

Ensuring the purity of platinum-cured silicone

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Platinum-cured silicone tubing plays a key role in manufacturing drugs and medicines in validated and non-validated processes in the pharmaceutical/biopharmaceutical industry. Though platinum-cured tubing is industry standard, platinum curing, in itself, does not guarantee a high level of tubing purity with low/safe levels of extractables. Watson-Marlow achieves ultimate purity by driving off cytotoxic extractables through post-curing, a process step many tubing manufacturers ignore. Some producers believe post-curing is not necessary, claiming that the naturally lower extractables of platinum-cured tubing (compared with peroxide-cured silicone) is sufficient. This bulletin outlines the importance of post-curing for the high-purity pharmaceutical/biopharmaceutical market, describing the key effects on the tubing and the key benefits for the user.

Overview

Post-cure is the post-extrusion process of baking tubing for a number of hours in an industrial oven that has a high air throughput to strip away volatiles. Post-cure achieves two key objectives:

1) It drives off volatile cyclic siloxanes (silicone oligomers) that would otherwise remain in the finished tube as leachables. Cyclic siloxanes are cytotoxic and therefore, if left in the tubing, could leach into the product flow and either contaminate the product or affect cell culture.

2) It stabilises the physical properties of the tubing by completing the crosslinking and condensing of any residual functional groups. Full crosslinking ensures a more stable structure resulting in lower hysteresis and more stable flow in a peristaltic pump.

What volatiles does post-curing remove?

In production of the silicone polymer—the raw material for the silicone tube—a cyclic siloxane/oligomer mixture is introduced as a process aid. However, it performs no function in the finished polymer and so it is vacuum devolatilised at high temperature to remove the oligomer from the polymer. The result is high molecular weight polymer but with a residual 0.5 to 2 weight percent residual oligomer. If the tubing is not post-cured, the residual

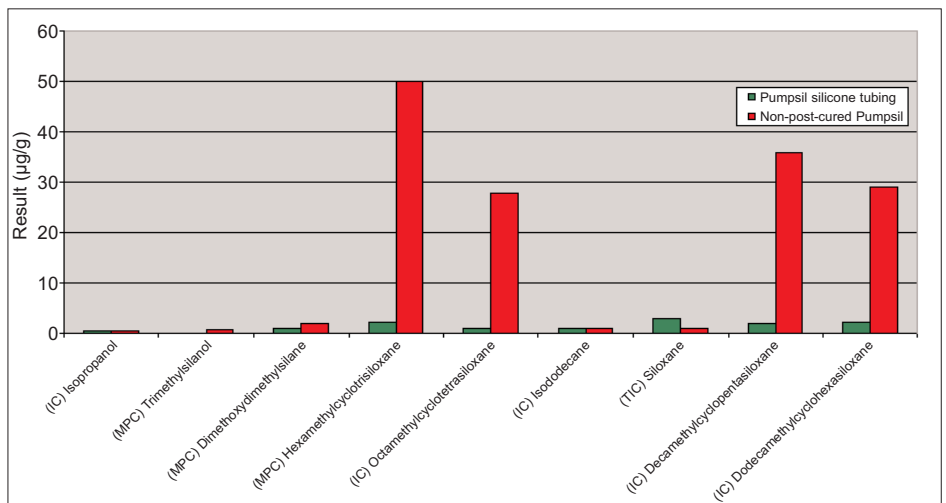
0.5 to 2 weight percent remains in the tubing as an extractable.

Post-curing induces both physical and chemical changes in silicone tubing. Physical changes occur with the volatilisation (i.e. removal from the tube) of low molecular weight cyclic siloxanes and other oligomers. These residual oligomers are volatilised in the tubing post-cure cycle which leaves the finished tube with significantly lower extractables than a non-post-cured tube (see the graph below).

Why is it important to remove cyclic siloxanes?

Cyclic siloxanes are cytotoxic. In a test carried out by Toxicon, an independent test laboratory, a mix of three cyclic siloxanes was tested using the MEM Elution test (ISO 10993-5, 1999: (Biological Evaluation of Medical Devices Part 5: Tests for In-Vitro Cytotoxicity) and USP 29 NF 24, 2006 (87)

This graph shows the difference in extractables levels between post-cured and non-post-cured Pumpsil silicone. The comparison is for illustration purposes only: all production Pumpsil tubing is fully post-cured. As can be seen, post-curing dramatically reduces the levels of cyclic siloxanes in the finished tube



How we do it

Watson-Marlow's post-cure oven operates at 200C/390F for a cycle time of four hours (plus warm-up and cool-down).

Watson-Marlow's post-cure ovens were specially designed to ensure we achieved the necessary airflow of 100 litres of air per kg of tubing per minute.

Each oven is capable of post-curing 150kg of tubing per cycle, with means an airflow of 15,000 litres/minute (530cfm). To heat the air, each oven is equipped with 78kW of electrical heating and a heat exchanger on the exhaust vent, which reclaims 50% of the waste heat, thereby boosting the rating of each oven to 120kW. Many manufacturers do not post-cure at all. Some manufacturers use a so-called



"in-line" post-cure, but this is ineffective as full post-cure takes significantly longer than any in-line oven would allow. Ovens which do not have the requisite air throughput will not adequately strip off the volatiles. The result will be a tube with higher levels of extractables.

that platinum-cured silicone is cleaner and purer than the peroxide-cured silicone that the industry used prior to platinum curing.

However, if not removed, the cyclic siloxanes (or silicone oils) can affect the process or contaminate the product.

Toxicon carried out headspace GC-MS tests on some commercially available platinum silicone tubes. The test results are summarised in the graph below and clearly show how Watson-Marlow's post-cure removes cyclic siloxanes, resulting in a tube with dramatically lower extractables.

Biological reactivity test, in vitro). The test sample showed a severe reactivity (grade 4) at the 48 hour observation and therefore the mix of cyclic siloxanes was cytotoxic. Grade 4 / severe reactivity means a reduction in viable cell count of approximately 70%.

The cyclic siloxane mix was equal parts of octamethyl cyclotetrasiloxane, decamethyl cyclopentasiloxane and dodecamethyl cyclohexasiloxane. The test was carried out at 25% dilution of this mix.

Comparison of different platinum-cured tubing

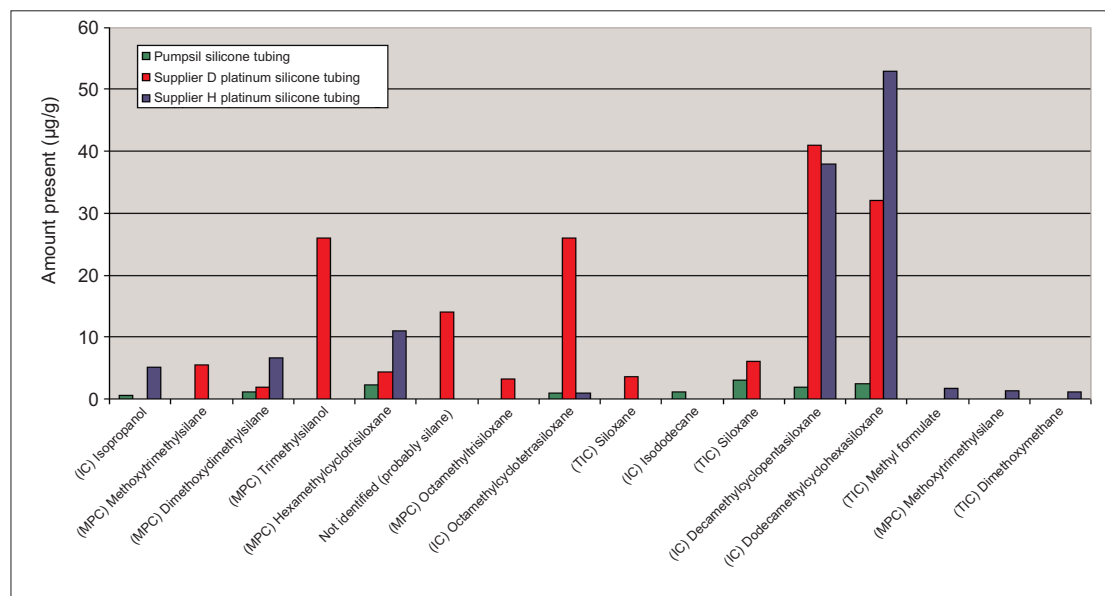
Watson-Marlow post-cures all its Pumpsil platinum cured tubing. Many other manufacturers do not post-cure their tubing, working on the basis

How does post-curing improve performance?

Post-curing induces chemical changes including the continued crosslinking and condensation of reactive functional groups. The continued crosslinking between vinyl and hydride groups occurs because some of the functional groups are less reactive than others and can only be made accessible with increased heat and time. The final crosslinking increases the shore A hardness of the tubing by 4 points. All of the physical property changes are the result of a tighter network and an increased crosslink density.

In the case of peristaltic pump tubing, post-curing will help immediately with lower extractables. This factor alone makes post-curing critical for

Different platinum-cured silicones include different quantities of impurities. Pumpsil is noticeably better than the others



Measuring volatiles: Headspace GC-MS

Headspace GC-MS is a technique used to analyse the volatile content of a material. A sample of the material is sealed in a vessel which is then heated to 180C. The sample is heated for a period of 40 minutes, which ensures that volatile compounds throughout the structure of the material are volatilised. A sample of the air above the material (or "headspace") is then analysed using Gas Chromatography and Mass Spectroscopy to establish what volatiles are present. The mass spectra for the unknown compounds in the air sample are identified by comparing with a mass spectra database of known compounds.

biopharmaceutical applications. In addition, the stable network structure will result in fewer chemical changes over time that would lead to changes in flow rate.

Decreasing the number of defects in the net-

work structure will lower the hysteresis, and in turn this will lengthen tubing life. Lower hysteresis will also improve restitution and maximise the flow rate.

Summary

Post-curing platinum-cured silicone tubing minimises extractables and creates a cleaner, purer tube. In turn, this ensures that any product passing through the tube will remain clean and pure, without the risk of cross-contamination.

Post-curing also ensures full crosslinking within the structure of the tube, ensuring more stable flow characteristics.



Watson-Marlow's cleanroom for Pumpsil manufacture

FAQs

Why use headspace GC-MS and not TOC?

TOC or Total Organic Carbon is an indirect measure of organic molecules present in aqueous solutions, measured as carbon. The sample for test is prepared by carrying out an extraction in WFI (Water For Injection) which is oxidised either by heat or combined heat/UV/oxidising agent to establish the amount of carbon present.

Only compounds soluble in water are identified by the test. The cyclic siloxanes outlined here are virtually

insoluble in WFI and will not be identified.

As an aside, it is not possible to carry out a TOC using a solvent instead of water, because the carbon in the solvent will mask the carbon in the material being analysed.

If siloxanes are practically insoluble in WFI, why should users with aqueous solutions be concerned?

If any of the compounds or products present in the company's solution flowing

through the tube acts as a surfactant, then this will allow the siloxanes to move into the solution. Unless it can be shown that the siloxanes do not enter the product flow, then the risk remains that a cytotoxic compound could be introduced into the product.

In an entirely separate piece of research, Merck (Westpoint, PA, USA) carried out research which showed that when product was transferred to a sterilising filter through silicone tubing which had not been post-cured, the effectiveness of the filter was reduced through contamination with cyclic siloxanes.

Continued overleaf

FAQs continued

See
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17089693

What does 'severe re-activity' mean in practice?

It indicates that there is a reduction in viable cell count in the sample of around 70%.

When I look up siloxanes on Google, I find they are used in all sorts of everyday products. Why should I be concerned?

Aside from the work that Watson-Marlow has carried out to prove that cyclic siloxanes are cytotoxic, there are some other studies which show that the risks are either known or knowledge of the risks is developing. In the Danish study (see below) steps are being taken to remove siloxanes from common use.

Examples include:

Octamethylcyclotetrasiloxane (CAS 556-67-2), from the raw material MSDS:

Ingestion: Rodents given large doses via oral gavage of octamethylcyclotetrasiloxane (1600mg/kg day, 14

days) developed increased liver weights relative to unexposed control animals due to hepatocellular hyperplasia (increased number of liver cells which appeared normal) as well as hypertrophy (increased cell size).

Polydimethyl siloxane data from Toxnet:

Enter "polydimethyl siloxane" as the search term at <http://toxnet.nlm.nih.gov>

UK government work:

<http://www.defra.gov.uk/ENVIRONMENT/chemicals/ukrisk.htm>

Danish study on the use of and alternatives to siloxanes:

See http://www2.mst.dk/common/Udgivramme/Frame.asp?pg=http://www2.mst.dk/udgiv/publications/2005/87-7614-756-8/html/helepubl_eng.htm. The key paragraphs are copied below:

"Only few siloxanes are described in the literature with regard to health effects, and it is therefore not possible to make broad conclusions and comparisons of the toxicity related to short-chained linear and cyclic siloxanes based on the present evaluation. Data are primarily found on the cyclic siloxanes D4 (octamethylcyclotetrasiloxane) and D5 (decamethylcyclopentasiloxane) and the short-linear HMDS (hexamethyldisiloxane)....

"Subacute and subchronic toxicity studies show that the liver is the main target organ for D4 which also induces liver cell enzymes. This enzyme induction contributes to the elimination of the substance from the tissues. Primary target

organ for D5 exposure by inhalation is the lung. D5 has an enzyme induction profile similar to that of D4. Subacute and subchronic inhalation of HMDS affect the lungs and kidneys in rats.

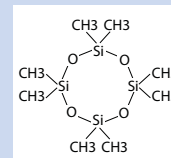
"None of the investigated siloxanes shows any signs of genotoxic effects in vitro or in vivo. Preliminary results indicate that D5 has a potential carcinogenic effect.

"D4 is considered to impair fertility in rats by inhalation and is classified as a substance toxic to reproduction in category 3 with the risk phrase R62 ('Possible risk of impaired fertility').

"Based on the reviewed information, the critical effects of the siloxanes are impaired fertility (D4) and potential carcinogenic effects (uterine tumours in females). Furthermore there seem to be some effects on various organs following repeated exposures, the liver (D4), kidney (HMDS) and lung (D5 and HMDS) being the target organs."

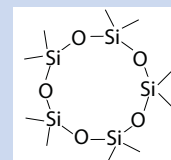
Also see: <http://www.mst.dk/udgiv/publications/2005/87-7614-756-8/pdf/87-7614-757-6.pdf> (Annex 8).

What are the key cyclic siloxanes also known as?



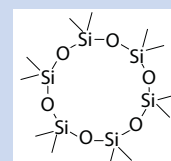
Octamethyl cyclotetrasiloxane
CAS no 556-67-2
Chemical formula
 $C_8H_{24}O_4Si_4$

Also known as: cyclic dimethylsiloxane tetramer, Cyclodimethicone, D4



Decamethyl cyclopentasiloxane
CAS no 541-02-6
Chemical formula
 $C_{10}H_{30}O_5Si_5$

Also known as: Decamethylcyclopentasiloxane; Cyclic dimethylsiloxane pentamer; Cyclomethicone, Polydimethylsiloxane



Dodecamethyl cyclohexasiloxane
CAS no 540-97-6
Chemical formula
 $C_{12}H_{36}O_6Si_6$

Also known as: Cyclic VMS

