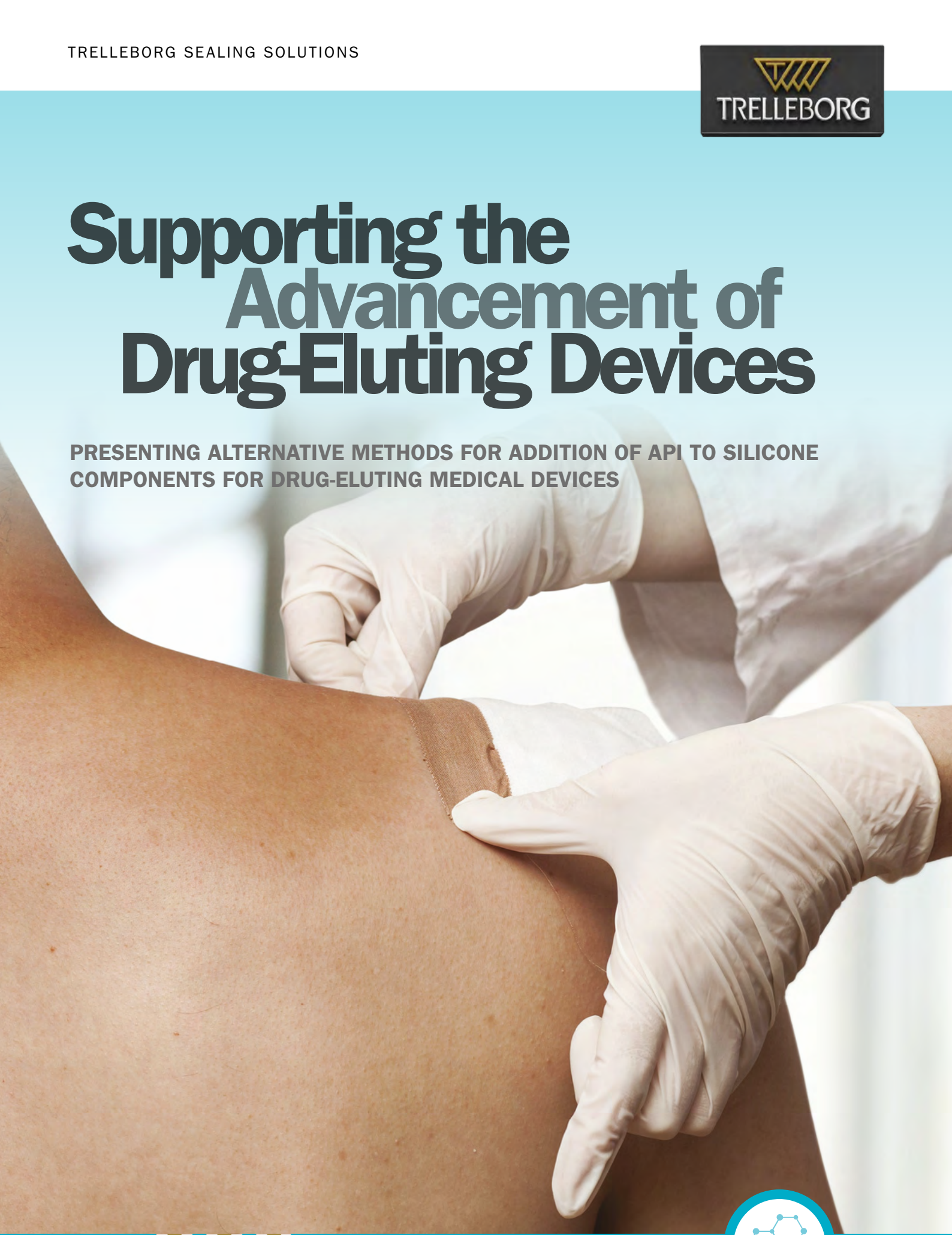
Supporting the Advancement of Drug-Eluting Devices

PRESENTING ALTERNATIVE METHODS FOR ADDITION OF API TO SILICONE COMPONENTS FOR DRUG-ELUTING MEDICAL DEVICES



Introduction

Over the past years there has been a stepped change in the treatment and control of medical conditions. Pills and injections can be viewed as imprecise, irregular and inconsistent in their delivery of drugs. Hence the rapid growth and development of drug device combination products, in particular those that elute regular controlled doses of drugs precisely and consistently to a treatment area.

To the extent that combination products can successfully be developed for manufacture in volume and to consistently meet drug efficacy as well as regulatory requirements, the demand for these products will undoubtedly grow. This will be driven by trends in the market, such as an aging population, increasing chronic disease, and global healthcare concerns related to obesity, diabetes and infectious diseases combined with the benefits that drug device combination products can offer.

Drug device combination products, defined as a device integrated with drugs, can be produced in and by a variety of materials and processes. One of the most successful materials for production of combination products, in particular implantable ones, is silicone, and this will be the focus of this whitepaper. Two methods of adding Active Pharmaceutical Ingredients (API) to silicone, the addition of API to raw silicone and the impregnation of vulcanized silicone with API by immersion, will be discussed.

The traditional method of adding API to raw silicone is proven and effective. However, it is limited to APIs that are resistant to a vulcanization process and exposure to heat. A newer method of impregnation of vulcanized silicone by API potentially broadens the APIs that can be used in drug-eluting silicone devices. This whitepaper presents test results that prove that this method works, potentially opening drug-eluting devices to delivery of a wider range of API.

What are combination products?

The FDA defines combination products in 21 CFR 3.2(e) to include:

1. A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

What is a drug-eluting device?

There are two categories of drug-eluting devices: biodegradable and non-biodegradable. Biodegradable drug-eluting devices (also referred to as bioresorbable) use biocompatible materials such as polyester amide (PEA) and Poly Lactic-co-Glycolic Acid (PLGA) to deliver drugs, and once implanted, decompose over time.

Non-biodegradable drug-eluting devices (also referred to as biodurable) use biocompatible materials like silicone rubber (polydimethylsiloxane or PDMS), polyethylene-vinyl acetate (EVA), and thermoplastic polyurethane (TPU) to deliver drugs. Of these options, silicone is considered a preferred choice based on extensive testing and proven results in healthcare and medical applications over decades.

Typical polymer based drug-delivery combination products

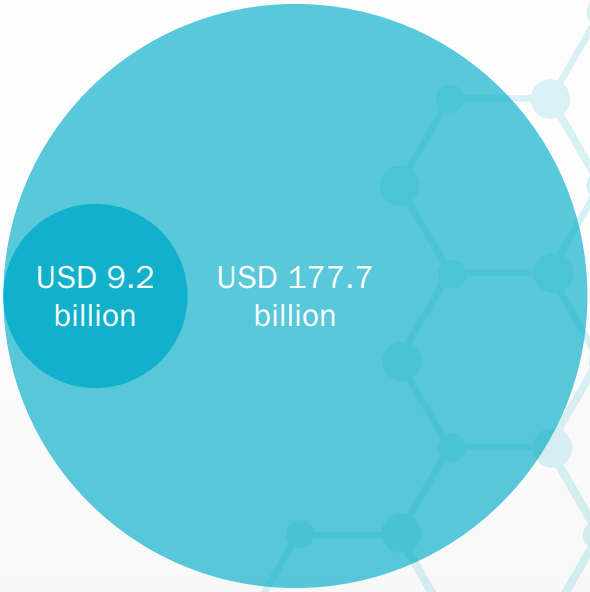
The best-known examples of combination product is the drug-eluting stent (DES), which is a scaffold coated with a drug to prevent scar tissue from growing and re-blocking an artery, and contraceptive vaginal rings. However, drug-eluting applications are increasing in the areas of hormone regulation, autoimmune conditions, diabetes, oncology, pain management, abuse deterrence, and CNS Healthcare.

The segments for such devices can be divided according to the different systems of the body they are focused to: orthopedic devices, breathing stents, gastrointestinal and urinary systems, devices for cardiovascular diseases, neuronal implants, and wound dressings.

Market size and drivers

According to Grand View Research, Inc., the global drug eluting stent market alone is anticipated to reach USD 9.2 billion by 2024 and the overall drug device combination market is expected to reach USD 177.7 billion.

Source:
https://www.grandviewresearch.com/



The growth of the global drug device combination products market is attributed to the increasing incidence of chronic diseases such as prostate cancer, cardiovascular diseases, colorectal cancer, diabetic neuropathy; increasing concerns related to obesity and diabetes; and a growing geriatric population. In addition, several government initiatives and CSR activities conducted by leading players are expected to boost growth. Moreover, increasing popularity of minimally invasive surgeries and portable or wearable devices such as nebulizers, inhalers or patch pump systems will also have an effect.

The unprecedented adoption rate of these products is also believed to be a consequence of the inherent benefits of combination drug delivery devices over traditional pharmacological alternatives to deliver therapeutics, which in turn influences pharmaceutical, biotechnology, and medical device companies to work toward further developing these products for subsequent commercialization.

Advanced polymer engineering is a significant enabler of modern-architecture medical devices and combination products. In particular, advanced silicone processing can offer significant advantages to drug device combination products due to the material's distinct benefits in terms of biocompatibility and permeability amongst others combined with the diverse processing possibilities in both low and high volume.

Advantages of combination and drug-eluting devices

Implantable drug-eluting devices (also referred to as implantable drug delivery systems) offer several unique advantages over conventional oral or parenteral drug delivery methods:

- Provides localized, site-specific sustained, controlled and targeted drug delivery.
- In diabetes care, the controlled release as opposed to the bolus-type delivery facilitates consistent API concentrations within an optimal therapeutic range.
- Lower dosage requirements as the systemic drug levels are reduced, and the drug is released in close proximity to the targeted areas.
- Combats one of the greatest challenges in healthcare by improving patient compliance; about 50% of conventional medications are not used as prescribed.
- Makes it easier for an increasingly older population to administer drugs to themselves; in an aging population, compliance becomes less certain and therefore more important.
- Due to the above mentioned systemic reduction in drug dispersion, the side effects of drugs can be minimized.
- Simplifies treatment regimens, with potentially fewer visits to the practitioner, relieving strain on health services.

Silicone

Silicones expanded into healthcare and medical applications in the 1950's after extensive use in the aerospace industry in the previous decade. Within twenty years, a considerable body of work established that silicone oils and cross-linked siloxane systems did not give rise to harmful consequences when performing subcutaneous, intracutaneous, and intramuscular administrations. In 1954, McDougall reported the cultures of various tissues of warm blooded animals, known to be extraordinarily sensitive to foreign influences, showed no deviation from the usual growth picture on contact with liquid, semisolid, and rubberlike silicone products. Silicones have been characterized as biologically and toxologically inert as a result of this work.

Silicones have several unique characteristics that make them attractive for drug-eluting combination devices. These are leading to the continual development of such devices for use in various medical specialties including cardiology, ophthalmology, and women's health.

The reason why silicone is suitable for drug-eluting combination devices are as follows:

- Silicone elastomers are proven to be inert and bio stable, being considered to be the gold standard in terms of biocompatibility.
- Polydimethylsiloxane polymers exist within the material in a helical conformation with weak intermolecular forces between polymer chains. This contributes to the high free volume of silicone rubber and to its exceptional permeability.
- Silicone elastomers can be processed in a multitude of ways from extrusion to molding, casting, coating and immersion; either on their own or in combination with other materials and substrates. A myriad of components and products of simple and most complex construction are therefore made possible.

Methods to add API to silicone

Two methods of adding API to silicone for drug delivery devices exist. The established method is the addition of API to raw silicone. The alternative and more recent development is the impregnation of API into vulcanized silicone by immersion.

Addition of API to raw silicone

This method of bacterial buildup prevention 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 usually within a cleanroom environment specific to each drug. After homogenization, the silicone-drug mixtures can be formed into desired shapes and vulcanized using various fabrication processes including molding and extrusion.

Compatibility of the API with the silicone grade needs to 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. This method is therefore most suited to the addition of API unaffected by the temperatures required for vulcanization of silicone. Alternatively, the APIs can be added to silicones that can be vulcanized at relatively low temperatures. However, this limits APIs that can be used or the types of silicone they can be combined with.

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 impregnation method of vulcanized silicone with API has the advantage that the API cannot interfere with the cure chemistry of the silicone and that the API is uniformly impregnated throughout the component.

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 particulate size and distribution of particles are minimized.

Key elements of the process included:

1. Dissolving a drug, or combination of drugs, in a solvent that swells silicone rubber
2. Immersing vulcanized silicone components in the drug solution
3. Removing the components from the solution after a certain immersion period
4. Allowing the volatile solvent to evaporate, leaving the non-volatile drug component impregnated within the silicone matrix.

Trelleborg immersion-impregnation studies

If the impregnation method of adding API to vulcanized silicone is going to present itself as a viable method of extending the range of API for drug-eluting devices, the method's effectiveness had to be proved.

Trelleborg Sealing Solutions therefore undertook two immersion-impregnation studies.

In the first, investigators quantified the relationship between two input variables (clindamycin-rifampicin solution concentration and immersion time) and the process output (concentration of the antibiotics impregnated in silicone probants).

The second study investigated the immersion-impregnation process as a platform manufacturing technology capable of accommodating various solvents and drugs.

Study 1 – Evaluate the impact of immersion parameters on impregnation of antibiotics

The purpose of the study was to evaluate the relationship between two input variables and the process output. It involved two antibiotics, clindamycin hydrochloride and rifampicin. Both of the drug's powders were dissolved in chloroform, a solvent that swells silicone rubber.

Probants for the study were lengths of 50 durometer silicone tubing. Input variables were the concentration of drugs in solution and the immersion time. The process output was the concentration of drugs impregnated in the tubing.

A dissolution technique as well as an HPLC analytical method were developed to quantify the mass of drugs impregnated in the various probants.

Hydrocephalus shunts provided a convenient test case. Product labeling for the devices notes that the shunts contain 0.15% by weight clindamycin and 0.054% rifampicin. Literature submitted to the FDA indicates that the manufacturer has established acceptance ranges for both drugs; +/- 45% for clindamycin and +/-60% for rifampicin.

Results of Study 1

Data from the study is summarized in Figure 1

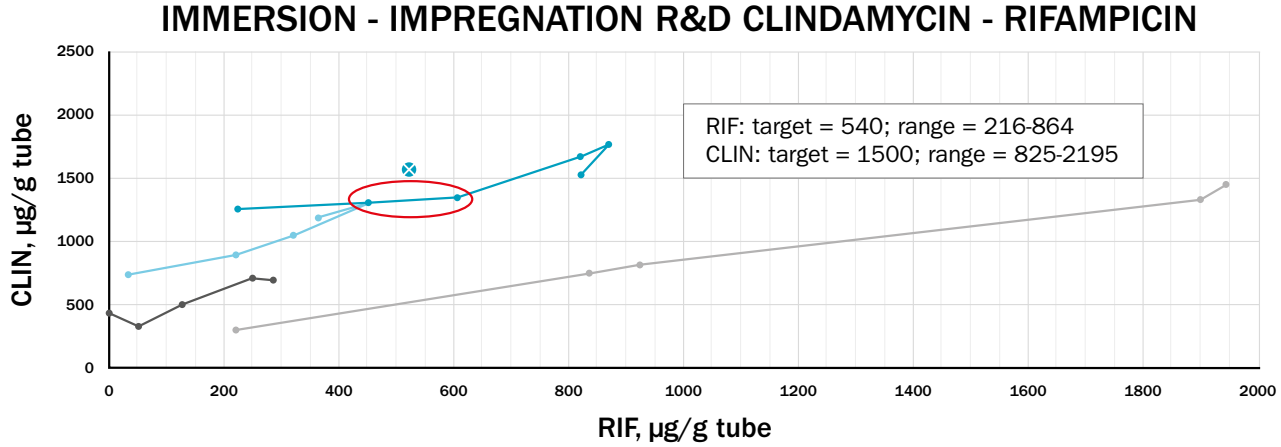


Figure 1

Rifampicin and clindamycin concentrations are shown on the x and y axes respectively. The target, expressed as 1500 micrograms of CLIN and 540 micrograms of RIF per gram of tube, is shown as the white X. Data points within the white box would meet the manufacturers' acceptance criteria. The colored lines represent different solutions containing different drug concentrations. Each line is made up of 5 data points. Each data point represents the drug content of a probant immersed for 5, 15, 30, 60, or 120 minutes.

After some trial and error, investigators prepared two solutions, represented as the blue and gray lines, which impregnated probants with drug concentrations that were easily within the acceptance zone, and in two cases, circled in green, very close to the absolute target.

Figure 2

A final part of the study confirmed that the immersion process did not impact the antimicrobial efficacy of the drugs. As shown in Figure 2, a zone of inhibition test demonstrated that the probants had a powerful inhibitory effect on the growth of Staphylococcus aureus.

Study 2 – Investigate the immersion-impregnation as a platform process technology

The purpose of the second study was to investigate the immersion-impregnation process as a platform technology by evaluating impregnation from solutions containing various solvents and drugs.

Methodology for this study differed from the clindamycin-rifampicin research in three key areas. First, the objective of the initial study was to impregnate silicone rubber with a very specific concentration of two antibiotics. The goal in this second study was to impregnate probants with the highest possible concentrations of four different drugs. Second, unlike the original study that involved the preparation of numerous low concentration solutions, the second study evaluated drug impregnation from only saturated solutions. And third, the first study measured drug content using HPLC analysis. In this follow-up study, the mass of impregnated drug was quantified gravimetrically by comparing the weights of probants before immersion and after devolatilization.

Four active pharmaceutical ingredients were investigated;

- Dexamethason acetate, a glucocorticosteroid, used to treat inflammatory and autoimmune conditions; the drug is included on the World Health Organization's list of Essential Medicines.
- Ethinyl estradiol, a synthetic hormone found in oral contraceptives as well as transdermal patches used for hormonal replacement therapies.
- Paclitaxel a chemotherapy drug, also added as an anti-proliferative agent in stent coatings to prevent restenosis.
- Triamcinolone acetonide, a corticosteroid, administered as eye drops to treat macular edema and under investigation as a treatment for age-related macular degeneration; recently approved, as in injection, for treatment of pain associated with osteoarthritis.

Nine solvents were evaluated. Solvent polarities ranged from 0.45 Debye for 1-4, dioxane to 3.96D for dimethyl sulfoxide. Probants were lengths of silicone rod extruded from a 35-durometer high consistency rubber. Seven pieces of rod, each 20 mm in length, were placed in vials that were then filled with solvent. Rods were removed from the solvent after soak periods ranging from 5 minutes to 6 hours.

Results of Study 2

Rod length

Rods immersed in chloroform and tetrahydrofuran increased in length by approximately 50% while rods soaked in acetone and 1,4-dioxane increased by 10-15%. For four solvents, dimethylformamide, dimethyl sulfoxide, ethanol, and methanol, expansion was less than 10%. The length of rods immersed in water were unchanged.

The data also shows that the swelling occurred over the first 120 minutes of immersion and that longer soaking periods resulted in no statistically significant dimensional changes. Rod length as a function of solvent and immersion time is in Figure 3.

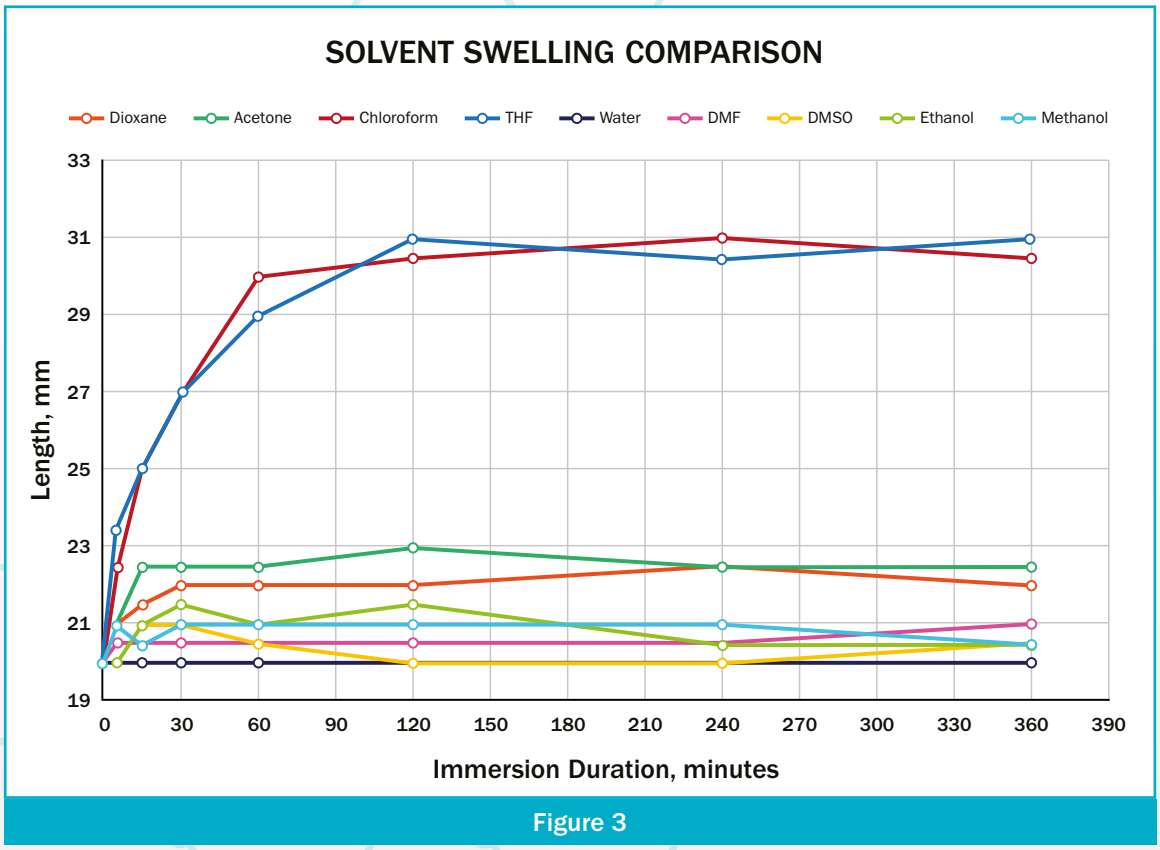


Figure 3

Saturated Drug Solutions

The solubility of the four API were evaluated in various solvents. Approximately 2 ml of solvent was added and weighed to a 15-ml glass vial. Small quantities of the drug, typically less than 50 mg, were added to the solvent until undissolved powder was seen in the liquid. Additional solvent was then added in a drop wise fashion until a clear solution was observed.

Figure 4 summarizes the drug concentrations of the various saturated solutions produced in this study.

API	Solvent	Solubility (mass API/mass solution)
Dexamethasone Acetate	Acetone	5.4%
	Chloroform	<0.5%
	DMF	31.1%
	DMSO	5.5%
	THF	12.3%
Ethinyl Estradiol	Acetone	19.3%
	Chloroform	1.1%
	THF	38.0%
Paclitaxel	Chloroform	8.9%
	THF	22.8%
Triamcinolone Acetonide	Chloroform	<0.5%
	DMF	24.7%
	THF	3.4%

Figure 4

Probant Preconditioning results

Even completely vulcanized silicone rubber contains polymer chains that are not crosslinked into the elastomeric matrix. Silicone manufacturers refer to these uncrosslinked polymers as “loose juice.” It is well documented that these uncrosslinked polymers can be extracted from silicone rubber by exposure to various organic solvents. The mass loss associated with the extraction of these polymers was quantified by immersing probants in four solvents for 24 hours. Probants were then allowed to devolatilize for an additional 24 hours.

Mass loss ranged from 2.5% to 3.0%. Trelleborg investigators understood that immersing probants in drug-solvent solutions would result in two competing and simulataneous diffusion processes; drug would diffuse from solution into the silicone rubber while at the same time uncrosslinked polymers would diffuse from the rubber into solution. Calculations regarding the mass gain associated with drug impregnation would be skewed by mass loss associated with polymer extraction. To avoid this problem the remaining silicone rod was pre-conditioned by soaking for 24 hours in chloroform followed by a 24 hour devolatilization.

Immersion-Impregnation Results

The pre-conditioned rod was cut into 10 mm lengths, weighed, and then immersed in eight different saturated drug solutions. After a 2 hour immersion period, the probants were removed from solution, quickly weighed, allowed to devolatilize for 24 hours, and then reweighed.

Results are summarized in Figure 5.

Solution	Solution Concentration (mass API/mass solution)	Initial mass, grams	Mass after 2 hour Immersion, grams	Final mass after 24 hour devolatillzation, grams	Experimental API Concentration in Elastomer (mass API/mass impregnated elastomer)
Dexamethasone Acetate in DMF	31.1%	00811	0.0860	0.0831	2.41%
Dexamethasone Acetate in THF	12.3%	0.0819	0.1606	0.0871	5.97%
Ethinyl Estradiol in Acetone	19.3%	0.0872	0.0998	0.0869	Not Detected
Ethinyl Estradiol in THF	38.0%	0.0833	0.1023	0.0841	0.95%
Paclitaxel in Chloroform	8.9%	0.0816	0.2114	0.0827	1.33%
Paclitaxel in THF	22.8%	0.0842	0.1493	0.0853	1.29%
Triamcinolone Acetonide in DMF	24.7%	0.0820	0.0852	0.0819	Not Detected
Triamcinolone Acetonide in THF	3.4%	0.0837	0.2379	0.0866	3.35%

Figure 5

Discussion Points

The test results highlighted a number of discussion points:

1. For six of the eight probants, the mass after impregnation and devolatilization was greater than the initial mass. Trelleborg investigators reasonably attribute this mass increase to drug impregnated within the silicone rod.

2. The mass of impregnated drug ranged from 0.95% (ethinyl estradiol in THF) to 5.97% (dexamethasone acetate in THF). To put these numbers in perspective, recall that the combined clindamycin and rifampicin concentration in the previously mentioned hydrocephalus shunts is 0.204%. This means the relatively low drug content of probants impregnated with estradiol is still nearly 5 times greater than the total antibiotic content of the neurological shunts.

3. Study investigators had assumed that the mass of impregnated drug would be equal to the mass of solution absorbed by the probant during immersion multiplied by the concentration of the drug within the solution.

   However, the data shows that this was not the case. Consider the probant immersed in the saturated THF-dexamethasone solution. Immersion caused the probant to increase in mass by 0.0787 grams (0.1606 – 0.0819). The solution contained 12.3% dexamethasone acetate.

   Investigators assumed therefore that the wet probant now contained 0.0097 grams of drug (0.0787 grams x 0.123) and that the weight of the probant after devolatilization would reflect this added mass.

   In fact, the mass of the devolatilized sample increased by 0.0052 grams (0.0871 – 0.0819). The actual mass increase was 54% of the predicted increase. The probant immersed in the THF-triamcinolone acetonide solution gave similar results; the actual mass increase was 56% of the predicted mass.

4. The data suggests that the silicone probants introduce a partitioning effect between the drug solute and solvent. It's likely that this effect is attributable to the drug's reduced solubility in silicone relative to its solubility in solution. It's possible that the solubility of the drug may be enhanced by modifying the backbone of the silicone polymer or the surface of the reinforcing silica filler.

Conclusion

The variety, versatility, and exceptional permeability of silicone elastomers are characteristics that have made this family of materials attractive for drug-device combination products. In the majority of cases, these devices are produced by combining a drug powder with a silicone raw material; the mixture is formed into a shape, then vulcanized.

Undoubtedly, as the proven method of production of drug-eluting devices, this method will remain the process of choice despite its limitation to API unaffected by vulcanization. Test results presented in this whitepaper prove the viability of impregnation of vulcanized silicone and how potentially this technology could extend the range of APIs that can be considered in drug-eluting device concepts.

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