Ultrasonic Atomization for Advanced Coating of Balloon Catheters

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History of development leading up to Coated Balloon Catheters

Major advances have been made in the past few decades in the percutaneous treatment of artery diseases. The development of each new technology has been spurred by the downfall of the previous technology. Balloon angioplasty emerged as a minimally invasive solution to previous treatment methods which typically involved significant opportunity for complications. This treatment method came with its own disadvantages due to its inability to prevent vessel recoil and neointimal proliferation. Intracoronary stenting through Bare Metal Stents (BMS) overcame the acute recoil of balloon angioplasty, but was unable to prevent the occurrence of in-stent-restenosis (ISR) caused by excessive neointimal proliferation. Drug Eluting Stents (DES) utilize agents that effectively reduce the occurrence of this neointimal proliferation and increase or eliminate the time needed for subsequent treatment. The agents consist of an antiproliferative drug and a specially designed polymer coating to control the release profile of the drug over time. Ultrasonic Atomization technology has proven successful in the application of these agents on to DESs.

Even with the benefits provided by DESs, it is still important to address its drawbacks. The antiproliferative drugs are not able to completely eliminate the possibility of ISR and may react to the drug or polymer coating. Managing restenosis of an installed stent becomes extremely difficult. Revascularization techniques coupled with antiproliferative drug delivery is necessary for successful treatment of this condition.

Drug-Eluting Balloons (DEBs) have emerged in recent years as a successful treatment alternative for restenosis and other forms of arterial diseases. The idea of delivering antiproliferative drugs to the site of an interventional procedure has existed for some time. However, the successful development of BMS coupled with their easy application inside the body took priority over developing effective transfer methods. Even though DEB is a relatively new technology, there are significant benefits that these devices can offer. Driven by the limitations of DESs, DEBs are still able to deliver the important antiproliferative drugs necessary to prevent restenosis without the use of a stent. For diseased areas where a stent may not be applied, such as in small vessels, torturous vessels, or calcified lesions, DEBs still can provide treatment.

Other advantages include rapid release and homogenous transfer of the drug to the vessel wall and the absence of both stent and polymer, allowing the original anatomy to remain intact and reducing the chance of chronic inflation or late thrombosis.

DEB Technology and Coating Requirements

The purpose of these DEBs is to deliver antiproliferative drugs to the cell walls. Although the method of accomplishing this feat varies between manufacturers, there are some similarities. The lasting effect of paclitaxel coupled with its quick uptake into vascular cells makes it the drug of choice in this application across the board.

The DEB catheters are required to travel through significant lengths of blood vessels before reaching the point of delivery. It is most often necessary to protect the paclitaxel in some type of binder during travel through the body. In many of the DEBs currently undergoing clinical trials, the paclitaxel is interspersed in a hydrophilic matrix, allowing the coating to swell during travel through the body and allowing the release of the paclitaxel upon inflation of the balloon catheter. The coating should also maximize the amount of paclitaxel release from the hydrophilic matrix.

The characteristics of this coating are extremely important in making DEBs successful. DEBs claim to deliver a homogenous application of drug to the vessel walls at a fast rate, typically less that one minute. Other factors for success include the amount of drug delivered and maintaining a uniform surface concentration.

Alternative Methods for coating DEBs

Several different coating technologies are possible for the application of these drug/binder combinations onto the balloons. The balloon can be coated using ultrasonic atomization, dip coating of the balloon into a liquid bath, and pipetting the liquid onto the device.

Each method has its own benefits and disadvantages. As previously discussed, the ideal equipment for DEB coatings should meet the following criteria.

1.) Coating Uniformity: Minimal variance across the full length and diameter of balloon.

2.) Repeatability: Coating method must be able to maintain consistent application both in coating morphology and uniformity from balloon to balloon.

3.) Compatibility with chemicals: Coating technology must be proven to not damage or degrade the drug or polymer performance and will not fail due to chemicals or solvents used.

4.) Process Variables: Independent and easy process variable control is necessary for process and coating development and optimization. Results of this includes the ability to easily change coating thickness or morphology.

5.) Minimal Operator Intervention necessary for maintaining or cleaning coating equipment which minimizes possible contamination.

One of the possible coating technologies which meet all of these criteria is Ultrasonic Atomization.

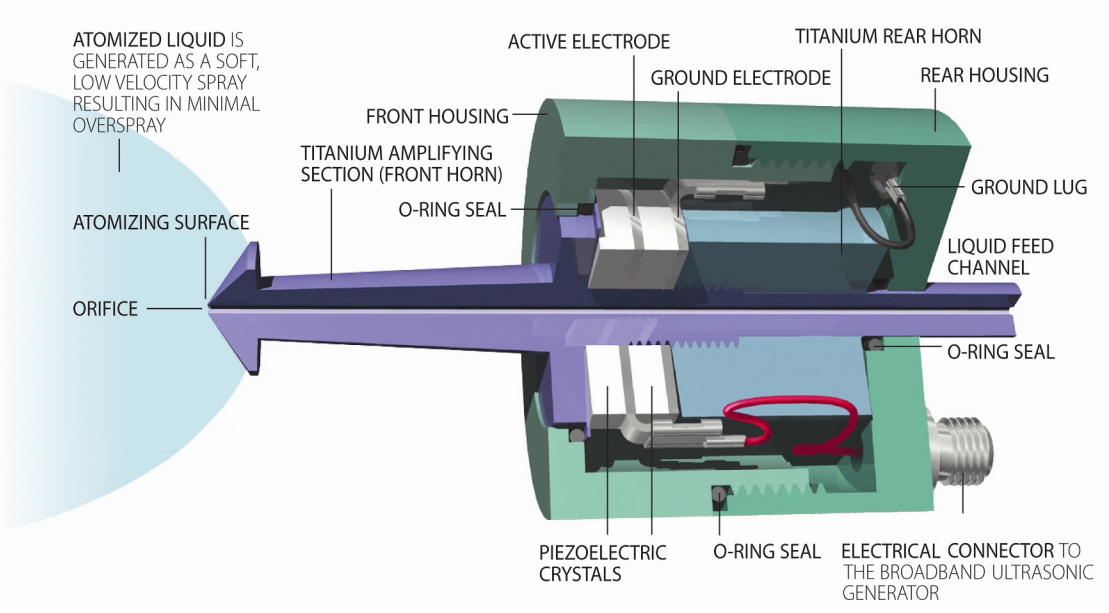

Fig. 1 Cross Section of an Ultrasonic Atomizer with Liquid Flow Through the Center

Ultrasonic Technology

Ultrasonic Atomization technology is a very high-tech atomization technique that is used for spray coating. As you can see in the Figure 1, the liquid is fed through the center of the nozzle, allowing unrestricted flow out of the orifice, and creating a thin liquid film on the surface of the nozzle. When this surface that is set to vibrate at a certain frequency perpendicular to the surface, the liquid absorbs the vibrational energy and standing waves are created in the liquid film. These standing waves form a mathematically definable array of crests and troughs depending on the characteristics of the liquid and the frequency that the surface is vibrating at.

When the amplitude of vibration is increased, it causes the waves to also increase their amplitude to the point of becoming unstable. Droplets are ejected off of the tips of these unstable waves. The median droplet diameters that are created from these waves were predicted using Lord Rayleigh's research in the late 19th century and form according to the following equation.

Eq.1 $$D_{N,0.5} \sim (8\pi\sigma/\rho f^2)^{1/3}$$

Where f is the frequency of the vibrating surface, σ is the surface tension of the liquid, and ρ is the density of the liquid.

This equation was later proven in experimental studies by Lang and the following empirical equation was founded.

Eq. 2 $$D_{N,0.5} = .34\,(8\pi\sigma/\rho f^2)^{1/3}$$

Multiple frequency atomizing nozzles are available. For the application of drug/polymer it has been proven that 120 kHz and higher frequencies provide optimal coating characteristics. This high frequency atomization technique is widely used in high volume medical manufacturing today.

As a reference point, a typical 180 kHz nozzle atomizing water will produce a median droplet size of 13 microns. As the surface tension of the solvent and the density increases or decreases, a change in the median droplet size often occurs. The properties of ethanol cause the droplet created to be about 72% of the size of the water droplets due to the different liquid properties, resulting in a median droplet size of about 10 microns.

Incorporating a precise liquid delivery system allows the thin liquid film to continue ejecting droplets with diameters defined by this equation. Due to the fact that atomization is only occurring on the vibrating surface, the amount of liquid atomized is dependant only on the rate that the liquid is delivered to the surface. This characteristic allows ultrasonic atomizers to accommodate extremely low flow rates that are needed when coating DEBs

Another defining characteristic of Ultrasonic Nozzle Atomization is the spray plume that is created. Droplets are released from the atomizing surface with a very low velocity, typically .25 to .4 m/s. A typical pressure atomizer produces droplets with velocities typically between 10-20 m/s. This difference in velocity allows Ultrasonic Atomizers to produce droplets with 1/10,000th the kinetic energy of pressure atomizers.

This soft spray is extremely useful in maximizing transfer efficiency to the devices and results in significant cost savings when dealing with expensive drug/binder combinations.

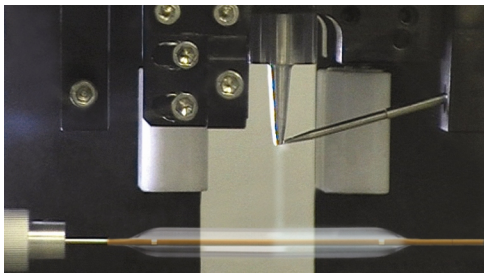

Fig. 2 Ultrasonic Atomizing Nozzle Spraying Onto a DEB

The soft spray also allows the droplets to be accurately directed towards the substrate using low pressure air shaping gas, typically nitrogen. Depending on the exact substrate

and air shaping selected, the focused region can be anywhere between .25mm wide up to 6mm. The droplets created in this small spray plume are forced to wet out and create a thin film on the balloons. With low concentrations of drug/binder in solvent it is very easy to scale down to the nanometer range thickness.

These Ultrasonic Atomizing Nozzles are incorporated into multi-axis handling systems to control the movement of the nozzle and substrate. In order to get the most uniform coatings, the balloon is set to rotate at a fixed speed while the nozzle reciprocates over it. This allows for the circular spray pattern to overlap and achieve down to +/-2% uniformity differences which has been proven in DES applications for many years.

Conclusion

DCBs is still an evolving technology. The concept of delivering a spike of antiproliferative drugs to vascular tissue as a safe method of treating restenosis and artery disease has had significant preliminary success. The coatings that are applied and the methods behind application still require more development and results of current trials will need to help clarify some of the mixed messages that have been seen early on in this process.

Ultrasonic Atomization Technology is a precise spray technique which is inherently able to adapt to this specific application. Allowing almost complete separation of independent variables makes this an ideal technology for manufacturing needs from process development to mass production. Ultrasonic atomization technology has been used for DES development and production for many years and shows indications of being highly successful in this new area of medical treatment.