) [11]. Controlling coating thickness, morphology, and drug distribution requires both consistent droplet generation and predictable wet film formation, which ultrasonic spray coating can provide within these regimes [2].

2.1.5 Implications for Coating Quality and Process Control

The physics of atomization discussed in this section have a direct effect on the quality of the coating that comes after it [2]. Narrow droplet size distributions help with even wetting and lower the random variation in deposition, which helps keep the weight of the coating consistent across devices and batches. Ultrasonic atomization has a low shear force, which lowers the risk of drug breakdown or polymer damage even more. This is especially important for sensitive therapeutic payloads [7].

From a process control point of view, separating droplet generation from high-pressure gas flow makes the control space easier to manage than with pneumatic spraying [2]. Ultrasonic frequency, flow rate, and formulation properties become the main tools for controlling atomization behavior. This makes scaling and alignment with Quality-by-Design principles more predictable [11]. The ideas presented here are the foundation for understanding how droplets move, settle, and how wet films change over time, which will be covered in the next section.

2.2 Comparison of Ultrasonic and Pneumatic Atomization Mechanisms

Although both ultrasonic and pneumatic spraying are used to deposit liquid coatings, the physical mechanisms governing atomization, droplet transport, and deposition differ fundamentally between the two approaches [1], [2]. These differences have direct implications for coating uniformity, process controllability, material efficiency, and suitability for drug-eluting medical device manufacturing. A comparative understanding of these mechanisms is therefore essential for selecting appropriate coating technologies and designing robust processes [4].

2.2.1 Atomization Mechanism and Droplet Size Distribution

In pneumatic spraying, liquid atomization is achieved through the interaction of a liquid stream with high velocity compressed gas [14]. The liquid jet or sheet is fragmented by aerodynamic shear forces, producing a wide distribution of droplet sizes. The resulting droplet size distribution is typically broad and highly sensitive to gas pressure, nozzle geometry, and liquid flow rate. This stochastic breakup mechanism makes precise control of droplet size challenging, particularly when operating at the low flow rates required for small medical devices [29].

By contrast, ultrasonic atomization is driven by capillary wave instabilities generated at a vibrating liquid surface [1]. Droplet size is primarily determined by ultrasonic frequency and liquid properties, resulting in a narrower and more predictable droplet size distribution [2]. Because droplet formation is decoupled from high-velocity gas flow, ultrasonic spraying enables greater consistency in droplet generation and reduced sensitivity to minor fluctuations in operating conditions.

2.2.2 Droplet Momentum and Transport Behavior

The high gas velocities used in pneumatic spraying impart significant momentum to droplets, which can lead to rebound, splashing, and poor deposition efficiency when coating small or intricate substrates [27]. Overspray and material loss are common, particularly when targeting narrow features or rotating components such as stents. In addition, high droplet momentum increases the likelihood of shadowing effects, where certain regions of the device receive insufficient coating due to geometric obstruction [4].

Ultrasonic spray coating operates with minimal carrier gas velocity, resulting in droplets with substantially lower momentum [2]. This low-energy deposition promotes gentle impaction and spreading, improving deposition efficiency and spatial control. The reduced momentum also enables more precise targeting of coating material, making ultrasonic spraying particularly well suited for complex three-dimensional medical devices.

2.2.3 Shear Forces and Material Integrity

Sensitive materials may be negatively impacted by the high shear forces that pneumatic atomization exposes liquid formulations to during breakup [7]. High shear can cause phase separation, polymer chain scission, or drug degradation in drug-polymer solutions, which could change coating performance and drug-release behavior. Processing biologically active or shear-sensitive payloads increases these risks.

In contrast, ultrasonic atomization uses mechanical vibration instead of high-velocity shear to produce droplets [1]. Consequently, the liquid experiences a much-reduced shear environment. This feature facilitates the processing of cutting-edge therapeutic agents with a lower risk of degradation and makes ultrasonic spray coating more compatible with sensitive drug formulations.

2.2.4 Process Control and Parameter Space

The parameter space governing pneumatic spray coating is inherently complex, involving interactions between gas pressure, gas flow rate, liquid flow rate, nozzle geometry, and environmental conditions [14]. Small changes in any of these variables can lead to disproportionate changes in atomization behavior, complicating process development and control. Defining robust operating windows and design spaces for pneumatic spraying is therefore challenging, particularly in regulated manufacturing environments [23].

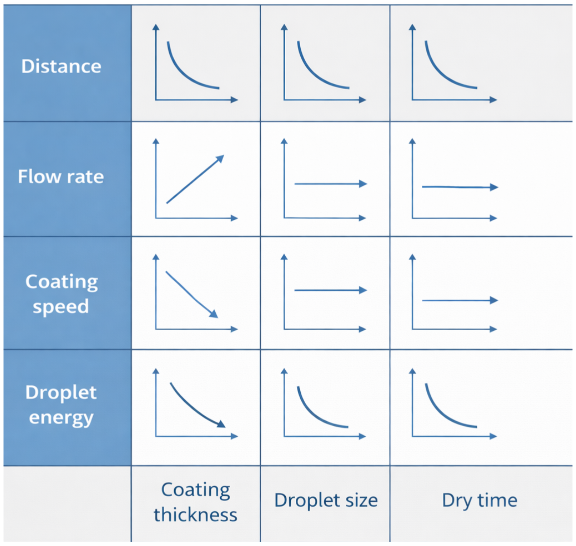

Figure 6 Relation between different spraying parameters [2]

Figure 6 illustrates the collective impact of critical ultrasonic spray coating process parameters on droplet characteristics and coating results, highlighting the interrelated dynamics of deposition and drying in coating formation [2]. The frequency of the ultrasonic waves and the properties of the formulation mostly determine the size of the droplets. The flow rate of the liquid and the parameters of the motion system mostly determine the deposition rate. This separation makes it easier to develop processes and use Design of Experiments and Quality-by-Design methods [11]. Because of this, people often think that ultrasonic spray coating is easier to optimize and validate by rules.

2.2.5 Environmental and Safety Considerations

The high air flow rates and pressures used in pneumatic spraying increase solvent misting and aerosol generation, which can pose challenges related to operator exposure, solvent containment, and environmental compliance [23]. These issues often necessitate extensive exhaust and filtration systems, adding complexity and cost to manufacturing operations.

Ultrasonic spray coating typically operates with lower air flow rates, reducing solvent aerosolization and improving material utilization efficiency [2]. This characteristic supports improved environmental control and aligns with increasing emphasis on sustainable and safe manufacturing practices.

2.2.6 Implications for Medical Device Manufacturing

The fundamental differences between ultrasonic and pneumatic atomization translate directly into differences in manufacturing performance [4]. For drug-eluting medical devices, where precise control over coating thickness, drug dose, and uniformity is critical, the narrower droplet size distribution, lower shear environment, and improved deposition efficiency of ultrasonic spray coating provide clear advantages [2]. While pneumatic spraying may remain suitable for larger or less demanding applications, ultrasonic spray coating has become the preferred technology for precision coating of small, complex, and high-value medical devices [24].

2.3 Droplet Transport, Deposition, and Wet Film Formation

The uniformity, morphology, and reproducibility of the coating are largely determined by the behavior of the droplets during transport to the substrate and their subsequent interaction with the surface after ultrasonic atomization [16], [18]. The features of the deposited coating are ultimately determined by downstream processes, such as droplet flight dynamics, evaporation, impaction, spreading, and coalescence, while atomization physics controls the initial droplet size and distribution. Understanding these coupled phenomena is crucial for reliable process development and control for drug-eluting medical devices, where coating tolerances are limited and geometries are complex [4].

2.3.1 Droplet Transport and Flight Dynamics

In ultrasonic spray coating, droplets move from the nozzle to the substrate mostly by low-speed carrier gas flow and gravity [2]. Ultrasonic droplets usually move at relatively low speeds, while pneumatic spraying droplets have a lot of initial momentum because the air is compressed. This lower momentum makes it less likely that the object will bounce back or splash when it hits something, which makes it easier to deposit and control the space, especially for small or complicated surfaces like stents [27].

The size of the droplets, the speed of the carrier gas, the distance between the nozzle and the substrate, and the conditions in the air all affect the path of the droplets as they fly. Smaller droplets are more affected by aerodynamic drag and can slow down quickly, while larger droplets have more inertia and stay in motion longer. Because of this, the distance between the nozzle and the object becomes very important. If the distance is too great, droplets are more likely to evaporate or change direction. If the distance is too short, droplets can pool or wet deposit. In practice, the distance between the nozzle and the substrate is chosen to find the right balance between good droplet dispersion and controlled evaporation before impact [2].

2.3.2 Solvent Evaporation During Droplet Flight

As soon as droplets form, the solvent starts to evaporate [19]. This process continues during transport and after deposition. How much evaporation happens before impact depends on the size of the droplets, the vapor pressure of the solvent, the temperature of the air, the relative humidity, and the time the droplets spend in the air. In ultrasonic spray coating, where droplets are usually small and move slowly, evaporation during flight can be a big problem that needs to be carefully controlled [16].

It can be helpful to partially evaporate the solution before it hits the surface because it makes the solution thicker and stops droplets from spreading, which improves pattern definition and stops edge beads from forming. But if too much evaporation happens, droplets may reach the substrate in a semi-dried or solidified state, which can cause poor coalescence, rougher surfaces, or porous coatings. This balance is very important for drug-polymer systems because losing the solvent too soon can cause the drug to crystallize or separate into different phases within individual droplets [19].

So, controlling the evaporation of the solvent is done by a mix of formulation design (choosing and mixing solvents), environmental control (temperature and humidity), and process parameters (flow rate, nozzle distance, and traverse speed). These variables together decide how droplets evaporate over time and have a big effect on the final shape of the coating [16].

2.3.3 Droplet Impaction and Spreading on the Substrate

Upon reaching the substrate, droplets undergo impaction and spreading, processes governed by the interplay between inertial forces, surface tension, and substrate surface energy [16]. The extent of spreading determines the footprint of individual droplets and influences the rate at which neighboring droplets coalesce to form a continuous wet film.

For ultrasonic spray coating, the relatively low impact velocity of droplets promotes gentle spreading without splashing, reducing the risk of satellite droplet formation [2]. Substrate surface properties, including roughness, chemistry, and pre-treatment, play a significant role in wetting behavior. Poor wetting can result in incomplete coverage or non-uniform films, while excessive wetting may promote pooling and thickness gradients. In medical device manufacturing, surface treatments such as plasma activation are often employed to optimize surface energy and improve coating adhesion [20].

2.3.4 Wet Film Formation and Coalescence

As more and more droplets land on the substrate, they combine to make a temporary wet film [16]. The evolution of this wet film is a dynamic process that is controlled by the rate of deposition, the rate of solvent evaporation, and the flow of surface tension. To get smooth, defect-free coatings with even thickness and drug distribution, it's important to make sure that the wet film forms evenly.

If the rate of deposition is higher than the rate of evaporation of the solvent, the surface may become too wet, which can cause pooling, sagging, or bridging between the parts of the device. On the other hand, if evaporation happens faster than deposition, droplets may dry before they fully join together, which can lead to rough or uneven films. For devices with fine features or a lot of curvature, like stents, these effects are even stronger because of localized changes in droplet accumulation and airflow [27].

People often use layer-by-layer deposition strategies to control how wet films behave when they are sprayed on with ultrasonic spray coating. Manufacturers can gradually increase the thickness of the coating while keeping the film intact by applying several thin layers with controlled drying times in between. This method lowers internal stresses, makes adhesion better, and gives you more control over how drugs are distributed and released [2].

2.3.5 Implications for Coating Defects and Uniformity

The interaction of droplet transport, evaporation, and wet film dynamics directly affects the most common coating problems seen in ultrasonic spray processes [27]. Webbing and bridging can happen when droplets stay too wet and join together between nearby features. When a solvent evaporates, the flow of surface tension can cause edge beads to form. Non-uniform thickness can happen when the flux of droplets or the flow of air in a certain area change.

Knowing how these things work lets you choose the right process parameters to reduce defects. For instance, lowering the flow rate or raising the traverse speed can lower the local deposition density. Changing the volatility of the solvent or the temperature of the substrate can change the rates of evaporation. Adding motion control strategies, like synchronized rotation and translation, makes uniformity even better on complex three-dimensional substrates [2].

2.3.6 Relevance to Process Control and Scale-Up

From a manufacturing point of view, droplet transport and wet film formation are important links between the physics of atomization and the quality of the final coating [4]. These phenomena are very sensitive to changes in the environment and the way the equipment is set up, so they are very important to pay attention to when scaling up and transferring processes. Strong control over how droplets settle helps keep the weight and shape of the coating more consistent, which is in line with Quality-by-Design and regulatory standards [11], [23].

The ideas in this section are the basis for understanding how process parameters affect coating results after the first atomization. In the next section, these ideas are compared to the mechanisms that control pneumatic atomization. This shows the main benefits of ultrasonic spray coating for precision medical device applications.

3. Ultrasonic Spray Equipment Architectures for Medical Device Coating

For ultrasonic spray coating to work well in making medical devices, it needs to be based on the right atomization physics and the right design and integration of equipment subsystems that control droplet generation, spray shaping, substrate motion, and liquid delivery [2], [17]. Industrial medical device coating systems need to be very accurate, repeatable, and strong while working in regulated manufacturing environments. This is different from laboratory-scale coating setups. This part talks about the main types of equipment used in ultrasonic spray coating systems, with a focus on focused ultrasonic technologies that are commonly used in medical devices that release drugs [24].

3.1 Ultrasonic Nozzle Architectures:

Hypotube-Fed Focused Nozzle vs Shroud-Based Focused Nozzle, Commercial examples of these architectures include the MicroMist and AccuMist systems (Sono-Tek Corp)

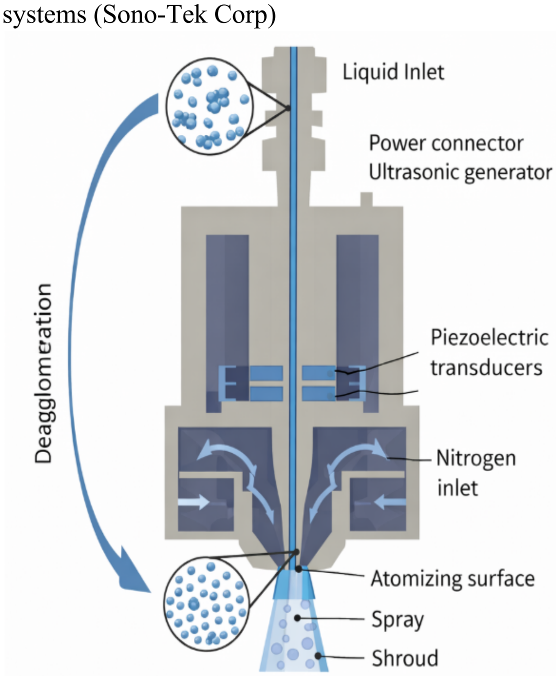

Figure 7 Shroud-Based Focused Spray Nozzle [2]

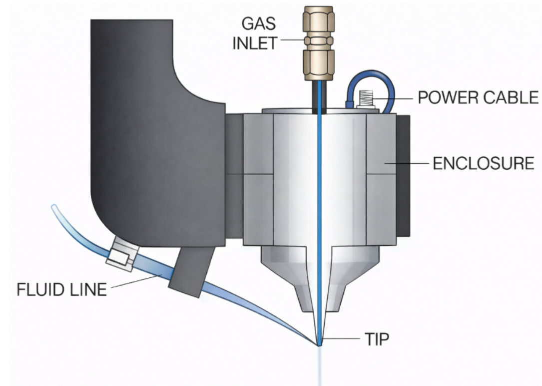

Figure 8 Hypotube-Fed Focused Spray Nozzle

Ultrasonic spray coating systems for medical devices commonly employ focused ultrasonic nozzle designs that combine ultrasonic atomization with controlled air shaping [2]. Among these, Hypotube-Fed Focused Nozzle and Shroud-Based Focused Nozzle architectures (Figure 7 and Figure 8 respectively) represent two closely related but functionally distinct approaches optimized for precision coating applications.

Hypotube-Fed Focused Nozzle nozzles utilize a focused ultrasonic transducer coupled with low-pressure shaping air to produce a highly collimated spray beam. The ultrasonic vibration generates droplets via capillary wave breakup, while the shaping air constrains the spray plume, enabling beam widths on the order of sub-millimeter to a few millimeters. This narrow beam capability is particularly advantageous for coating small-diameter devices such as coronary stents, where precise targeting of coating material is required to avoid overspray and non-uniform deposition [24].

Shroud-Based Focused Nozzle systems build upon the MicroSpray ultrasonic nozzle concept by incorporating an air-shroud diffusion chamber that further conditions the spray plume. In this architecture, atomized droplets are entrained within a controlled airflow that homogenizes droplet distribution across the beam cross-section. The resulting spray profile exhibits high spatial uniformity, making Shroud-Based Focused Nozzle systems well suited for applications requiring consistent coating across slightly larger or more complex surfaces, while still maintaining fine control over deposition [24], [25].

From a manufacturing perspective, both architectures offer advantages over conventional spray nozzles, including reduced satellite droplet formation, lower sensitivity to gas pressure fluctuations, and improved repeatability [2]. The choice between Hypotube-Fed Focused Nozzle and Shroud-Based Focused Nozzle is typically driven by device geometry, required beam width, and tolerance for overspray rather than fundamental differences in atomization quality.

3.2 Spray Shaping and Beam Control

Spray shaping is an important part that sets industrial ultrasonic spray coating systems apart from simple ultrasonic atomizers [2]. In medical device applications, where it is very important for the coating to be placed accurately and evenly, uncontrolled spray dispersion can cause unacceptable changes in the weight and shape of the coating.

In focused ultrasonic systems, low-pressure air streams that surround the atomized droplet plume are used to shape the spray. In ultrasonic systems, shaping air is used to keep the droplet stream in place, guide it, and stabilize it. This is different from pneumatic spraying, where air is used to atomize the droplets [2]. The normal pressures for shaping air are between 0.5 and 2 psi (3.4 – 13.8 kPa). This is enough to make the spray beam narrower without giving the droplets too much speed.

Beam width is an important setting that can be changed. It is chosen based on the size of the device, the spacing of the features, and the desired coating resolution. Narrow beams let you coat only certain areas, while slightly wider beams make throughput and uniformity better for substrates that aren't too geometrically constrained. Beam shaping also changes how long droplets stay on a surface and how they evaporate, which in turn affects the formation of wet films and the shape of the coating [16].

To keep the process stable between production runs, it is important to have precise control over the parameters that shape the spray. Changes in shaping air pressure, nozzle alignment, or airflow symmetry can cause small but important changes in how the coating is spread. Because of this, industrial systems often use fixed mechanical fixtures and calibrated air delivery parts to reduce drift and reliance on the operator [24].

3.3 Motion Systems: Rotation, Translation, and Masking

While ultrasonic nozzles define droplet generation and beam geometry, substrate motion systems determine how coating material is distributed across the device surface [2]. For medical devices with cylindrical or complex three-dimensional geometries, coordinated motion is essential to achieve uniform coverage.

Rotational motion is commonly used for devices such as stents, catheters, and shafts, allowing circumferentially uniform exposure to the spray beam. Rotation speed directly influences local deposition rate and must be synchronized with spray flow rate and traverse speed to avoid banding or thickness gradients. In many systems, continuous rotation is combined with axial translation of either the nozzle or the substrate to generate helical coating patterns that promote uniformity [29].

Translational motion provides control over axial coating distribution and enables application of coatings over defined regions of the device. High-precision linear stages are typically employed to ensure repeatable positioning and velocity control. Acceleration and deceleration profiles must be carefully managed to prevent localized over-deposition at stroke endpoints.

Masking strategies are often integrated into motion system design to protect non-functional regions of the device from coating or to create defined coated zones. Masks may be physical (fixtures or sleeves) or virtual (motion-based exclusion zones), depending on device design and production requirements. Effective integration of motion control and masking is particularly important for combination products where coating placement is tightly linked to clinical function [4].

3.4 Liquid Delivery Systems: Pumps, Pulsation, and Filtration

The liquid delivery subsystem plays a critical role in ensuring stable ultrasonic atomization and consistent coating deposition [2]. Drug-polymer solutions must be delivered to the ultrasonic nozzle at precisely controlled flow rates while maintaining formulation integrity and cleanliness.

Syringe pumps (Figure 9) and precision gear pumps are commonly used to provide low, steady flow rates compatible with ultrasonic atomization. However, even small pulsations in flow can translate into fluctuations in droplet flux and coating weight. Pulsation dampeners and optimized pump selection are therefore essential components of industrial coating systems [24].

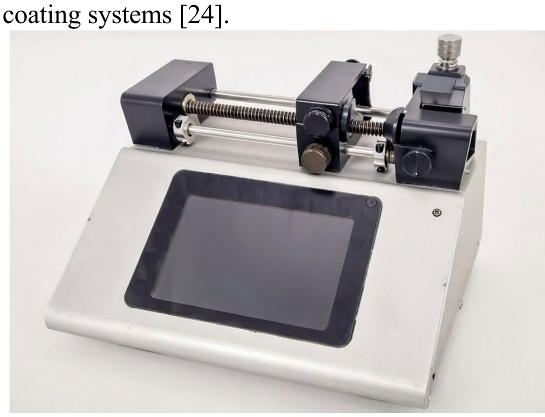

Figure 9 Syringe Pump

Filtration is another important factor to think about because ultrasonic nozzles are sensitive to particles and agglomerates that can mess up atomization or clog the nozzle [24]. Inline filters with pore sizes chosen based on the properties of the formulation are usually used before the nozzle. It is important to find a balance between filtration efficiency and acceptable pressure drop, as well as to make sure that the system works with solvent systems.

Stability of the solution over time is also a concern, especially for formulations that are likely to precipitate or separate into different phases [7]. To keep the coating consistent over long runs, you can use agitation, temperature control, and recirculation methods. These steps work together to make sure that liquid delivery doesn't become a secret source of variability in how well the coating works.

Table 1: Comparison of Hypotube-Fed Focused Nozzle and Shroud-Based Focused Nozzle ultrasonic spray equipment architectures

Subsystem	Hypotube-Fed Focused Nozzle **Architecture**	Shroud-Based Focused Nozzle **Architecture**	**Manufacturing Implications**
Ultrasonic nozzle	Focused ultrasonic atomizer with shaping air	Ultrasonic atomizer with air-shroud diffusion	Both enable fine droplet control
Spray beam width	Very narrow (sub-mm to few mm)	Narrow to moderate, highly uniform	Hypotube-Fed Focused Nozzle favored for small devices
Spray uniformity	High, sensitive to alignment	Very high, homogenized profile	Shroud-Based Focused Nozzle reduces sensitivity
Shaping air role	Beam confinement	Beam homogenization	Low-pressure, non-atomizing
Motion integration	High precision required	Slightly more tolerant	Depends on geometry
Typical applications	Coronary stents, micro-features	Stents, balloons, small implants	Selection driven by geometry

Table 1 shows the main differences in architecture and manufacturing between hypotube-fed focused nozzles and shroud-based focused ultrasonic nozzles used to coat medical devices. Both architectures can make fine droplets using ultrasonic atomization, but they are different in how they form spray beams, how uniform they are, and how sensitive they are to integration. Hypotube-fed focused nozzles have very narrow beam widths that are great for coating small or very detailed devices with high precision. However, they need more precise alignment control. Shroud-based focused nozzles, on the other hand, give a more even spray and are more forgiving of alignment changes, which makes them better for slightly larger or more complicated shapes. So, the choice between these architectures is mostly based on the shape of the device, the level of coating precision needed, and the strength of the manufacturing process, not on major differences in atomization ability.

4. Materials and Formulations for Drug-Eluting Medical Device Coatings

The performance of ultrasonic spray coating processes is strongly influenced by the selection and formulation of coating materials [4]. For drug-eluting medical devices, coating formulations typically consist of a therapeutic agent dispersed or dissolved within a polymeric matrix, delivered using one or more volatile solvents. These components must be carefully selected to ensure compatibility with ultrasonic atomization, process stability during manufacturing, and reliable clinical performance following implantation [7], [21]. This section reviews the materials commonly used in drug-eluting coatings and examines formulation considerations critical to ultrasonic spray coating.

4.1 Polymers Used in Drug-Eluting Coatings

Polymers are the main building blocks of drug-eluting coatings. They act as drug carriers, change the rate at which drugs are released, and keep the coatings stable [7]. The polymer you choose has a direct effect on how well the coating sticks, how strong it is, how quickly it breaks down, and how quickly it releases drugs. So, the choice of polymer is usually based on a mix of clinical needs, regulatory history, and how easy it is to make [20], [21].

Poly(ethylene-co-vinyl acetate), poly(n-butyl methacrylate), and other acrylic or fluorinated systems that don't break down have been used a lot in early-generation drug-eluting devices because they are strong and their release behavior is easy to predict [5], [30]. These polymers make stable coatings that can handle mechanical deformation when the device is crimped and deployed. But their long-term presence in vivo has raised worries about chronic inflammation in some cases [5], [6].

Biodegradable polymers, such as poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), and polycaprolactone, have garnered heightened interest as alternatives that gradually resorb post-drug release [7], [21]. These materials allow for temporary drug delivery while reducing long-term exposure to polymers. From a manufacturing point of view, biodegradable polymers can be harder to work with because they have shorter processing windows, are more sensitive to solvent selection, and are more likely to break down when exposed to heat or mechanical stress [7].

Polymer molecular weight and concentration are very important for ultrasonic spray coating because they directly affect how thick the solution is and how well it atomizes [2]. Polymers with high molecular weight may make mechanical properties better and allow for longer release, but they can also make the viscosity too high for ultrasonic atomization to work properly [28]. So, choosing a polymer is often a trade-off between how well it works in the clinic and how easy it is to make.

4.2 Solvent Systems and Volatility Considerations

Solvents play a critical role in ultrasonic spray coating by enabling polymer dissolution, drug dispersion, and controlled deposition onto the device surface [19]. Ideal solvent systems must dissolve all formulation components, be compatible with ultrasonic atomization, evaporate predictably, and meet regulatory and environmental requirements [22].

Commonly used solvents include alcohols, ketones, esters, and chlorinated solvents, selected based on polymer solubility and drug compatibility [22]. Solvent volatility is a key parameter governing droplet evaporation, wet film formation, and final coating morphology [16], [19]. Highly volatile solvents promote rapid drying and can reduce pooling or sagging; however, excessive evaporation during droplet flight may lead to premature drying, poor coalescence, or porous coatings. Conversely, low-volatility solvents increase wet film lifetime but raise the risk of webbing, bridging, and thickness non-uniformity [27].

In practice, solvent blends are frequently employed to balance evaporation rate and wetting behavior [19]. By combining fast- and slow-evaporating solvents, manufacturers can tailor drying kinetics to the specific geometry and coating strategy. Substrate temperature and ambient conditions further influence solvent evaporation and must be considered as part of the overall formulation-process interaction [16].

From an ultrasonic atomization standpoint, solvent surface tension and density also affect droplet size and spray stability [1]. Solvents with excessively low surface tension may produce overly fine droplets that dry rapidly, while high surface tension solvents may require higher frequencies or flow adjustments to achieve stable atomization [2].

4.3 Drug-Polymer-Solvent Interactions

The interactions between drug, polymer, and solvent are central to both manufacturing performance and clinical functionality [7]. These interactions determine drug solubility, distribution within the polymer matrix, and release behavior following implantation [8].

Drugs may be molecularly dissolved within the polymer solution or present as suspended solids, depending on solubility and formulation design [7]. In dissolved systems, solvent evaporation during coating leads to homogeneous drug distribution, provided that phase separation does not occur. In suspension-based systems, particle size, dispersion stability, and sedimentation behavior become critical concerns, particularly during extended coating runs [22].

Ultrasonic spray coating introduces additional considerations related to droplet-scale phenomena [19]. Rapid solvent evaporation can concentrate drug and polymer locally within individual droplets, potentially leading to drug crystallization or polymer phase separation prior to film coalescence. These effects can influence surface morphology, drug-release kinetics, and batch-to-batch reproducibility [8], [20].

Careful formulation design, including control of drug loading, solvent composition, and deposition rate, is therefore essential to ensure consistent microstructure formation [7]. Layer-by-layer deposition strategies are often used to mitigate segregation effects by allowing controlled drying between passes and allowing gradual buildup of coating thickness [2].

4.4 Formulation Stability and Nozzle Fouling Risks

Formulation stability during ultrasonic spray coating is a critical but often underappreciated aspect of process robustness [2]. Drug-polymer solutions may be prone to precipitation, phase separation, or viscosity drift over time, particularly under conditions of solvent evaporation or temperature variation [7].

Nozzle fouling represents a significant operational risk in ultrasonic spray coating systems [24]. Accumulation of dried polymer or drug residues at the nozzle tip can disrupt capillary wave formation, alter droplet size distribution, and lead to intermittent or unstable spraying. Fouling is exacerbated by highly volatile solvents, high solids content, and insufficient flow or purge strategies [2]. To mitigate these risks, industrial coating systems typically employ a combination of formulation filtration, nozzle purge routines, controlled ambient conditions, and periodic cleaning protocols [24]. Inline filtration is particularly important to remove particulates or agglomerates that could interfere with ultrasonic atomization. However, filtration must be carefully designed to avoid excessive pressure drop or unintended removal of suspended drug particles [22].

Long-term stability considerations also extend to solution handling and storage [7]. Agitation, temperature control, and limited exposure to ambient conditions are commonly used to maintain formulation homogeneity during production. Together, these strategies ensure that formulation-related variability does not undermine the inherent precision of ultrasonic spray coating processes.

5. Process Parameters, Quality-by-Design, and Manufacturing Control

For drug-eluting medical devices, ultrasonic spray coating is not merely a deposition step but a critical manufacturing process that directly influences clinical performance and regulatory compliance [4]. Achieving consistent coating requires systematic identification, understanding, and control of process variables that govern atomization, deposition, and film formation. Quality-by-Design (QbD) principles provide a structured framework for linking process parameters to coating quality attributes and for establishing robust operating windows suitable for commercial manufacturing [11]-[13]. This section reviews critical process parameters, quality attributes, experimental strategies, and control methodologies relevant to ultrasonic spray coating.

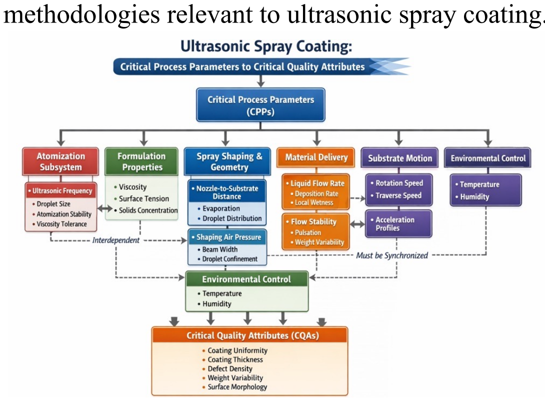

Figure 30 Qualitative CPP-CQA interaction map for ultrasonic spray coating

5.1 Critical Process Parameters (CPPs)

As shown in figure 10, Critical Process Parameters (CPPs) are defined as process variables that have a direct and significant impact on one or more Critical Quality Attributes (CQAs) [12]. In ultrasonic spray coating, CPPs span multiple interconnected subsystems, including atomization, spray shaping, substrate motion, formulation delivery, and environmental control, and their effects are often interdependent, necessitating a holistic approach to process development [4]. Ultrasonic frequency is a primary CPP governing droplet size and atomization stability; higher frequencies produce finer droplets but reduce tolerance for higher-viscosity formulations, thereby directly influencing coating uniformity, wet film behavior, and defect formation [1], [2]. Liquid flow rate controls the rate of material deposition and local wetness, with excessive flow leading to pooling, webbing, or bridging, while insufficient flow may result in incomplete coverage or poor layer coalescence; flow stability is particularly critical, as pulsation can translate directly into coating weight variability [2]. Solution properties, including viscosity, surface tension, and solids concentration, are formulation-driven CPPs that strongly affect atomization behavior, and even small changes in polymer concentration or solvent composition can shift the process outside a stable operating region [2], [28]. Nozzle-to-substrate distance further influences droplet evaporation and spatial distribution, where increased distance promotes solvent evaporation but risks premature drying, while reduced distance increases wet deposition and pooling [16]. Spray shaping air pressure affects beam width and droplet confinement; although it does not drive atomization, variations in shaping air can alter the deposition footprint and coating uniformity [24]. Substrate motion parameters, including rotation speed, traverse speed, and acceleration profiles, control local dwell time and coating thickness distribution and must be carefully synchronized with flow rate to avoid axial or circumferential non-uniformity [29]. Finally, environmental conditions such as temperature and humidity significantly influence solvent evaporation rates and wet film evolution, and uncontrolled environmental variability is a common source of drift in coating performance in manufacturing environments [23].

5.2 Critical Quality Attributes (CQAs)

Critical Quality Attributes (CQAs) represent measurable properties of the coated device that must be controlled to ensure clinical performance and patient safety [12]. For drug-eluting medical devices, CQAs extend well beyond cosmetic appearance and include functional and mechanical characteristics that directly influence therapeutic efficacy [4]. Coating weight and drug dose are among the most critical attributes, as they determine the amount of drug delivered to the target site; tight control of coating weight variability is therefore essential, particularly for low-dose devices [20]. Thickness uniformity plays a key role in both drug-release kinetics and mechanical integrity, as non-uniform coating can lead to localized over- or under-dosing and increase the risk of cracking or delamination [27]. Surface morphology and microstructure further influence drug distribution, release behavior, and interaction with surrounding biological tissue, with parameters such as roughness, porosity, and phase separation commonly evaluated using microscopy-based techniques [8], [19]. Adhesion and overall mechanical integrity are also critical CQAs, ensuring that coatings remain intact during device handling, crimping, and deployment; inadequate adhesion poses a significant clinical risk [6]. Finally, drug-release performance, typically assessed through in-vitro elution testing, integrates the combined effects of formulation, process parameters, and coating structure, serving as a key functional attribute that links manufacturing performance directly to clinical outcome [8], [21].

5.3 Design of Experiments (DOE) Strategies for Ultrasonic Coating

Design of Experiments (DOE) is a crucial tool for process development because ultrasonic spray coating is multivariate [11]. The systematic assessment of CPP effects and interactions made possible by DOE makes it easier to determine reliable operating windows.

To find high-impact parameters among frequency, flow rate, nozzle distance, traverse speed, and formulation properties, early-stage screening designs are frequently employed [11]. Later response surface approaches enable interaction exploration and fine-tuning of parameter ranges.

CQAs like coating weight, thickness uniformity, and defect incidence are commonly mapped to DOE outputs [4]. These connections serve as the foundation for design spaces that adhere to regulatory requirements and QbD principles [12].

5.4 Scale-Up and Technology Transfer Considerations

There are more difficulties than just translating parameters when scaling ultrasonic spray coating processes from lab or pilot settings to commercial manufacturing [4]. Although the basic physics of ultrasonic atomization are naturally scalable, if equipment configuration, motion architecture, environmental control, and throughput requirements are not properly managed, they can have a substantial impact on coating results [2].

Maintaining droplet deposition behavior when system geometry changes is an important scale-up factor. Droplet residence time and solvent evaporation dynamics can be changed by variations in nozzle-to-substrate distance, airflow patterns, and enclosure design, which may cause the process to move outside of the designated design space [16]. Because of this, even when the same nozzle and formulation are used, scale-up efforts frequently necessitate re-optimizing motion parameters, spray shaping conditions, and environmental setpoints [24].

These risks are further increased by technology transfer between development and manufacturing sites [23]. Subtle but significant variations in process behavior can be introduced by differences in facility controls, automation platforms, and equipment vendors. Therefore, thorough documentation of Critical Process Parameters, their acceptable ranges, and their connections to Critical Quality Attributes is essential for successful transfer [12]. When paired with statistically supported design spaces, physics-based knowledge of atomization and wet film formation reduces reliance on empirical trial-and-error and speeds up transfer timelines [11].

Scale-up and transfer operations must show continuity of process understanding and control from a regulatory perspective [12]. Evidence that manufacturing-scale processes function within validated design spaces created during development is becoming more and more required by regulators. This lessens the burden of downstream validation and promotes effective lifecycle management of drug-eluting medical devices by taking scale-up and transfer requirements into account early in the process development process [13].

5.5 Process Capability and Statistical Process Control (SPC)

Once a coating process is set up, it needs to be controlled all the time to keep working well over time [23]. Statistical Process Control (SPC) is a common way to keep an eye on important process indicators and find early signs of drift.

Some of the most common things to keep an eye on are the weight of the coating, the flow rate of the solution, and the weather. Process capability indices, like Cp and Cpk, are used to see if the process can always meet the limits set by the specifications [11]. SPC implementation supports continuous improvement and provides objective evidence of process robustness for regulatory submissions and audits [23].

Table 2: Mapping of Critical Process Parameters (CPPs) to Critical Quality Attributes (CQAs)

CPP	Coating Weight	Thickness Uniformity	Morphology	Adhesion	Drug Release
Ultrasonic frequency	●	●	●	○	○
Flow rate	●	●	○	○	●
Solution viscosity	●	●	●	●	●
Nozzle distance	○	●	●	○	○
Shaping air pressure	○	●	○	○	○
Traverse /rotation speed	●	●	○	○	○
Substrate temperature	○	●	●	●	●

● High impact ○ Moderate impact

Table 2 shows a qualitative relationship between important Critical Process Parameters and Critical Quality Attributes for ultrasonic spray coating of medical devices that release drugs. The mapping shows that the process is very tightly linked, with many factors affecting coating performance at the same time instead of separately. Ultrasonic frequency, flow rate, and solution viscosity are all examples of parameters that directly control material delivery and atomization. These parameters have a big effect on coating weight, thickness uniformity, and morphology. Motion and geometry parameters have the biggest effect on thickness distribution. Environmental and thermal factors have a bigger effect on morphology, adhesion, and drug release behavior. This qualitative relationship emphasizes the importance of multivariate process development and endorses the utilization of Quality-by-Design and Design of Experiments methodologies for establishing robust operating windows.

Table 3: Typical Operating Windows for Ultrasonic Spray Coating (Literature-Based)

Parameter	Typical Range
Ultrasonic frequency	60-120 kHz
Solution viscosity	10-200 cP (100-200 mPa·s)
Flow rate	0.05-2.0 mL/min
Nozzle-to-substrate distance	10-40 mm
Shaping air pressure	0.5-2.0 psi (3.4 – 13.8 kPa)
Substrate rotation speed	100-2000 rpm
Ambient temperature	20-30 °C
Relative humidity	<40%

Note: Actual operating windows are formulation- and device-specific and must be established through DOE.

Table 3 shows the typical operating ranges for important ultrasonic spray coating parameters that have been reported in the literature. These ranges show the normal process space where drug-eluting medical devices can achieve stable atomization, controlled deposition, and good coating quality. The values in the table are helpful when you're first developing a process or choosing equipment, but they also show how much operating windows depend on the properties of the formulation, the shape of the device, and the conditions in the environment. These ranges should be seen as starting points, not hard and fast rules. This shows how important it is to use systematic Design of Experiments to find formulation- and device-specific design spaces for strong manufacturing.

6. Coating Defects, Failure Modes, and Mitigation Strategies

Despite the inherent advantages of ultrasonic spray coating, coating defects can arise if process parameters, formulation properties, or environmental conditions are not adequately controlled [2]. For drug-eluting medical devices, such defects represent a significant manufacturing and clinical risk, as they may compromise drug dose accuracy, mechanical integrity, or long-term device performance [4], [6]. Understanding the mechanisms underlying common coating defects is therefore essential for robust process development and effective risk mitigation. This section reviews the most frequently observed defect modes in ultrasonic spray coating, their root causes, and practical strategies for prevention.

6.1 Webbing and Bridging

Figure 41 Coating defect - Webbing and Bridging

Figure 11 shows that webbing and bridging happen when liquid that has been deposited flows over nearby features on the device surface, creating thin filaments or continuous bridges between struts, edges, or geometric discontinuities [27]. This defect is especially common in devices with small gaps and fine features, like coronary stents, where flow driven by surface tension can take over wet film behavior.

The main reason for webbing is too much moisture during deposition. When there is a lot of liquid flowing, not enough solvent evaporating, or not enough time between passes for the liquid to dry, droplets can come together to form long liquid films. These films are then pulled across gaps by capillary forces [16]. Low-viscosity formulations and high surface tension can make this behavior even worse by making fluids move more easily after they are deposited [2].

Mitigation strategies aim to lower the thickness of the local wet film and improve the control of solvent evaporation [27]. Some common ways to do this are to lower the flow rate, speed up the traverse, lower the deposition per pass, and use layer-by-layer coating methods with set drying times. Changing the composition of the solvent to speed up evaporation or slightly thicken the viscosity can also stop the web from forming. Sometimes, raising the temperature of the substrate or making the airflow around the device more even can help stop bridging by speeding up the removal of the solvent [16].

6.2 Coating Cracking and Delamination

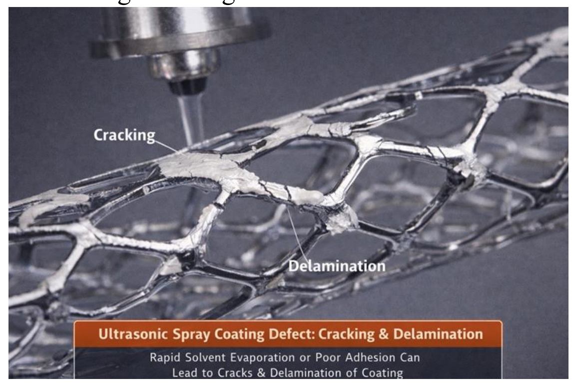

Figure 52 Coating defect - Cracking and Delamination

As shown in the Figure 12, cracking and delamination represent critical failure modes that compromise coating integrity and pose serious clinical risks [6]. Cracks may form during solvent evaporation due to internal stresses generated by rapid drying, high film thickness, or polymer shrinkage. Delamination can occur when adhesion between the coating and substrate is insufficient to withstand mechanical or residual stresses [20].

Root causes include overly thick coatings applied in a single pass, high polymer molecular weight, incompatible solvent systems, or inadequate surface preparation [7]. Mechanical stresses introduced during device crimping, expansion, or handling can further propagate existing defects [4].

Mitigation strategies emphasize stress reduction and adhesion enhancement [20]. Layer-by-layer deposition with intermediate drying steps significantly reduces internal stress accumulation. Surface treatments such as plasma activation improve substrate wettability and chemical bonding. Selecting polymer-solvent systems with appropriate glass transition temperatures and drying profiles also reduces cracking propensity. Mechanical integrity testing during development is essential to ensure coatings tolerate downstream processing [6].

6.3 Dose Non-Uniformity

Dose non-uniformity is when the coating weight or drug concentration is different in different places on the device surface or between devices in the same batch [4]. This flaw has a direct effect on how well the treatment works, and it is a major concern for drug-eluting medical devices in terms of regulation [12].

There are many things that can cause non-uniformity, such as unstable liquid flow, a misaligned nozzle, inconsistent motion synchronization, or changes in the environment [2]. Pulsation in liquid delivery systems and gradual nozzle fouling are especially sneaky because they can cause slow drift that is hard to notice without checking often [24].

Some ways to reduce the risk are to use low-pulsation pumping systems, check and clean the nozzles regularly, and keep a close eye on the motion parameters [23]. Gravimetric checks, sampling during the process, and Statistical Process Control (SPC) are all common ways to find trends before they go against the rules. In-line or near-real-time coating weight measurement makes control even better when possible [15].

6.4 Root Cause Analysis and Integrated Mitigation Strategy

Even though each defect may look different, they often have the same root causes, such as how wet film behaves, how solvents evaporate, and how processes change [16]. So, the best way to fix defects is to look at the whole picture instead of just changing one parameter at a time. Design of Experiments (DOE) gives you a structured way to find the most important factors and interactions [11]. This lets you make smart choices between different risks, like webbing and cracking.

Most of the time, successful ultrasonic spray coating processes use a combination of optimized formulation design, controlled deposition strategies, precision motion systems, and strong environmental control [2]. Preventive maintenance of nozzles and liquid delivery parts, along with strict process monitoring, makes sure that everything stays stable over time [23]. Manufacturers can greatly lower risk and make coatings stronger overall by building defect prevention into the design of the process instead of relying on end-of-line inspection.

7. In-Line Monitoring, Metrology, and Process Feedback Control

To make drug-eluting medical devices in a strong way, you need more than just good coating recipes. You also need to be able to find and control process variability quickly. In ultrasonic spray coating, the tolerances for coating weight are very tight, and defects may not be easy to see. To make sure that the quality of the product stays the same, you need good metrology and feedback control strategies [4], [12]. This section talks about the most common off-line and in-line measurement methods, what they can and can't do, and new ways to get real-time feedback on a process.

7.1 Gravimetric and Off-Line Analytical Methods

Gravimetric measurement remains the most widely used method for quantifying coating weight in ultrasonic spray coating processes [23]. Devices or coupons are weighed before and after coating using high-precision balances, and coating weight is calculated by difference. Gravimetric methods offer high accuracy and simplicity and are often used as reference measurements during development and validation. However, they are inherently off-line and provide limited insight into spatial uniformity or within-run variability.

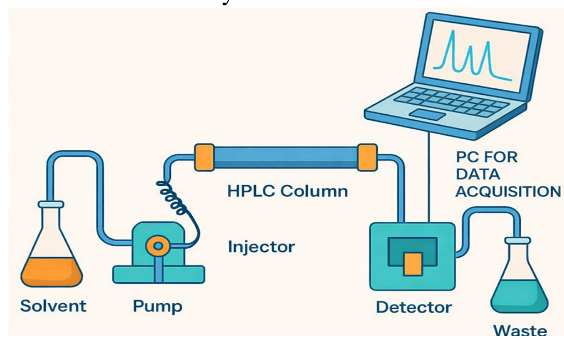

Figure 63 HPLC test process steps

Chemical analysis methods, most commonly high-performance liquid chromatography (HPLC), are used to quantify drug content and confirm dose accuracy as shown in the Figure 13 [8]. These techniques are critical for establishing drug-to-polymer ratios, verifying batch uniformity, and supporting regulatory submissions [21]. While highly accurate, HPLC is destructive, time-consuming, and unsuitable for real-time monitoring, limiting its use to development, validation, and periodic verification rather than routine process control.

Surface and structural characterization tools, including optical microscopy and scanning electron microscopy (SEM), are routinely employed to assess coating morphology, thickness uniformity, and defect presence [14]. These methods provide valuable qualitative and semi-quantitative information but are typically limited to off-line analysis due to sample preparation requirements and long analysis times.

7.2 In-Line and At-Line Thickness Measurement Techniques

Manufacturers are looking for ways to check the thickness and uniformity of coatings in-line or at-line instead of at the end of the line. Optical methods are some of the most promising because they can measure without touching the surface and can be added to automated coating systems [15].

Optical reflectometry and interferometry can be used to measure thin film thickness based on light reflection and interference patterns [15]. These methods work especially well on coatings that are clear or semi-clear, and they can give you high spatial resolution. But the roughness, curvature, or optical properties of the coating and substrate may make them less useful.

Laser triangulation and confocal displacement sensors provide alternative non-contact methods for indirectly measuring coating thickness or accumulation via surface profiling [15]. These methods may have trouble with small features or very curved shapes that are common in stents, but they are less sensitive to optical properties.

At-line methods, like quick gravimetric checks or automated imaging right after coating, are a good middle ground between real-time monitoring and strict analysis [23]. These methods make it easier to find drift more quickly than fully in-line systems do.

7.3 Process Indicators and Indirect Monitoring

Direct in-line coating weight measurement is still difficult in many ultrasonic spray coating processes [2]. Indirect process indicators are therefore frequently tracked as stand-ins for coating performance. Liquid flow rate, pump pressure, shaping air pressure, nozzle power or frequency stability, and environmental factors like humidity and temperature are some of these [23].

Real-time monitoring of these parameters allows for the early identification of deviations that could result in dose variability or coating flaws. For instance, slow increases in pump pressure could be a sign of nozzle fouling or filter loading, while variations in the surrounding humidity can have an impact on wet film behavior and solvent evaporation [16]. Despite being indirect, these signals offer important context for understanding coating results and preserving process stability.

7.4 Closed-Loop Control and Feedback Strategies

Closed-loop control is an important area for the future of ultrasonic spray coating [11]. Real-time measurements, either direct (like optical thickness) or indirect (like flow stability), are used in a closed-loop system to automatically change process parameters like flow rate, traverse speed, or number of coating passes.

For instance, if the measured coating thickness changes, the traverse speed or deposition time could be changed dynamically to make up for the drift. In the same way, flow or pressure sensors could be used to stop the coating process or start cleaning the nozzle before defects happen [23]. These kinds of systems aren't common in the making of medical devices yet, but they fit well with the principles of Quality-by-Design and the rules that say processes should be better understood and controlled [12].

To make sure that automated adjustments don't cause unintended changes, closed-loop control must be carefully validated [11]. Sensor reliability, response time, and data integrity are very important, especially in places where rules are strict and changes to processes must be explained and written down [13].

7.5 Role of Metrology in QbD and Regulatory Compliance

From a regulatory point of view, metrology is a key part of putting QbD into action [12]. Measurement systems give us the information we need to show that CPP-CQA relationships exist, set design spaces, and show that process control is still going on. Regulators are putting more and more pressure on manufacturers to use numbers instead of just their own experiences to explain process limits [13].

Integrating metrology into ultrasonic spray coating processes improves not only product quality but also development, technology transfer, and lifecycle management [4]. Manufacturers can meet regulatory requirements while still being practical and strict by combining strong off-line analytics with targeted in-line or at-line monitoring [23].

8. Future Directions and Research Gaps

Ultrasonic spray coating is a well-established and widely used technology for drug-eluting medical devices [2]. However, there are still some areas where more research and technological development are needed to support next-generation devices and stricter manufacturing standards. Future improvements are likely to focus on making processes more predictable, giving people more control in real time, making more formulations work together, and making the literature more consistent. This part talks about important areas of research and gaps that could lead to more new ideas.

8.1 Digital Twins and Physics-Based Process Modeling

The creation of digital twins—virtual representations of the coating process that combine physics-based models with experimental data—is one of the most promising future paths for ultrasonic spray coating [18]. Comprehensive models that connect nozzle operating conditions, formulation properties, motion parameters, and environmental conditions to final coating outcomes are still scarce, despite the study of individual aspects of ultrasonic atomization, droplet transport, and solvent evaporation [1], [16].

By enabling predictive simulation of coating weight, thickness distribution, and defect risk under various operating conditions, digital twins may lessen the need for intensive empirical testing. These models would be especially helpful for technology transfer between development and manufacturing sites, equipment modifications, and process scaling up [4]. However, creating accurate digital twins is a substantial but worthwhile research challenge that calls for better knowledge of coupled multiphase phenomena and high-quality experimental datasets.

8.2 AI-Driven Process Control and Advanced Automation

Artificial intelligence and machine learning techniques present novel prospects for improving the regulation of ultrasonic spray coating processes [11]. Using historical process data to train data-driven models can help find small connections between process variables and coating outcomes that traditional DOE methods might not pick up on. These models could help with adaptive control strategies that change process parameters based on measurements taken in real time or trends that are found.

Even though more people are interested, AI-driven control is still not widely used in the manufacturing of regulated medical devices. Problems include getting the data, making the model understandable, meeting validation requirements, and getting regulatory approval [12], [13]. Future research ought to concentrate on hybrid methodologies that integrate physics-based comprehension with machine learning, facilitating transparent and elucidative control strategies appropriate for regulated settings.

8.3 Greener Solvent Systems and Sustainable Manufacturing

Environmental and occupational safety factors are having a bigger and bigger impact on the development of coating processes [23]. Many drug-eluting coating formulations use volatile organic solvents, which make it hard to recover the solvent, release it into the air, and protect workers from exposure. An important area of research is finding ways to make greener solvent systems, such as water-based or low-VOC formulations that work with ultrasonic atomization [22].

Ultrasonic spray coating is naturally good for low-flow, low-overspray work [2]. However, the use of environmentally friendly solvents for many polymer-drug systems is limited by the way they are made. Future research should concentrate on polymer chemistry, solvent blending techniques, and process modifications that facilitate sustainable manufacturing while maintaining coating performance and stability [7].

8.4 Compatibility with Biologics and Advanced Therapeutic Payloads

As drug-eluting devices progress beyond small-molecule therapeutics, their compatibility with biologics, including proteins, peptides, and nucleic acid-based therapies, is becoming increasingly significant [21]. Ultrasonic spray coating may be beneficial for these applications because it atomizes with low shear [1]. However, there aren't many systematic studies that look at how ultrasonic energy, solvent exposure, and drying kinetics affect the stability of biologics.

There are still gaps in our knowledge about how the composition of the formulation, the conditions of atomization, and the strategies for deposition affect biologic activity and long-term stability in coatings [7]. To expand ultrasonic spray coating to new therapeutic methods and combination products, these gaps must be filled.

8.5 Standardization and Reporting Gaps in Literature

A continual issue in the ultrasonic spray coating literature is the absence of standardized reporting for process parameters and experimental conditions [2]. Numerous studies neglect essential parameters, including ultrasonic frequency, flow rate, nozzle-to-substrate distance, environmental conditions, or formulation characteristics, thereby constraining reproducibility and inter-study comparison.

Future research should prioritize standardized reporting frameworks that explicitly delineate equipment configurations, operational parameters, and measured results [11]. Using the same metrics and reporting methods would speed up the transfer of knowledge, help with model development, and make it easier for regulators to talk to each other. As ultrasonic spray coating becomes more popular, better standardization will be necessary for both academic research and industrial use to move forward.

9. Conclusion

Ultrasonic spray coating has changed from a niche deposition method to a key manufacturing technology for drug-eluting medical devices [2], [4]. This is because it can apply precise, repeatable, and low-shear coatings to complex, small-scale shapes. As combination products become more important in modern medicine, coating processes have become the most important factor in clinical performance, manufacturing strength, and regulatory success. The goal of this review was to connect basic knowledge of ultrasonic spray coating to real-world manufacturing situations by looking at it from the ground up to its use in industry.

The physics of ultrasonic atomization, which is based on capillary wave theory and frequency-dependent droplet generation, give ultrasonic spraying a predictable and controllable way to deposit materials that sets it apart from traditional pneumatic methods [1], [26]. These mechanisms, when used with controlled droplet transport, wet film formation, and solvent evaporation, make coating processes more efficient by reducing overspray, narrowing droplet size distributions, and improving deposition efficiency [2]. These traits are especially good for drug-eluting medical devices, which need to have very tight tolerances on coating weight, thickness uniformity, and drug distribution [4].

Advances in equipment architectures, such as focused nozzle designs, spray shaping technologies, precision motion systems, and stable liquid delivery platforms, have made it possible for industries to use ultrasonic spray coating [24], [25]. But just having the right tools isn't enough to make sure the process works. The choices of materials and formulations, including polymer chemistry, solvent volatility, and drug-polymer-solvent interactions, are just as important for determining atomization stability, coating morphology, and long-term performance [7], [20]. To keep manufacturing environments reproducible, it is important to manage formulation stability and reduce risks like nozzle fouling [24].

Using Quality-by-Design principles as a framework for bringing together physics, materials, and equipment into strong manufacturing processes [12]. By systematically identifying Critical Process Parameters and how they relate to Critical Quality Attributes, and using Design of Experiments and Statistical Process Control, it is possible to set up defensible operating windows and make it easier to scale up and transfer technology [11], [23]. The study of common coating flaws shows once again that the best way to make a process strong is to control how wet film behaves and how it dries ahead of time, not just at the end of the line [27].

Ultrasonic spray coating is a well-established technology, but there are still many ways to improve it. Better in-line metrology, predictive process modeling, and data-driven control strategies could make manufacturing even more stable and less variable [15], [18]. Key areas where focused research and collaboration are needed are moving toward greener solvent systems, making them work better with biologics, and making experimental reporting more standardized [7], [21].

In short, ultrasonic spray coating should not be seen as just another way to coat things; it should be seen as a way to make current and future drug-eluting medical devices. Ultrasonic spray coating is well-positioned to meet the changing clinical, regulatory, and performance needs of combination products because it combines basic knowledge with disciplined process development and control [4].

Declarations

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Author ORCIDs

Hardikkumar Jayantibhai Lathiya, https://orcid.org/0009-0000-4605-343X; Pranav Heramb Kolapkar, https://orcid.org/0009-0001-3844-9861

Author Contributions

Hardikkumar Jayantibhai Lathiya : Conceptualization of the review topic, comprehensive literature review and critical analysis of ultrasonic spray coating technologies, comparative evaluation of focused beam architectures and process control strategies; synthesis and interpretation of findings, development of the manuscript structure, drafting of the original manuscript; preparation of figures, tables, and schematics, writing of the "Future Directions" section, integration of feedback; and final approval of the manuscript. Pranav Heramb Kolapkar: Assistance in literature collection and organization; contribution to summarizing selected studies; support in formatting tables and references; proofreading and language editing; minor revisions for clarity and consistency; and approval of the final manuscript.

References

[1] Lang, R.J., Ultrasonic atomization of liquids. J. Acoust. Soc. Am., **34** (1) 6–8 (1962)

[2] Stryckers, J., Deferme, S., D'Haen, J., Ultrasonic spray coating: Process fundamentals and applications. Surf. Coat. Technol., **206** (21) 4316–4324 (2012)

[3] Zhou, X., Li, M., Chen, Z., Ultrasonic spray deposition of TiO_2 thin films for functional coatings. Thin Solid Films, **615** 404–411 (2016)

[4] McDermott, M., McCarthy, S., O'Brien, J., Application of quality by design principles to coating processes for drug-eluting stents. J. Biomed. Mater. Res. Part B, **97B** (1) 1–12 (2011)

[5] Wessely, R., Kastrati, G., Schömig, A., Mechanisms of restenosis and drug-eluting stent coatings. Nat. Rev. Cardiol., **3** (7) 348–357 (2006)

[6] Finn, A.V., Joner, M., Nakazawa, G., Kolodgie, F.D., Virmani, R., Pathological correlates of late drug-eluting stent thrombosis. Circulation, **115** (18) 2435–2441 (2007)

[7] Uhrich, K., Cannizzaro, S.M., Langer, R.S., Shakesheff, K.M., Polymeric systems for controlled drug release. Chem. Rev., **99** (11) 3181–3198 (1999)

[8] Siepmann, J., Siepmann, F., Modeling of diffusion-controlled drug delivery. Adv. Drug Deliv. Rev., **64** 163–174 (2012)

[9] Taleb, S., Benlahbib, M., Belaid, A., Enhanced performance of flexible piezoelectric PVDF films fabricated by ultrasonic spray coating. Sensors, **21** (9) Article 3056 (2021)

[10] Spisni, G., Cavallini, M., Biscarini, F., Ultrasonic spray coating of functional polymer layers for bio-electrochemical devices. Nanomaterials, **13** (4) Article 721 (2023)
[11] Montgomery, D.C., Design and Analysis of Experiments, 9th ed. Wiley, Hoboken, NJ (2017)
[12] International Council for Harmonisation, ICH Q8(R2): Pharmaceutical Development. ICH Guideline (2009)
[13] International Council for Harmonisation, ICH Q9: Quality Risk Management. ICH Guideline (2005)
[14] Ohring, M., Materials Science of Thin Films, 2nd ed. Academic Press, San Diego, CA (2002)
[15] Raghavan, S., Sharma, A., Kumar, P., In-line optical metrology techniques for thin-film coating processes. Appl. Opt., **53** (4) 123–131 (2014)
[16] Czajkowski, T., Borra, J.P., Borghese, A.F., Spray coating dynamics: Droplet impact, spreading, and evaporation. Exp. Fluids, **51** (6) 1547–1560 (2011)
[17] Senturia, S.D., Microsystem Design. Kluwer Academic Publishers, Boston, MA (2001)
[18] Middha, S., Vanka, S.P., Numerical investigation of droplet deposition and evaporation in spray coating. Int. J. Heat Mass Transf., **49** (19–20) 3511–3521 (2006)
[19] Liu, Y., Chen, H., Wang, J., Effect of solvent evaporation on polymer thin-film morphology during spray coating. Langmuir, **32** (45) 11544–11553 (2016)
[20] Bansal, A.K., Langer, R.S., Surface properties of drug-polymer coatings and implications for controlled release. J. Controlled Release, **161** (2) 433–441 (2012)
[21] Venkatraman, S.S., Boey, F., Lao, L.L., Implantable drug delivery systems: Design and engineering considerations. Adv. Drug Deliv. Rev., **64** 111–129 (2012)
[22] Sheskey, P.J., Cook, W.G., Cable, C.G., Handbook of Pharmaceutical Excipients, 8th ed. Pharmaceutical Press, London (2017)
[23] Basu, S., Kumar, R., Statistical process control in pharmaceutical and medical device manufacturing. Int. J. Pharm. Sci. Rev. Res., **34** (2) 56–64 (2015)
[24] Sono-Tek Corp., Ultrasonic Spray Coating Technology for Medical Devices. Application Note, Milton, NY (2022)
[25] PerkinElmer Inc., Ultrasonic Spray Deposition Techniques for Biomedical Coatings. Technical White Paper, Waltham, MA (2019)
[26] Freund, J.B., O'Rourke, A.D., Dynamics of droplet formation in ultrasonic atomization. Phys. Fluids, **14** (1) 347–358 (2002)
[27] Thompson, M.R., Kline, R.E., Spray coating defects: Formation mechanisms and mitigation. J. Coat. Technol. Res., **9** (4) 389–402 (2012)
[28] Sen, A.K., Micro- and nanoscale droplet generation using ultrasonic excitation. Microfluid. Nanofluid., **12** (5) 839–852 (2012)
[29] Park, J.H., Kim, Y.K., Lee, D.J., Effect of process parameters on coating uniformity in ultrasonic spray coating. Surf. Eng., **35** (3) 245–253 (2019)
[30] Virmani, R., Kolodgie, F.D., Farb, A., Pathological mechanisms of drug-eluting stent failure. J. Am. Coll. Cardiol., **44** (6) 1024–1033 (2004)