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Coating Drug-eluting Arterial Stents Using Ultrasonic Spray Nozzles

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Abstract

One proven method used to treat clogged arteries employs tubular, mesh-like metal structures, known as stents, inserted into an affected artery to relieve the blockage. Bare metal stents often cause a condition called restinosis, the buildup of scar tissue around the stent, causing re-blockage. To counter this, polymer coatings containing drugs that are released over time are used to inhibit restinosis. Applying coatings to stents, which have intricate geometries, is challenging. Using ultrasonic atomizing spray nozzles has proven effective in achieving continuous and uniform coatings. This paper describes the unique nozzle designs employed, the methodology used, and the results obtained.

Introduction

The implantation of stents into arteries using balloon angioplasty has become an accepted technique in the treatment of arterial disease, where constricted or partially blocked blood vessels are involved.

Stents are tubular, mesh-like structures designed for mechanical flexibility and long-term durability. An example of one is shown in Fig. 1. Typically, they are laser-cut from metals such as stainless steel or nitenol (a nickel and titanium-based alloy). The size of a coronary stent is on the order of 1.5 to 3 mm in diameter by 15 to 30 mm long. Brain stents are much smaller, and leg stents are much larger. Once implanted at the site of an arterial lesion, a stent's role is to keep the blood vessel open and permit the normal flow of blood through the artery.

Figure 1

The flexibility of a stent is key to its performance. There are two reasons for this, one is the technique used for implantation and the other has to do with its operating environment. With respect to implantation, the most common method employs a balloon catheter, consisting of a hollow tube that is approximately a meter long, terminating in a deflated rubber balloon, over which the stent is placed and compressed against the balloon. When the target site is reached, the balloon is inflated by pressurizing it through the hollow catheter tube, which, in turn causes the stent to expand so that it pushes open the artery wall at the site. The balloon is then deflated and the tube is removed. Obviously, this implantation technique requires the stent to be flexible.

The operating environment is important. Arteries are flexible and are constantly subjected to the forces generated by the pulsating pumping action of the heart. Thus the stent must have the capability to react dynamically in a manner similar to its host environment.

Drug-eluting Stents

Stenting has gained considerable favor in the treatment of arterial disease because it is relatively non-invasive. The alternative to stent implantation is by-pass surgery, which is highly invasive and complex. For a few years, surgeons were reluctant to prescribe stent implantation over multiple by-pass surgery because there was a serious drawback to their use. It turns out that bare metallic stents are attacked by the body's natural immune system. Cellular masses can form around the stent in response to the body's natural inclination to rid itself of foreign objects. The result of these cell formations can cause re-occlusion of the artery. This condition, known as restinosis, has been proven to occur about 25% of the time.

Over the past several years, this problem has been addressed through the introduction of stents coated with powerful drugs that inhibit cell formation. Usually these drugs are embedded in a polymer, either a biodegradable type (such as polylactide co-glycocide) or a non-biodegradable polyurethane-based elastomer. The major characteristics that these coatings must exhibit are a) pliability (because of the flexibility of the stent), b) adhesion to the stent's surface, and c) the ability to provide a smooth and continuous surface finish. The polymer/drug matrix allows the drug to be released (or eluted) slowly, over a period of several months, thereby inhibiting the formation of cell masses, and hence significantly reducing the probability of restinosis. Clinical trials using drug-eluting stents showed that the occurrence of restinosis could be reduced to the 2-3% level, versus 25% for uncoated stents. This result has had a major impact in treating conditions where multiple arteries are involved. Now, stent therapy has become a viable alternative to multiple by-pass surgery. At a 25% restinosis level, implanting uncoated stents in several arteries was just not plausible. Now it is. Of course, even in cases involving implanting a single stent in a single location, the reduced risk of using a drug-eluting stent is obvious.

Spray Coating Stents

Spray nozzles are the primary method used to apply coatings to stents. Other techniques, such as vacuum and super-critical CO_2 deposition are methods under development, but are not in commercial use. Dip coating is not a viable alternative because of its tight geometry. The spacing between struts, particularly where they join each other, can be as small as 50 μ. Dip coating would result in the bridging of these areas, something that is not allowed, since the bridged coating could eventually break off and enter the blood stream. Even spray-coated stents can exhibit bridging if not processed properly.

Coating a stent properly is a technological challenge. The photomicrographs shown in Figs. 2a through 2c illustrate what can occur. Fig. 2a depicts a perfectly coated stent. It features a smooth, continuous coating, without any webbing or surface defects. In Fig. 2b, the coating shows significant webbing. In the last photomicrograph, Fig. 2.3, the coating exhibits an

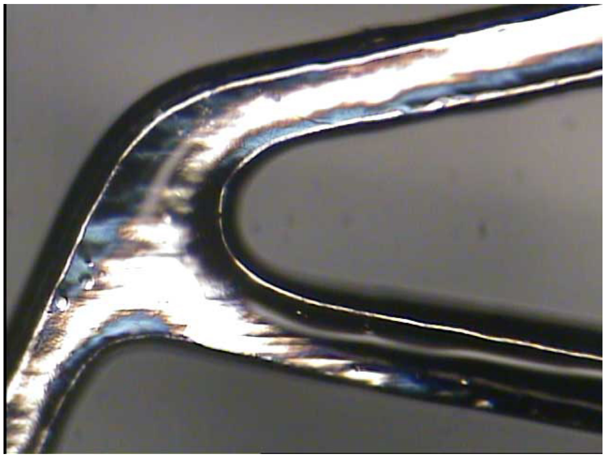

Figure 2a

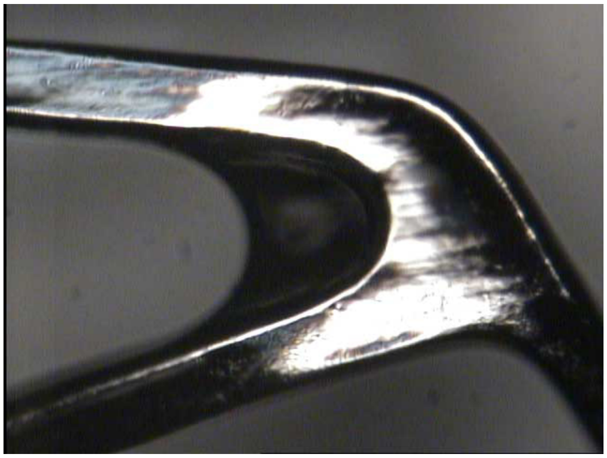

Figure 2b

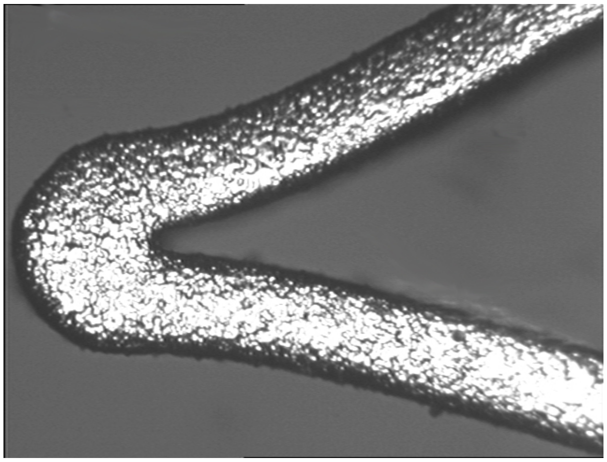

Figure 2c

irregular, bumpy surface caused by the drops drying before they reach the target.

It is important that the coatings be uniform (both inside and outside), free from holes or other defects, and reproducible with a few percent weight gain from one stent to the next.

Spray Methods

The industry has adopted two types of spray nozzles, twin-fluid and ultrasonic nozzles. In this paper, we shall focus on ultrasonic nozzle technology, since currently it is perceived as the best method for achieving the desired results.

The operating requirements in this application call for flow rates on the order of 20-100 μl/min, spray diameters in the range of 0.5-2 mm, and very small median drop diameters. Ultrasonic nozzles are capable of meeting these requirements. Fig. 3 shows one coating strategy. The stent is placed on a mandrel that is attached to a rotating shaft. The nozzle is mounted above the stent. The shaft not only rotates, but also translates such that the stent is sprayed along its entire length. Typically, several traverses are required to achieve the proper coating weight.

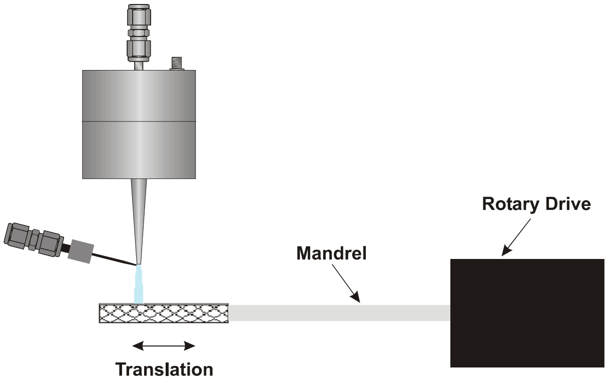

Figure 3

The sprayed liquid consists of the polymer/drug system dissolved in a suitable organic solvent and diluted to approximately 0.5-2% by weight. Typically, high vapor pressure solvents are used, so that drying occurs quickly. Repeated traverses, coupled with low flow rates, produce the best coatings and maximum material transfer efficiency. By varying rotational speed, distance of the spray from the stent, and number of traverses (and, therefore flow rate), a process can be optimized. Often, stent coating is done in a nitrogen environment. Nitrogen promotes better liquid flow characteristics since it acts to lower the surface tension of the liquid as it contacts the stent surface.

Ultrasonic Atomization

Aside from the operational parameters described above, the key to successful coatings is specifying an appropriate type of ultrasonic nozzle. First, a brief explanation of ultrasonic atomization is in order. When a liquid film is placed on a smooth surface that is set into vibrating motion such that the direction of vibration is perpendicular to the surface, the liquid absorbs some of the vibrational energy, which is transformed into standing waves. These waves, known as capillary waves, form a rectangular grid pattern in the liquid on the surface with regularly alternating crests and troughs extending in both directions as shown in Fig. 4.

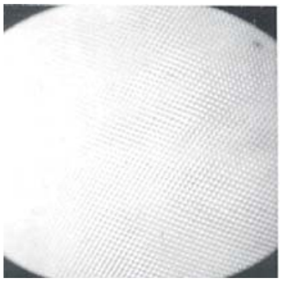

Figure 4

When the amplitude of the underlying vibration is increased, the amplitude of the waves increases correspondingly; that is, the crests become taller and the troughs deeper. A critical amplitude is ultimately reached at which the height of the capillary waves exceeds that required to maintain their stability. The result is that the waves collapse and drops of liquid are ejected from the tops of the degenerating waves normal to the atomizing surface.

The number median drop diameter ($D_{N,0.5}$) expected is inversely proportional to the vibration frequency (f) to the two-thirds power. This relationship was discovered in the late 19th century by Lord Rayleigh [1]. Specifically,

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

where σ is surface tension of the liquid, and ρ is its density.

Experimental studies by Lang and others [2][3] further quantified this relationship. Lang established that the proportionality constant is 0.34, so that

$$D_{N,0.5} = 0.34(8\pi\sigma/\rho f^2)^{1/3}. \qquad (2)$$

A typical ultrasonic nozzle is shown in cross-section in Fig. 5. Disc-shaped ceramic piezoelectric transducers convert high frequency electrical energy from an oscillator/amplifier into vibratory mechanical energy at the same frequency.

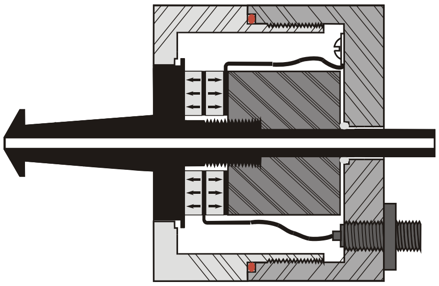

Figure 5

The transducers are sandwiched between two titanium cylinders, which act to concentrate and amplify the vibration amplitude at the atomizing surface. Titanium is used because of its good acoustical characteristics, corrosion-resistance, and high strength.

One of the principal attributes of ultrasonic nozzles results from the atomization being solely a surface phenomenon. The amount of liquid atomized depends exclusively on the rate at which liquid is introduced onto the surface.

Therefore, in principle, ultrasonic nozzles have infinite variability with respect to flow rate. Although practical considerations related to nozzle design limit this variability to a fixed amount, the ability to precisely adjust flow rates by adjusting the rate at which liquid is delivered to the nozzle is very useful.

The other major attribute of ultrasonic nozzles, one that distinguishes these devices from all other atomizing devices, is the low velocity character of the spray, typically 0.25 to 0.4 m/s as compared to 10 to 20 m/s for standard pressure atomizing nozzles. This 100-fold reduction in spray velocity is equivalent to a 10,000 times reduction in kinetic energy.

The liquid is delivered to the atomizing surface through a feed tube that runs the length of the nozzle. The relatively large liquid feed orifice assures freedom from clogging. Alternatively, liquid can be delivered to the atomizing surface externally.

Ultrasonic Nozzles for Stent Coating

There are two principal ultrasonic nozzle designs that are in common use in coating stents. Both rely on the use of a low-pressure gas stream to shape the slow-moving drops into a narrow spray beam. The operating frequency of both designs is 120 kHz, which for water yields a value for $D_{N,0.5}$ on the order of 18 μ.

The first design (nozzle A) is represented in Fig. 6. Compressed gas, typically at 1 psi, is introduced into the diffusion chamber of the gas shroud, which produces a uniformly distributed flow of air around the nozzle stem.

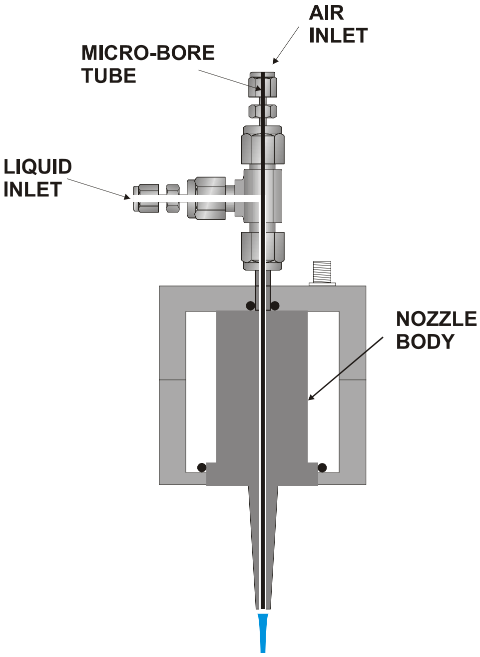

Figure 6

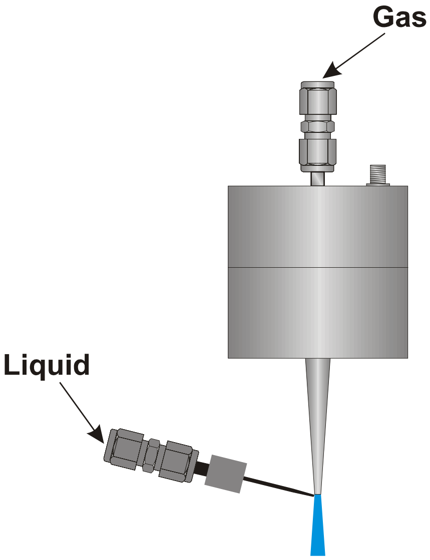

Figure 7

The ultrasonically produced spray at the tip of the stem is immediately entrained in the gas stream. An adjustable focusing mechanism on the gas shroud allows complete control of spray width.

The spray envelope is conical. Moving the focus-adjust mechanism in and out controls the width of the bow. The distance between nozzle and substrate can be varied from near contact to approximately two inches. The narrowest beam diameter achievable at the focal plane is approximately 1.75 mm.

The second design (nozzle B) is depicted in Fig. 7. It consists of feeding liquid to the atomizing surface through an externally mounted cannula. The gas is fed through the nozzle orifice. The gas stream draws the spray to it, creating an extremely narrow spray beam, as small as 0.5 mm. The distinguishing feature of this technique of course is that the liquid feed is external. This means that the liquid is completely isolated from nozzle vibrations up to the time that atomization occurs. This translates into a high degree of spray stability and a greater degree of reproducibility, from one spray cycle to the next.

Spray Characteristics

In addition to displaying different diameter spray beams, the two nozzle designs described above produce different results in terms of both drop size distribution and the properties of the liquid being sprayed. A series of experiments were conducted using a Malvern Spraytec particle size analyzer to obtain distributions. Fig. 8 summarizes the results. Four (4) time-averaged distributions are shown, two for nozzle A (one for water and the other for isopropyl alcohol), and the corresponding two for nozzle B. Both the number distribution and the volume distribution are plotted for each case. The flow rate was 100 μl/min.

The first observation is that the number median drop sizes agree with theoretical predictions of Eq. 2, $D_{N,0.5}=18\ \mu$. The values of both σ and ρ for alcohol are different than that for water ($\sigma_{wat}=73$ dynes/cm and $\sigma_{alc}=22$ dynes/cm; $\rho_{wat}=1$ and $\rho_{alc}=0.8$). The resulting number median drop size for alcohol is about 72% that for water, or about 13 μ.

The distributions for water appear to closely follow a lognormal distribution shape, whereas for alcohol, the distribution is noticeably skewed toward larger diameters, particularly for nozzle B. Moreover, in each case, the spread of the distributions for alcohol is considerably greater than that for water. In addition, the number and volume distributions for each nozzle spraying water are very similar. They nearly overlap. The same is not true when spraying alcohol.

These observations suggest that there is significant coalescing occurring, particularly for alcohol. This can be explained by the lower surface tension of alcohol compared to that of water. The lower surface energy promotes coalescence.

Since the diameter of the spray beam for nozzle B is considerably smaller than for nozzle A (0.5 mm versus 1.75 mm), the spatial density of spray from nozzle B is considerably greater than from nozzle A. This difference explains why, for the same liquid, nozzle B exhibits more coalescence than nozzle A.

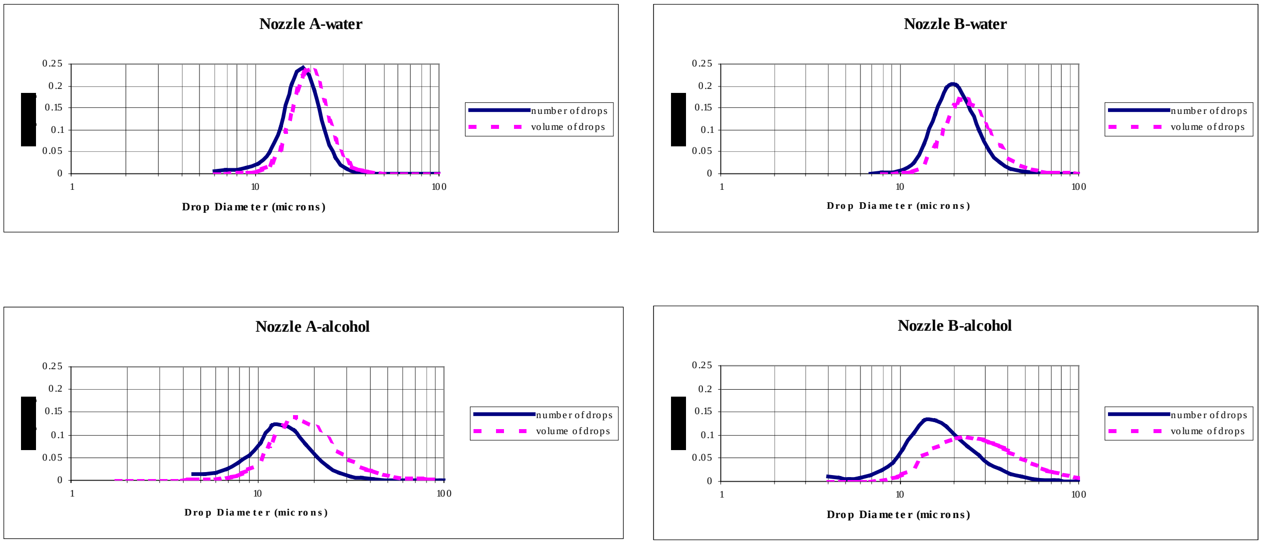

Figure 8

The Effects of Drop Size on Stent Coatings

Drop sizes have an impact on stent coatings in that size influences the solvent evaporation rate, and hence the drying time. It is not possible to predict how a particular polymer/drug/solvent system will behave during the coating process since the interaction of the three-part solution with the stent surface is relatively complex. In very general terms, an abundance of large drops is acceptable if the drying rate is rapid, which occurs for solvents with high vapor pressures such a tetrahydrofuran (THF) or chloroform. This is not the case for low vapor pressure solvents such as dimethylacetamide (DMAC).

The width of the distribution should be examined to determine if it plays a role in coating behavior. The sharpness of the distribution, Δ_V, is by defined as the difference between the diameter for which 90% of the volume of drops in a sample have smaller diameters than that diameter ($d_{90\%}$), less the diameter for which 10% of the volume of drops meet that condition ($d_{10\%}$). Following are the values of Δ_V associated with Fig.8:

	Nozzle A Δ_V (μ)	Nozzle B Δ_V (μ)
Alcohol	17	19
Water	11	14

These results shows that the values of Δ_V for both nozzles are similar for a given liquid, so that this measure may not be significant.

Summary

Coating arterial stents is a challenging spray application. The fact that these devices are used in life-threatening situations places stringent demands on the manufacturing processes used to produce them. Ultrasonic spray nozzles are ideally suited to the application since they are capable of producing very low flow rates, precisely shaped spray patterns, low-velocity delivery, and relatively small drops. The techniques used in coating may vary, as may the drug/polymer system. These variances make it important to optimize the entire system for each specific circumstance. The two nozzles described in this paper display different spray properties, but both play a role in stent coating. The selection of which one to use depends on the exact nature of the process and the materials being sprayed.

References

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