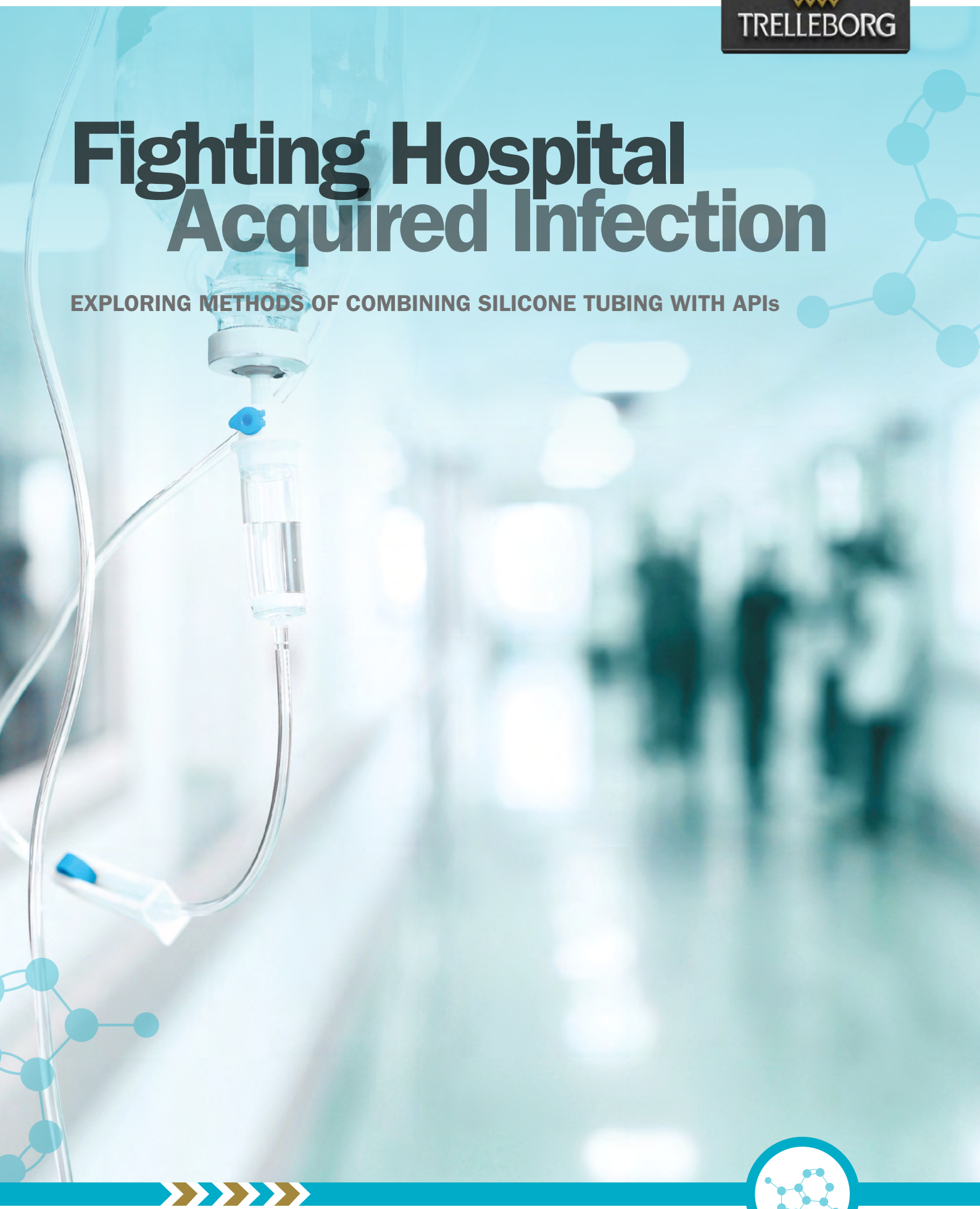
Fighting Hospital Acquired Infection

EXPLORING METHODS OF COMBINING SILICONE TUBING WITH APIs



Introduction

Healthcare-Associated Infections (HAI) are a major, yet often preventable threat to patient safety. They can have a significant impact on the survival rate of patients that undergo procedures and treatments, so the minimization of these infections is an important focus globally. For instance, the Department of Health and Human Services in the U.S. has stated that elimination of healthcare–associated infections is a priority, while in the U.K., the government monitors healthcare-associated infections on a monthly basis and publishes guidelines on reduction and prevention of infection.

There is evidence of a decrease in hospital-acquired infections, however, they still remain a significant issue. In particular, catheter-associated infections are difficult to prevent, due to their inherent positioning both inside and outside of the body.

Catheter tubes are usually made of silicone, and though the material is biocompatible and bio-stabile, it is not immune to bacterial colonization. Techniques exist that can reduce this colonization including coating, addition of antibiotic Active Pharmaceutical Ingredients (API) to raw silicone and the impregnation of vulcanized silicone with API through immersion. In this whitepaper, the three techniques are outlined and test results presented that prove the effectiveness of the impregnation method.

Trends and statistics related to HAI

Over recent years, massive strides have been made in the reduction of HAI. A U.S. survey by the Centers for Disease Control and Prevention (CDC) conducted in 2014 and released in 2016, found reductions for nearly all HAI. However, this study restates the original estimates from 2011, which found 4.0% of inpatients in U.S. acute care hospitals had at least one infection related to the hospital, yielding a much reduced estimate of 721,800 infections in that year.

Despite significant improvements, survey results indicate that on any given day, approximately one out of every 25 patients in U.S. acute care hospitals still has at least one infection, leaving room for continued action.

In the same report, just under 50% of all HAI were associated with devices or operating procedures. Overall, the 2014 data shows the most significant decrease of 50% among Device Related Infections (DRI), particularly regarding bloodstream infections.

The Surgical Site Infections (SSI) which account for 21.8% of all infections have decreased by 17%. Although rates have lowered overall since the 2008 baseline studies, there was a significant increase of colon surgery SSIs as well as little to no change in abdominal hysterectomy and catheter associated urinary tract infections (CAUTIs) reported between 2013 and 2014.

Sources:

https://wwwnc.cdc.gov/eid/article/22/9/15-1440_article

https://www.cdc.gov/hai/surveillance/index.html

Silicone: Material of choice for implantable devices

Silicone is a material of choice for medical devices and can be fabricated to produce tubing, coatings, thin membranes, and a myriad of types of molded components. Silicone tubing is used for catheters, shunts and various types of implants. Enjoying a 60 year history as an implant material, silicone represents the gold standard for biocompatibility and bio-stability. However, it is not immune to bacterial colonization. Like other hydrophobic materials, various microorganisms can attach or adhere to silicone surfaces.

Three techniques for reduction of colonization of bacteria on silicone tubing

Coating

Coatings of API are applied to silicone catheters by spraying or dipping. The coatings must be durable and adhere effectively to the silicone substrate in a variety of applications in different conditions. Analytical techniques are used to measure coating uniformity.

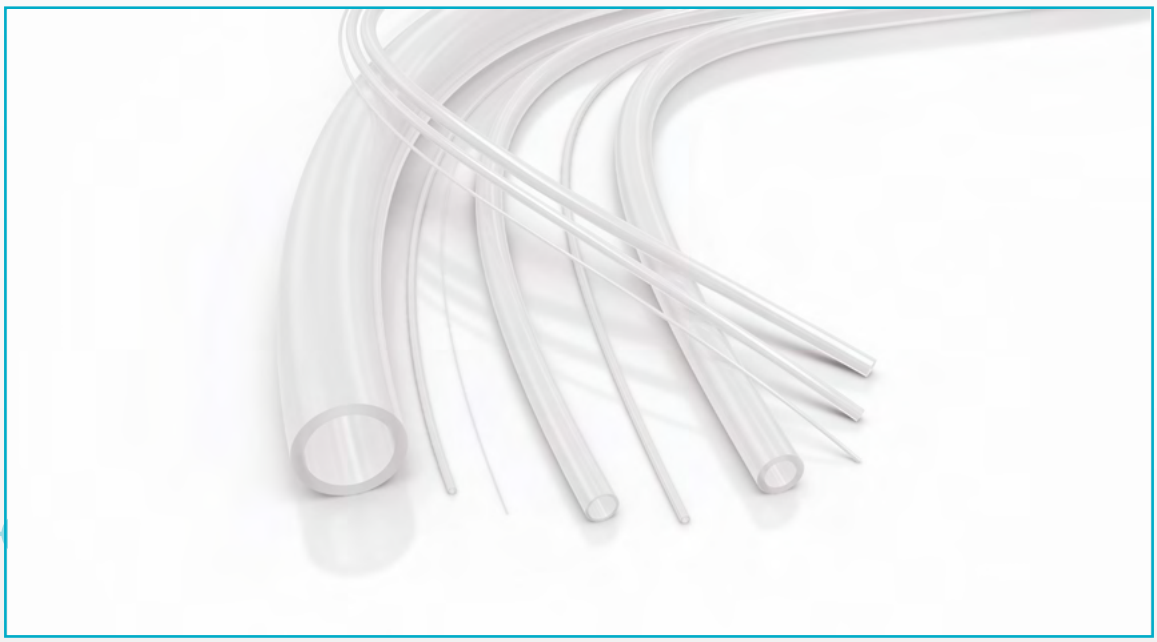
Though probably the most cost-effective method of treatment, coating has some disadvantages. Achieving good uniformity in coating and adhesion can be challenging and is subject to a number of variables relating to substrate geometry, materials, and process. Cracking or peeling of coatings may occur. In some cases, it can be hard to apply a coating to the inner lumen surface of a catheter. Also, the antimicrobial efficacy of thin coating can be limited in duration.

Addition of API to raw silicone

This second method used to prevent bacterial buildup involves the adding of antibiotic API, such as chlorhexidine, gentamycin, xifaxin, and doxycycline in powder form to silicone raw materials using various types of mixing equipment. After homogenization, the silicone-drug mixtures can be formed into desired shapes and vulcanized using various fabrication processes including molding and extrusion.

The key advantage of this method compared to coating is that the API is effectively and consistently present within the silicone. However, certain aspects need to be investigated before specification.

Compatibility of the API with the silicone grade should be confirmed as some API can inhibit or even poison the cure system of certain silicones. Also, particular drugs are not stable at elevated temperatures. In these applications, silicones that can be vulcanized at relatively low temperatures may be used but this limits the type of API that can be used.



Impregnation of vulcanized silicone with API by immersion

The impregnation method is based on the fact that the attractive forces between silicone polymer chains are quite weak. This contributes to the high free volume of silicone elastomers and their exceptional permeability, making this biomaterial especially attractive as a matrix for drug-device combination products.

The vast majority of silicone medical components are manufactured from raw material formulations containing polydimethylsiloxane (PDMS) polymers reinforced with amorphous non-crystalline silica. Vulcanized PDMS elastomers can be readily swollen by immersion in various organic solvents. Using this characteristic, vulcanized silicone can be immersed in a solution containing API to impregnate the vulcanized silicone with active drugs.

The advantage of the impregnation method of vulcanized silicone with API is that the API cannot interfere with the cure chemistry of the silicone and that the API is uniformly impregnated on the surface of the inner lumen.

Immersion is usually conducted at room temperature thereby eliminating concerns regarding the thermal degradation of the API, expanding the types of APIs that can be used. Solutions are by definition, homogenous mixtures of solute and solvent. Silicone components immersed in these drug solutions are exposed to a uniform environment.

Dissolved drugs are impregnated within the silicone elastomer as discrete molecules. Concerns and costs associated with specifying and maintaining a particular size and distribution of particles are minimized.

Test results proving the effectiveness of impregnated tubing in lowering bacteria growth

Immersion experiments have conclusively demonstrated the mass transfer of two antibiotics Clindamycin Hydrochloride (CLIN) and Rifampicin (RIF) from chloroform solutions to silicone tubing – for details of these tests see whitepaper Tests to prove the effectiveness of impregnation of vulcanized silicone with API by immersion. Following on from these tests, a study of the Kirby-Bauer Zone of Inhibition (ZOI) assessed the impact of drug content of silicone tubes on the gram-positive coccal bacterium, Staphylococcus aureus.

Test methodology

Test articles were chosen so that antimicrobial efficacy could be evaluated across a range of samples produced under varying conditions and containing differing drug concentrations.

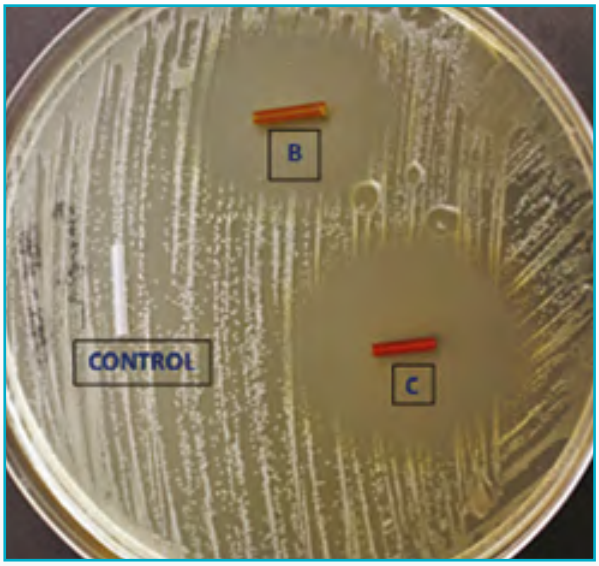
Immersion conditions and drug content are summarized below.

Test Article	Relative Solution Concentration	CIN Content in tube (µg drug/g tube)	RIF Content in tube (µg drug/g tube)
Control	NA	0	0
B	X	810	923
C	5X	4874	10276

Three test articles were placed on an agar plate that had been inoculated with a suspension containing Staphylococcus aureus. The plate was photographed after a 24 hour incubation period.

Results

- The drug-impregnated tubing had a powerful inhibitory effect on the growth of Staphylococcus aureus and clear zones of inhibition are seen surrounding test articles B and C.
- As expected the higher drug concentrations in sample C produced a larger Zone of Inhibition (ZOI) of 18 millimeters.
- Sample B, which contained lower concentrations of both drugs had a ZOI of 14 millimeters.
- No ZOI was observed around the control sample.



Conclusion

Though HAI have been significantly reduced, those related to catheters continue to be a challenge. While it is doubtful that device related infection from catheters can ever be completely eliminated, various silicone antimicrobial strategies have shown to be effective at reducing the incidence of infection.

This paper presented the various techniques used to prevent bacterial buildup on silicone. API mixed with raw silicone is the traditional method of producing drug-eluting catheters. Though this method is proven, an alternative method where API is impregnated into vulcanized silicone, expands the types of API that can be used in catheters. The relatively new method has been proven in a program of testing by Trelleborg Sealing Solutions that conclusively shows the effectiveness of impregnation on bacteria buildup.

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