Introducing APIs to Silicone and Controlling Elution Rates

REVIEWING THE METHODS FOR INTRODUCING AN ACTIVE PHARMACEUTICAL INGREDIENT TO RAW SILICONE AND EXPLORING A NEW MEANS OF CONTROLLING LONG-TERM ELUTION RATES

Introduction

Single-entity combination devices, which are therapies containing manufactured components that have both device and drug elements, have shown the potential to address some of the most challenging chronic conditions patients face today. Through continued development of these technologies, patients will realize significant improvements to their quality of life, such as spending less time managing their condition, minimization of side effects from the therapeutics, and an overall greater confidence in the therapy's ability to treat their condition. The scientific community has also focused heavily on researching these technologies due to the potential benefits and have suggested their viability in addressing both chronic and life-threatening conditions.

Market projections share this optimism, with an expectation that device developers and pharmaceutical companies will continue to invest in bringing these unique solutions to market. However, to achieve the expected impact, manufacturing processes must continue to evolve, while the number of drug compounds formulated into these unique therapies also increases. Most existing drug compounds exhibit various sensitivities that may cause them to break down at different points in the manufacturing process, which present significant hurdles to these expectations. Because of this, it is critical for manufacturers to understand the methods in use today.

This whitepaper provides insight into the above, delivering a baseline understanding of what combination products are, their market potential, and describing the manufacturing methods in use today. To provide as much insight as possible, several case studies detail applications Trelleborg and its partners have worked on to explore alternative manufacturing methods that would allow for the expansion of the number of drug forms capable of formulating into single entity combination products. Sharing of this information is with the hope that it inspires the reader to further explore and consider this delivery form, thus making their own contributions to this unique and promising field of therapy.

What is a Combination Product?

Combination products involve the integration of multiple drug, device and biological elements into a single therapeutic product.

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.

Market

Market Statistics:

Trends in the medical device market favor devices that are smaller, smarter, and less invasive. A considerable focus is on precision, especially for products used for drug delivery, as too much or little of a desired drug can adversely affect the patient's experience, recovery, and daily life.

The combination product market continues to show strong signs of growth, especially for implantable, portable, and wearable devices that elute regular controlled doses of an Active Pharmaceutical Ingredient (API) precisely and consistently to a treatment area. In addition to ensuring an accurate dosage over an extended period, the precision release of an API helps to reduce the chances of side effects by minimizing dosage and optimizing the drug presence at the target site.

Valued at 215.4 billion USD in 2019, the global market size for drug delivery devices will have an anticipated compound annual growth rate (CAGR) of 10% through 2025. This projected growth rate is supported by the trend toward the increased adoption of devices that effectively deliver precise amounts of a drug to a targeted site. Reasons for the growth of this market are given as 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 population.

The global implantable drug delivery devices market is forecast to grow from $18.82 billion USD in 2020 to 29.85 billion USD by 2025, a CAGR of 10%. Of this market, non-biodegradable devices account for the largest market share, the majority of which are polymeric matrix-based] systems. [1]

Key Market Trends:

Technological advancements in the drug delivery device market have made devices with this function more patient-friendly, accessible, and accurate. Moreover, the increasing popularity of minimally invasive surgeries and portable, wearable, and implantable devices will impact market growth positively. The combination of these trends position drug-eluting devices as highly effective options for medical device manufacturers.

The injectable method of administration will still expand at the quickest rate. Products in

[1] https://www.globenewswire.com/news-release/2021/08/12/2279463/28124/en/Global-29-84-Billion-Implantable-Drug-Delivery-Devices-Markets-2015-2020-2020-2025F.html

this category include prefilled syringes and pen injectors. The growth of other markets, such as syringes made from chemically inert polymers, are also driving the growth of the drug delivery device market and advancement of the devices.

While projections anticipate strong market growth, manufacturers are facing challenges. One major challenge is the inefficiency in delivering poorly soluble drugs. Additionally, the potential for the uncontrolled release of drugs is a concern, as this may lead to adverse side effects.

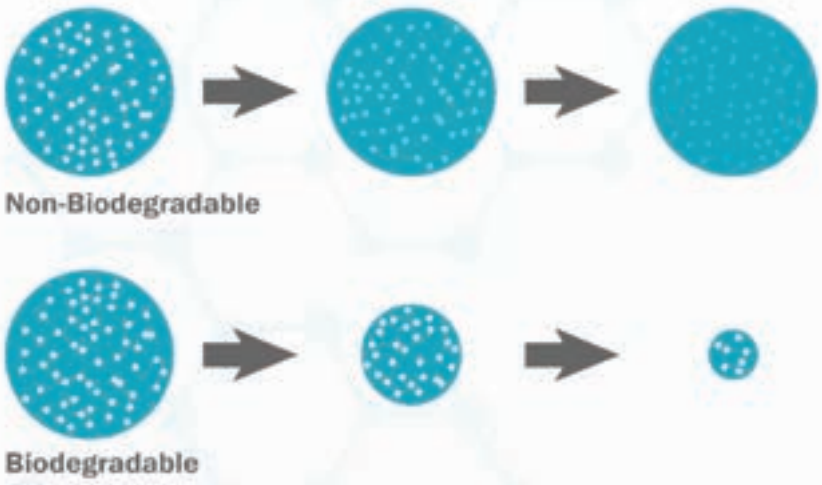
Combination products also involve components that not normally controlled by medical device regulatory authorities. This raises regulatory, policy, and review management challenges for both the manufacturers of devices and governing authorities.

Defining a Drug-Eluting Device

Drug-eluting devices can be separated into two categories, biodegradable and non-biodegradable.

Biodegradable (or bioresorbable) drug-eluting devices use biocompatible materials, such as polyester amide (PEA), to deliver drugs. Once implanted, the devices decompose over time.

Non-biodegradable (or biodurable) drug-eluting devices use biocompatible materials like silicone rubber, thermoplastic polyurethane (TPU), and others to deliver drugs. Silicone is the preferred material for devices due to its predictability in manufacturing, as well as the relative ease in modifying its chemical makeup.



Current uses for drug-eluting devices

Drug-eluting products, whether implanted, wearable, portable, or used during medical procedures, are a popular means of monitoring chronic-disease, guarding against inflammation and infection, and for drug delivery.

Drug-Eluting Main Product Applications

- Female Healthcare
- Wound Care
- Steroidal Collars
- Pacemaker Leads
- Ophthalmic Devices
- Solid Implant Dosage Forms

Advantages of API Elution

- Controlled release of the API instead of bolus-type delivery, enabling consistent maintenance of API concentrations within an optimal therapeutic range.
- Implanted devices provide localized, site-specific, sustained, and targeted drug delivery.
- When contrasted with systemic administration, this approach permits delivery of longer-term therapeutic dosages while minimizing adverse side effects.
- Improved patient compliance; most healthcare practitioners agree that with an aging population, compliance becomes less certain and therefore, more important.
- Improved functionality helping to prevent local as well as systemic infection.
- Lowering of dosage requirements results from reduction of systemic drug levels through delivery of the drug to targeted areas within the body.
- Simplified treatment regimens lead to fewer visits to the practitioner, relieving the strain on health services.

Methods of combining an API and Silicone

Silicone stands out as one of the most successful materials to support the production and advancement of combination products. Its biocompatibility and porousness make it a perfect fit for implantable devices. Two established methods of adding an API to silicone include the addition of an API to raw silicone and the impregnation of vulcanized silicone with an API by immersion. Another more recent method is to use a silicone membrane to control the release of the API over the lifetime of the product

Adding an API to Raw Silicone

Introducing an API into silicone requires the expert meshing of chemistry and engineering. The process usually involves the combination of Liquid Silicone Rubber (LSR) with an API before fabrication into a silicone part. Ideally, the API combines with both sides of the raw silicone immediately before extrusion, molding, or sheeting.

The advantage of adding an API to silicone before fabrication is the achievement of an accurate mass ratio of drug to silicone. Typically, the ratio is plus or minus 5% of the target mass ratio or better, making this process ideal for creating devices designed to deliver a precise dose of medication, such as a skin patch for pain medication or a vaginal ring for contraception. It is most common for the addition of a powder-form API to the silicone. This is usually the most stable form of the drug, though liquid drug formulations are also suitable.

Manufacturing Considerations

There are several crucial manufacturing factors to consider when combining APIs with raw silicone. Some APIs can poison the silicone cure. For example, chlorhexidine, a common antimicrobial, is available as a base and an acetate. If the acetate mixes and cures well with silicone, the base will poison the silicone cure.

Temperature is another key consideration due to the upper stability limit of many drugs being relatively low. For example, most hormones used in contraceptives begin to degrade at temperatures over /248 °F, but many silicone formulations have a cure temperature of /392 °F. In this case, and others, it is essential to select a low-temperature curing silicone and to carefully control the manufacturing process to ensure the temperature does not exceed the stability limit of the drug.

An additional factor is that many APIs are hazardous in powdered form, so stringent engineering controls must be put in place and safety procedures must be carefully monitored.

Impregnating Vulcanized Silicone with an API

A second method of introducing an API to silicone is to immerse a finished silicone part in a drug-loaded solvent to impregnate it with a drug, such as an antibacterial or antimicrobial.

There are several advantages to this process; it is a relatively mature technology, the timeline is usually short because the design/manufacturing process for the product doesn't change, regulatory approval is typically easier to obtain, and the results are highly repeatable.

However, the drawback is that this process is not as precise as adding an API to raw silicone from a mass ratio perspective, so it is only appropriate when precise drug-release rates are not critical. A good application for this method is an anti-inflammatory released from a pacemaker lead. The API is there to improve the safety or efficacy of the device without control in micrograms per day. In addition, only silicone and some types of thermoplastic elastomers can be successfully impregnated with APIs.

Manufacturing Considerations

The manufacturing process involves adding an API to a solvent that completely solubilizes the drug to create a mixture that is 100% homogenous. Common solvents for this application include chloroform, benzene, and toluene. The solvent swells the silicone, allowing the API to impregnate the vulcanized piece. After the immersion period, removal of the component from the solution and allows the solvent to evaporate, leaving the API impregnated in the silicone matrix. Most often, APIs are added to some type of extruded material, such as a catheter or pacemaker lead, but this process works for calendared and molded components as well.

A number of variables, including the type of drug and the thickness of the materials, determine the amount of API that can be impregnated into the silicone. Manufacturers must be familiar with the required development and testing procedures involved in determining the degree of impregnation.

Additionally, labeling for enhanced products must be carefully considered. It is difficult and time consuming to prove the efficacy of drug additives, although anecdotal evidence shows that adding antimicrobials usually reduces infection rates and anti-inflammatories have positive effects. Many manufacturers include drug additives in product designs and simply claim that the addition may enhance performance or help prevent infection.

Silicone Membrane for Controlled Elution

When you create a dispersion of silicone, a lot of parameters are open. Instead of opening the material up to these variables, using a silicone membrane enables manufacturers to control the elution rate by punching holes in silicone.

One method is for the membrane, such as an extruded silicone tube, to have small windows punched in the sides. The tube, filled with compressed hard drug tablets and sealed on both ends with Room-Temperature Vulcanizing (RTV) silicone, elutes through these windows as the tablets dissolve.

Another method for using a membrane is to have windows in the extrusion initially covered with a Polyvinyl Alcohol Membrane (PVA). Once implanted, the membranes dissolve and the API elutes through the opened windows.

Manufacturing Considerations

The membrane method is well suited for products that require a controlled release of an API over an extended period. The silicone membrane can be over-molded or extruded onto the component, with the method varying based on the product.

Design variables include thickness of the membrane, concentration of the API, type and size of the silicone reservoir, ID/OD, and method in which the reservoir and membrane cross link. The pathway methodology is a key consideration for designing these products.

Trelleborg Drug-Eluting Product Studies

To prove the effectiveness of the methods of adding an API to silicone, studies were completed into the methods, as well as the effectiveness of different drugs.

Study 1 - Investigate the Effectiveness of a Silicone Membrane for controlling Long Term Elution Rates

The purpose of the study was to evaluate the effectiveness of a silicone membrane for controlling the flux rate over the life of a long-term intrauterine (IUD) product. The variables centered on the design of the device, with alterations made to the concentration of the API, type and size of the silicone reservoir, wall thickness, and cross-linking of the reservoir. Products eluted over a 28-day period and the daily elution rate was measured by a high-performance liquid chromatography (HPLC) system.

The output variable was the elution rate of the API.

The theory is that flux rate between the reservoir and membrane is so high that it will not impact the flux rate from the membrane to the outside. The continuous force of API diffusing into the membrane is at a constant flux rate. The predicate, Levonorgestrel, is expected to reduce its elution rate slowly over the five-year period such that 50% of the drug is remaining in the drug delivery product.

Results of Study 1

Results from the HPLC system showed that the product performed differently at lower API concentration levels. It also revealed that the thickness and durometer of the membrane had the largest impact on the rate. These variables were tested at different levels to determine the necessary parameters for an ideal elution rate.

The substantial impact that the membrane thickness had on the elution rate made it essential to have precise dimensional control during manufacturing. Even if the thickness is off by .0005 inch, differences in elution rate were detectable. Through successive engineering builds, the engineering team was able to determine the necessary variables to ensure the product performed near the level of the control.

It is typical for these long-term implantable devices to have a higher level of elution variation during the first few days after implantation. As the product approaches its equilibrium, the elution rate will stabilize.

Coefficient of variation of micrograms eluted per day for the control product was 3.14% throughout days 7 to 28 of the testing. The predicate device, the original device that was FDA approve, had variation of 7.37%, and the Trelleborg prototype tested at 3.43% over the same timeframe. Figure 1 shows the comparison of the levonorgestrel release rate in micrograms per day.

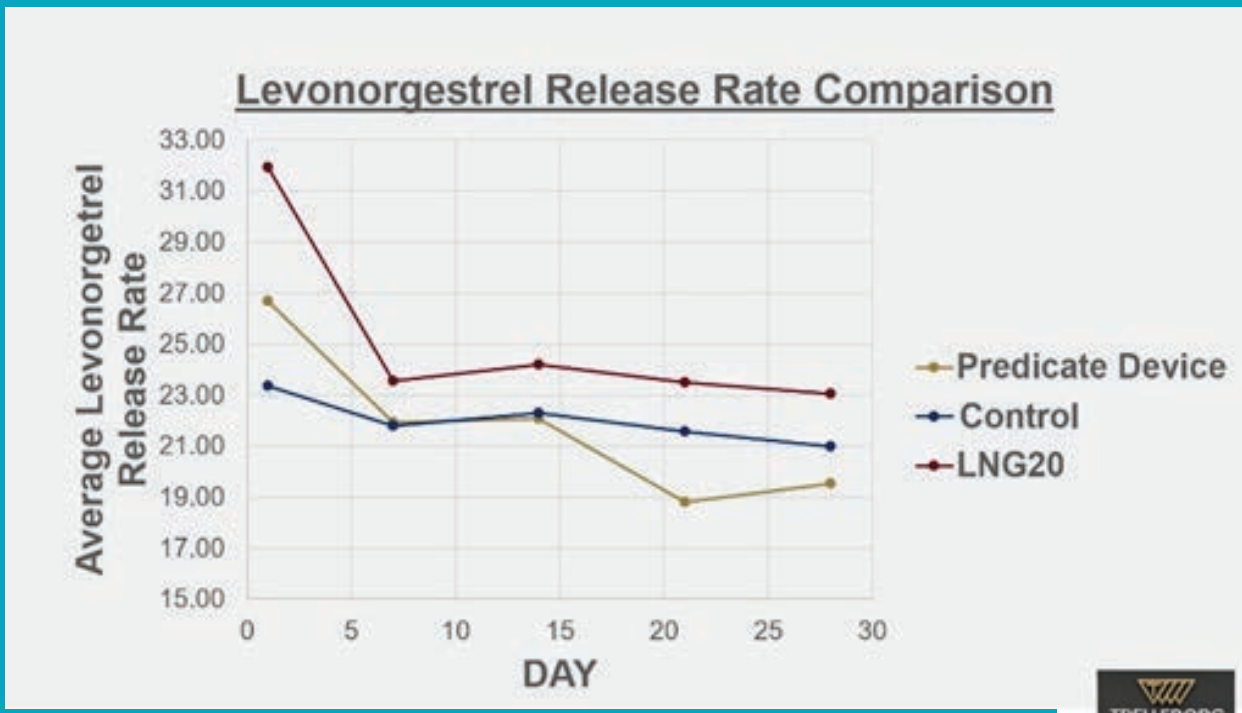


Figure 1

Once the prototype performed near the required standards, the team completed additional builds to improve the design and determine how to mold at large scale with minimal cost.

Study 2 – 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 (CLIN) and rifampicin (RIF).

Both of the drugs' powders were dissolved in chloroform, a solvent that swells silicone rubber. Application of the drugs were to lengths of 50 durometer silicone tubing. Input variables were the concentration of drugs in the 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 quantified the mass of drugs impregnated in the various samples. Hydrocephalus shunts, a small plastic tube that helps drain extra cerebrospinal fluid from the brain, 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 2

Data from the study is summarized in Figure 2

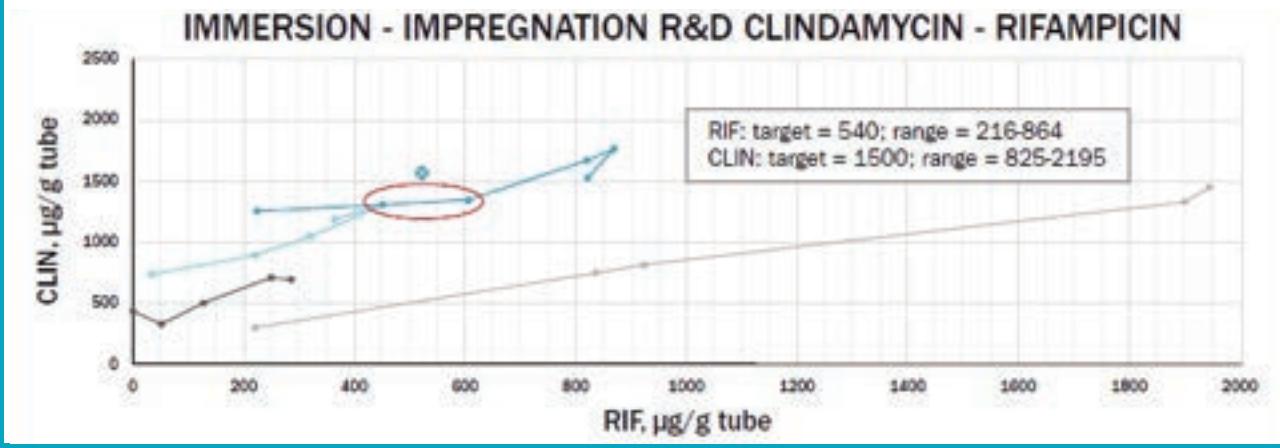


Figure 2

Rifampicin and clindamycin concentrations show on the x and y axes, respectively. The target, expressed as 1500 micrograms of CLIN and 540 micrograms of RIF per gram of tube, shows 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 includes five data points. Each data point represents the drug content of a sample immersed for five, 15, 30, 60, or 120 minutes.

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

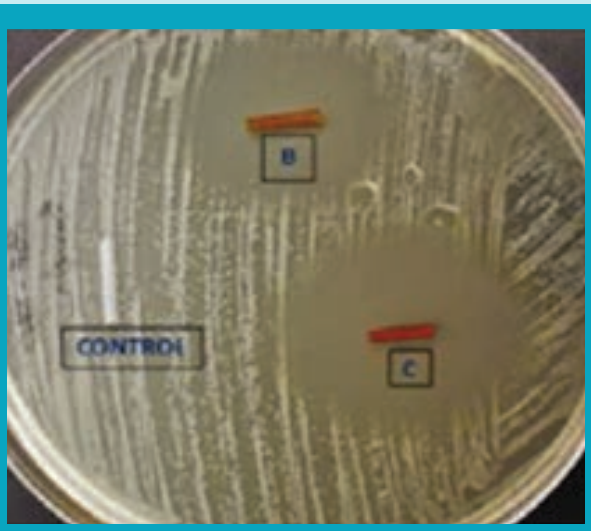


Figure 3

A final part of the study confirmed that the immersion process did not impact the antimicrobial efficacy of the drugs. As shown in Figure 3, a zone of inhibition test demonstrated that a powerful inhibitory effect on the growth of Staphylococcus aureus. Data from the study is summarized in Figure 2.

Study 3 – Investigate the immersion impregnation as a platform process technology

The purpose of the third 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 samples 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, gravimetrically quantifed the mass of impregnated drug by comparing the weights of samples before immersion and after devolatilization.

Figure 3

Four active pharmaceutical ingredients were investigated;

- Dexamethasone acetate, a glucocorticosteroid, used to treat inflammatory and autoimmune conditions. The drug is 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, 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 an injection, for treatment of pain associated with osteoarthritis.

After evaluation of nine solvents, solvent polarities ranged from 0.45 Debye for 1.4 dioxane to 3.96 Debye for dimethyl sulfoxide. Samples used 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 filled with solvent and removed from the solvent after soak periods ranging from five minutes to six hours.

Results:
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 4.

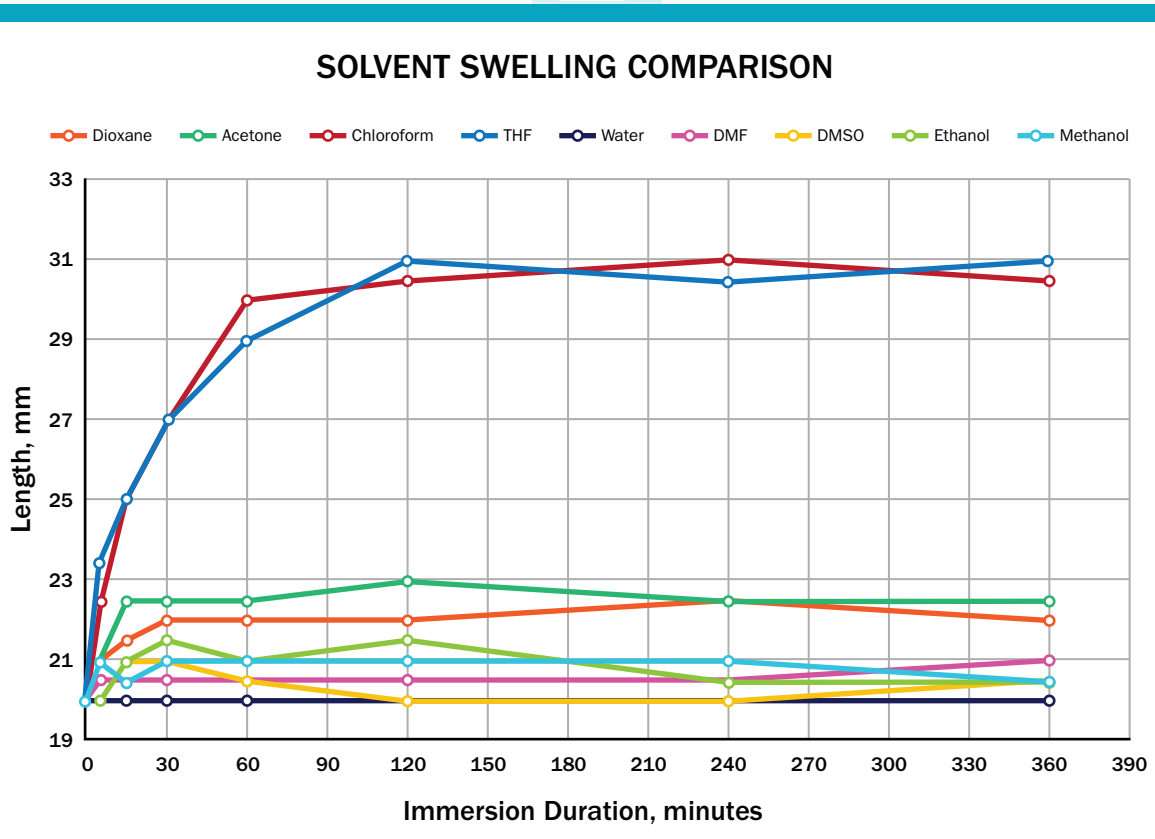


Figure 4

Saturated Drug Solutions

Evaluation of solubility of the four API was 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 drops until a clear solution was observed. Figure 5 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 5

Sample Preconditioning Results

Even completely vulcanized silicone rubber contains polymer chains that are not crosslinked into the elastomeric matrix. Silicone manufacturers refer to these un-crosslinked polymers as “loose juice.” It is well documented that these un-crosslinked polymers can be extracted from silicone rubber by exposure to various organic solvents. Qualification of the mass loss associated with the extraction of these polymers was through immersion of samples in four solvents for 24 hours. Samples then devolatilized for an additional 24 hours. Mass loss ranged from 2.5% to 3.0%. Trelleborg investigators understood that immersing samples in drug-solvent solutions would result in two competing and simultaneous diffusion processes; drug would diffuse from solution into the silicone rubber while at the same time un-crosslinked polymers would diffuse from the rubber into solution. Calculations regarding the mass gain associated with drug impregnation would skew 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 two-hour immersion period, the samples were removed from the solution, weighed, allowed to devolatilize for 24 hours, and then reweighed. Results are summarized in Figure 6.

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 6

Discussion Points

The test results highlighted a number of discussion points:

1. For six of the eight samples, the mass after impregnation and devolatilization was greater than the initial mass. Trelleborg investigators 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 to 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 samples impregnated with estradiol is still nearly five times greater than the total antibiotic content of the neurological shunts.

3. Study investigators had assumed that the mass of impregnated drug would be equalto the mass of solution absorbed by the sample during immersion multiplied by the concentration of the drug within the solution. However, the data shows that this was not the case. Consider the sample immersed in the saturated THF-dexamethasone solution. Immersion caused the sample 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 sample now contained 0.0097 grams of drug (0.0787 grams x 0.123) and that the weight of the sample 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 sample 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 samples introduce a partitioning effect between the drug solute and solvent. It is likely that this effect is attributable to the drug's reduced solubility in silicone relative to its solubility in solution and 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 considered in drug-eluting device concepts.

As market projections show, the drug delivery device market should continue to grow at a considerable rate. Recent advancements in medication administration techniques, rising demand for minimally invasive techniques due to enhanced patient outcomes, higher cost-efficiency, safety, and efficacy are all contributing factors projected to fuel demand. The increasing popularity of microscale implantable devices with multiple applications is yet another factor contributing to the projected growth.

Device manufacturers will continue to develop novel solutions using these technologies, ultimately resulting in higher quality and safer treatments to improve patient outcomes.

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With a curiosity and passion for emerging technologies, Zach works to build partnerships with people and organizations interested in delivering targeted therapies in novel ways. Having previously spent seven years in prototype manufacturing, he is very familiar with the journey product developers face. At Trelleborg Medical Solutions, he is backed by an experienced team eager to solve our partners' complex challenges by applying our expertise in drug delivery via silicone and polymer technologies.

Trelleborg is a world leader in engineered polymer solutions that protect essential applications in demanding environments. Its innovative solutions accelerate performance for customers in a sustainable way.

Trelleborg Medical Solutions partners with the world's leading medical device and biopharmaceutical companies, collaborating from concept to commercialization to bring to market impactful solutions that improve patient quality of life. It leverages decades of design and manufacturing experience, in-depth knowledge of polymer materials to deliver pioneering, engineered solutions for transformative health technologies.

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