

Extraction Strategies and Silicone Extractables

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Dow Corning Healthcare

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About the Authors

Regina M. Malczewski, Ph. D.



Gina received her doctorate in Biological Chemistry from the University of Michigan in 1982. After postdoctoral research at Michigan Molecular Institute in carcinogenic transformation processes, she joined Dow Corning in 1984. She has held various positions in Personal Care, Health and Environmental Sciences and Healthcare. Besides developing sensory methods for skin, hair and fragrance, and leading an extractables program, she has also monitored and performed many basic toxicology and biocompatibility tests on silicones. She is active in ASTM and the Society for Biomaterials and has also been involved in the Society of Cosmetic Chemists.

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Bill received a Bachelors of Science degree from Saginaw Valley State University in 2000. Most of his ten years at Dow Corning has been spent working on the development and performance of various analytical methodologies and techniques to better characterize both silicone and organic extractants from silicone and biological matrices. Bill is currently a technical service representative, primarily assisting fabrication customers with their understanding and processing of Dow Corning Healthcare materials. He has been involved with the American Society for Quality and is a current member of the American Chemical Society.

INTRODUCTION

In the pharmaceutical industry, the impact of processing equipment and packaging on drugs must be considered for manufacturers to claim compliance with Section 501 (a) (2) (B) of the U.S. Federal Food, Drug and Cosmetic Act. Adulteration can be a potential impact of any material in contact with drugs, including the tubing used in transfer or filling operations. Tubing and container extractables are not only addressed in US regulations but also in various pharmacopoeial monographs from Europe,¹ Japan² and the US.³

Extraction procedures vary with study intent, as described recently by Jenke.⁴ Extractions intended for biological studies have limited value from a chemist's perspective because the solvents used are those which are biologically tolerated, rather than the ones designed for solubilizing contaminants, reaction byproducts, or polymeric oligomers. Other solvent considerations include laboratory safety and assay utility. While what Jenke calls "Processes for Compositional Characterization of Delivery Systems" can be used for reverse engineering, they may disintegrate the material and require conditions that are not encountered during typical use. To characterize Dow Corning's silicone materials (including tubing), we have adopted procedures that employ solvents of varying polarity, as well as practical but rigorous time/temperature combinations, to produce non-physiological extracts that provide information about extractables under relevant—though "exaggerated"—conditions. We have tailored studies to meet customers' needs, while considering the chemistry of silicones and the sensitivity of assay methods. It has been our goal, when possible, to use the methods that best inform about potential extractables in a single extraction.

While our strategies have general applicability, the path we have taken has been specialized to meet our goals for Dow Corning's tubing and elastomers.

The Uses of Extraction Data

While the pharmaceutical industry may be most interested in characterizing the process extractables that may result in contamination of final drug, there are many other uses for extraction testing. Providing support and interpretation for toxicological studies dependent on evaluation of extracts, examining the impact of packaging on products, assessing the differences between "old" and "new" versions of products as part of change control (determining "equivalency"), competitive comparisons, and screening new product formulations

are some of the ways we have used extraction data within Dow Corning.

Once an objective has been set for an extraction study, many choices must be made to meet its goals. Some of the parameters for consideration are discussed below.

Solvent Choices

As mentioned above, solvent choices will depend on:

- product chemistry
- extraction yield (recovery)
- relevancy to use conditions
- assay requirements
- safe handling considerations
- extractable stability

Our typical extraction studies utilize exaggerated use conditions with several solvents to allow characterization and comparisons of potential process contaminants. Our procedures are designed not to alter or degrade extracted materials during the extraction or analysis time frames; special care is taken not to lose significant amounts of volatile extractables during these activities.

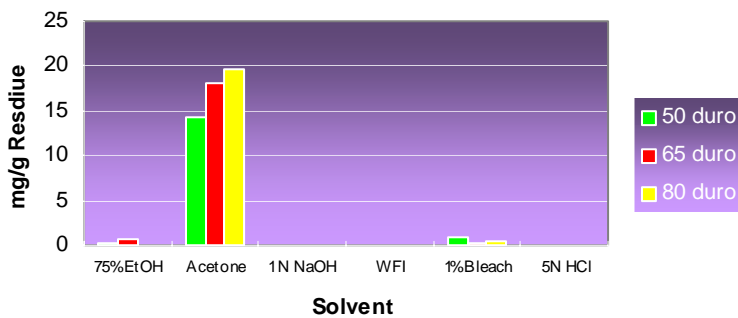
A solvent is chosen in which the product is not totally soluble. The solvent is ideal if it effectively removes components loosely bound in the polymer matrix. The product is most easily extracted if it retains solid form during extraction, although, if phase-distinct from the extractant, a liquefied sample may still yield useful information.

Silicones swell in some organic solvents (such as hexane), and recovery of extracts produced in those solvents is limited. Even if sufficient solvent can be recovered, results from only *part* of the extract (the rest entrained within the polymer matrix) may be difficult to extrapolate as representative of the entire solution. Little or nothing is usually known about the distribution of the extractables inside vs. outside the polymer in these situations.

Even small amounts of water in a suitable organic solvent can considerably decrease extraction efficiencies for silicones. Organic solvents should be as dry as possible. Another consideration is possible solvent preservation, since preservatives can be detected in assays such as gas chromatography. (An example is the butylated hydroxytoluene (BHT) found in tetrahydrofuran).

Extractable tests conducted on DOW CORNING® brand Pharma Tubing have employed procedures and solvents recommended by customers within the pharmaceutical industry. The studies described herein deal with extracts on tubing of different ages, with and without rinsing and autoclaving. Solvents include acetone, ethanol/water (75%/25%), 1% bleach (NaOCl), acid (5N HCl), base (1N NaOH) and Water for Injection (WFI). Figure 1 shows the variation in assay results due to the solvent used (expressed as mg residue per g of original sample).

Figure 1: Extraction Residues From Silicone Tubings



Assays dependent on specific instrumentation with different solvent compatibilities also dictate the extraction media to be used. For example, gas chromatography using standard columns does not permit analysis of aqueous solvents. Certain solvents (like tetrahydrofuran in some instances) can be used but produce tailing or large solvent fronts that distort or overwhelm the elution of small extractables. Likewise, UV interference from solvents like hexane and THF prevents the use of spectroscopy below specific wavelengths.

Flammable, carcinogenic or highly irritating solvents should also be considered carefully. Adequate safety equipment is always necessary, but risk vs. benefit assessments may be of particular interest in some cases.

Assay Choice

Assays on extracts should be chosen based on:

- chemical relevance to material extracted
- ease of validation
- extraction procedure (dilution vs. concentration)

-toxicological importance of different extractable (if a safety/risk assessment is to be the endpoint of the extraction study).

Assays should be designed to measure materials that are expected to extract; gas chromatography is not needed if the material is known to have no potentially volatile impurities. Silicon analyses are valuable for silicone elastomers, which can contain about 30% Si.

Assays with high detection limits or those requiring large background corrections have limited usefulness. Reproducibility and accuracy are also attributes of suitable assays, and are assessed through the process of validation, such as can be achieved using guidelines provided by the US Pharmacopeia⁵ or a number of statistical constructs.⁶

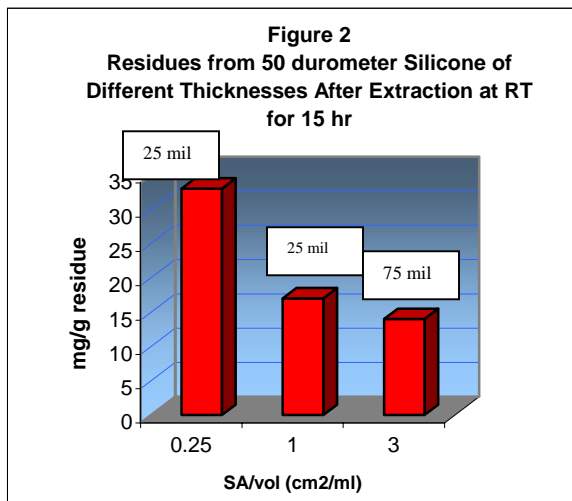
There are also many different procedures for a given assay. For example, Si detection by atomic absorption has been optimized at Dow Corning outside the use parameters typically recommended by instrument manufacturers. Assay sensitivities must always be similar for results from different laboratories to be successfully compared.

While extraction efficiency has proven best for us at high sample-to-solvent ratios (as assessed by total residue recovered; see Figure 2), extraction under these conditions produces a dilute solution that is not optimal for assay without concentration. Concentrating an extract may be unwise if little or nothing is known about possible volatile extractables, which can be lost during this process. Of course, the extract can be subdivided into portions that are processed as appropriate for specific assays, but generally we have found the most practical procedures are those that require little manipulation and involve guideline-suggested sample-to-solvent ratios.^{3, 7, 8} Our experience suggests that subdividing sample and using agitation are key for removing variation that occurs when large or complex samples do not have reproducible or controlled access to bulk solvent.

Choice of extraction assay may also be influenced by toxicological concerns or existing toxicological data, if understanding potential contamination is a goal of the study. If a particular set of extractables is known to have adverse biological effects, the best assays for detection of those materials should be chosen for such studies.

Other Procedural Considerations

Sample history and preparation should always be considered before starting an extraction study. Storage for long periods, especially at elevated temperatures, may remove volatile extractables. Materials may also cure into a matrix (or change in oxidation state and detectability) with time. Contact with packaging and the need for washing or rinsing (which should not be done unless necessary) should also be considered, as the results may become less relevant with additional procedural steps (Figure 3).



As already mentioned, existing extraction guidelines offer some useful suggestions for solvent-to-sample ratios. Sample configuration should be sufficient to discourage adhesion of pieces, allow for adequate solvent access, and permit complete submersion within an extraction container of reasonable size and inertness. Sample thickness (or tubing wall size) is also a factor in extraction efficiency; thinner samples may extract more completely in a limited time (see Figure 2). Time-temperature combinations should be sufficient for recovery of 90% of total extractables; practical considerations may also be length of workday and hands-on time. What cannot be accomplished in short times at high temperatures (perhaps because of safety considerations or concerns over loss of volatiles) can sometimes be achieved by longer times under more temperate conditions.

Our Experience

Tubing extractions at Dow Corning have shown the following:

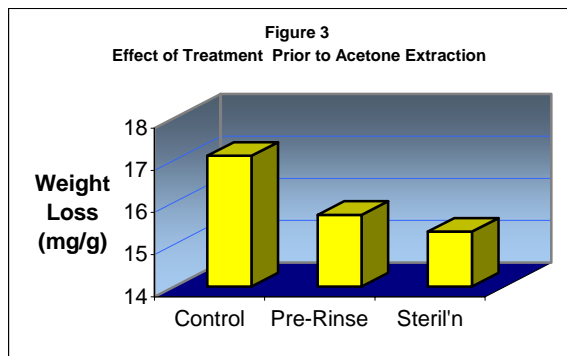
-Surface area:volume ratios of 3 cm²/ml using curved rectangular pieces 3 mm x 5 cm or 1 cm x 5 cm work

well. Thicker samples will not necessarily yield more extractables, unless conditions allow such extraction to go to completion. Diffusion of some solvents is faster through thinner pieces (Figure 4).

-Room temperature (RT) shaking overnight (16 hr) is highly efficient and is as effective as shorter periods of higher-energy extraction (such as sonication).

-Low molecular weight volatiles decrease with sample age, even with RT storage, over periods of several months. Although packaged tubing may entrap volatiles for longer periods than they would linger in slabs, there is a lower level of volatiles initially due to the high temperatures used during tubing processing.^{9, 10}

-Extractables decrease with rinsing, autoclaving and heat aging/post-cure at 177°C for 2 hr¹⁰ (Figure 3).



- Our Pharma Tubing extracts show low “Total Organic Carbon” (TOC) content, which can increase with catalyst type and composition in other silicone tubings. Aqueous extractables of Pharma tubings are overall very minimal, as measured by residue, Si and spectroscopic analysis. Washing results may therefore be a mechanical effect on surface extractables, rather than dissolution. Even small polydimethylsiloxanes have minimal solubility in water.¹¹

-Pt does not extract at quantifiable levels from Pharma tubing, even in rigorous solvents.

-Maximum levels of any identifiable extractable are below 1500 µg/g of original sample weight in any solvent, even under worst case conditions (eg., freshest samples, etc.)

-Residue weights may be impacted by water pick-up if samples are stored for long periods.

-While not yet specified, aqueous extractables of Pharma tubing may slightly decrease the pH of unbuffered systems.

Summary

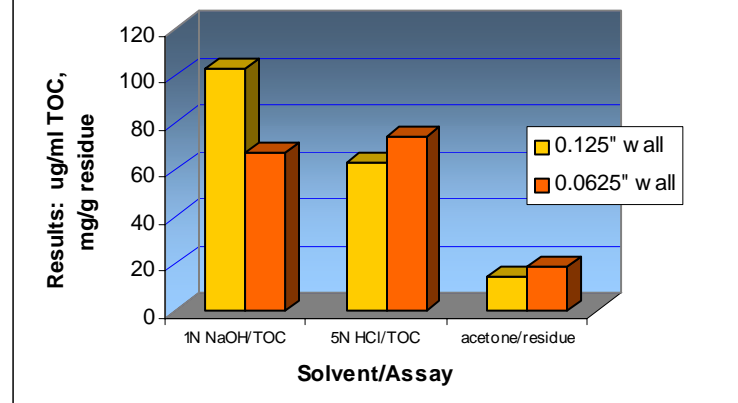
Extraction strategies are governed first by study objective; goals are met by the proper selection of study parameters such as solvent, assays and sample handling.

Of major consideration for thorough extraction of silicones is recovery of volatiles. Although aqueous assays may be informative, more silicone extractables are obtained in organic media. "Low extractables" is a relative term, but total levels obtained from silicone tubing are less than 30 parts per thousand even with the most rigorous solvent and procedure condition.

References

- ¹ European Pharmacopoeia, Monograph 3.1.9, "Silicone elastomers for closures and tubing"
- ² Japanese Pharmacopoeia XIV, section 11, "Plastic Containers for Pharmaceutical Products"
- ³ United States Pharmacopoeia <661>, "Containers—Physicochemical Tests"
- ⁴ D.R. Jenke, "Nomenclature Associated with Chemical Characterization of and Compatibility Evaluations for Medical Product Delivery Systems"; PDA J. Pharm. Sci. Tech. 57:97-108 (2003)
- ⁵ United States Pharmacopoeia <1225>, current edition, "Validation of Compendial Methods"
- ⁶ Evaluating the Measurement Process, 2nd ed., D.J. Wheeler and R.W Lyday, SPC Press, Inc., Knoxville, TN, 1989
- ⁷ ASTM Vol 13.01, F619-02, "Standard Practice for Extraction of Medical Plastics"
- ⁸ ISO 10993-12, "Biological evaluation of medical devices—Part 12—Sample preparation and reference materials", 1996
- ⁹ Dow Corning Internal Report 1998-I0000-44560
- ¹⁰ Dow Corning Internal Report 2000-I0000-48357
- ¹¹ Mazzoni, S.M., Roy, S., and Grigoras, S. 1997. Eco-relevant properties of selected organosilicon materials. The Handbook of Environmental Chemistry, Volume 3 Part H Organosilicon Materials; Ed. G. Chandra; Springer-Verlag, Berlin.

Figure 4.
Variations in Results with Tubing Wall Thickness
Pharma 50



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