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ClorDiSys

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Material and Packaging Selection and Compatibility with Chlorine Dioxide Gas Sterilization

Chlorine Dioxide Gas Properties

Chlorine dioxide gas (CD) is a unique single electron-transfer-oxidizing agent and has been termed a "stable free radical." CD has the microbiocidal properties of chlorine and is highly soluble in water, but unlike chlorine, its reaction chemistry does not lead to the formation of chlorinated organic products (trihalomethane and chloramine). CD is a respiratory irritant with an 8-hour timeweighted average exposure limit of 0.1 ppm; the 15-minute short-term exposure limit is 0.3 ppm. At use concentrations, CD is not flammable nor is it carcinogenic or ozone depleting (Long, Battisti, Elyath 2000). In addition, chlorine dioxide gas breaks down into chlorite, chlorate, and chloride which have relatively low toxicities in humans. CD gas and its derivatives, chlorite and chlorate, on the other hand, have relatively low toxicities in humans (11-13, 18, 24). They are not mutagenic (16, 17).

Chlorine Dioxide Gas Generation

Chlorine Dioxide (CD) gas by ClorDiSys is generated with the CD Cartridge (EPA label # 80802-1) and is registered with the US-Environmental Protection Association as a sterilant gas. The US-EPA label specifies chlorine dioxide can be used to sterilize prefilled syringes, cold chain products, medical devices, as well as other applications. Prefilled syringes and medical devices are typically sterilized in an ambient temperature vacuum sterilizer.

Chlorine dioxide is not sufficiently stable to be stored, it must be generated onsite at the point of use. There are many ways to generate CD gas and one method is using, a low-level chlorine gas (2%) which is passed over solid sodium chlorite CD Generating Cartridges which convert the chlorine to pure chlorine dioxide (>99% yield).

$$Cl_2(g) + 2NaClO_{2(S)} \text{ to } 2ClO_{2(g)} + 2NaCl_{(S)}$$

The 2% chlorine gas is mixed with nitrogen. This stoichiometrically limits the chlorine dioxide gas concentration to 4% which is significantly below the 10% level which is potentially explosive. Chlorine purity levels should be greater than 99%. The CD Generating Cartridges have a 1-year shelf life and generate CD gas for up to 300 minutes before they require replacement. The shelf life of reagent gas tanks are manufacturer specific and must be followed. The sterilizer control systems automatically prevent the CD Cartridges from being used for more than the allowable capacity. This process produces a pure chlorine dioxide gas and is injected into the target chamber for a fixed time or until a dosage setpoint has been met. The chlorine dioxide flow rate is 20 liters per minute +/- 4 liters per minute. After the exposure is completed, the gas is typically passed through a carbon scrubber to fully eliminate any chlorine dioxide gas. Alternatively, chlorine dioxide may be exhausted to the outside environment via house exhaust systems. Federal state and local regulations must be verified prior to exhausting CD gas.

Chlorine Dioxide Gas Properties and Cycle Monitoring

Sterilization chambers for chlorine dioxide include ambient pressure chambers or vacuum pressure chambers. The target chamber choice depends upon the product requiring sterilization. If the product is simple in its geometry and has no small openings, then an ambient pressure chamber can be used. If the product is complex in its geometry and has many lumens or tubing, or small openings, then a vacuum process may be required. A vacuum sterilizer will remove most of the air particles from both the chamber as well as internal portions of the device itself, then replace the air with humidity and CD gas. This allows the moisture, as well as the CD, to penetrate tight areas of a device or packaging.

The product must be wrapped in suitable packaging to maintain sterility. Tyvek packaging is often utilized to serve as the sterile barrier primary packaging since it allows CD gas to penetrate and does not allow organisms to contaminate the device inside. Primary packaging may also include blister packaging or other packaging alongside a gas permeable material, which includes Tyvek or medical grade paper. Product to be sterilized may also be placed into secondary packaging which can include unit cartons, display boxes, pouches, trays, etc. Additionally, items may be placed within tertiary packaging or shippers. Chlorine dioxide gas is compatible with the sterilization of cellulosic materials which permits the incorporation of paper labels on devices as well as fiberboard or corrugated packaging. This allows for the simplification of the sterilization process and flexibility on the packaging of a device.

Chlorine dioxide gas is considered a true ambient temperature process since the temperature is not manipulated by the process. Chlorine dioxide gas a yellow-green color and this allows the concentration to be monitored by a UV-Vis spectrophotometer. Throughout the cycle, samples of gas are pulled from the chamber and passed through the UV-Vis spectrophotometer to give a precise concentration reading. its concentration can be monitored and thus it has the ability to utilize product parametric release. Chlorine dioxide gas also has a boiling point between -20˚ C and -40˚ C at use concentrations, thereby making it a true gas at room temperatures (15-25˚ C). Being a true gas, it will not condense at use temperatures like a vapor would. Instead, a gaseous process is a more reliable and consistent process with better penetration. Chlorine dioxide has a molecular weight of 67.5 but stratification is not an issue with chlorine dioxide. Testing at ambient pressure was performed demonstrating that with minimal circulation, gas concentration is still evenly distributed throughout a chamber.

Sterilization Chambers

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For chlorine dioxide gas the typical pressure/temperature chamber sterilization cycle consists of the following steps

Step 1- Pull an initial vacuum to remove much of the air out of the chamber (typically 5-10 kPa).

Step 2- Perform a leak test to ensure that there is no significant air leakage into the chamber.

Step 3- Precondition. This step raises the relative humidity to the setpoint (generally 65-75%).

Step 4- Condition. This step holds the relative humidity at the setpoint for typically 30-90 min.

Step 5- Charge. This step raises the chlorine dioxide gas concentration to the setpoint (typically 1-30 mg/L).

(Above) Steridox-100 Chlorine Dioxide Gas Sterilizer

Step 6- Exposure. This step holds the chlorine dioxide gas concentration at the desired CD concentration, expressed in mg/L, until either the dosage or the exposure time is attained. If the concentration drops for any reason the Steridox-100 will inject more gas into the system until concentration returns to its desired setpoint.

Step 7- Aeration. This step removes the chlorine dioxide gas from the chamber by pulling vacuum and breaking with filtered air. Typically, 12 vacuum/break cycles are required to remove the gas to safe levels.

Step 8- Introduction of filtered air into the chamber to bring the chamber back up to ambient pressure (HEPA filtered air is an option).

Sample Material Compatibility with Chlorine Dioxide Gas Exposure

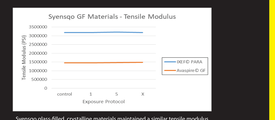
SYENSQO

Testing from Syensqo involved the following materials that are commonly used in healthcare and pharmaceutical applications. Chlorine dioxide exposure was highly robust and represented an atypically high dose cycle to mimic a challenging product's requirements. All testing indicates high material compatibility.

- IXEF GS-1022 GY02
- Udel P1700 NT15
- Veradel 3300 WH001
- Radel R-5100 NT15
- Avaspire AV-651 BG15
- Avaspire AV-651 BG20 GF30

Syensqo Material	Change in MW (%) from control to 50,000 ppm-hour exposure
Ixef® PARA	< 1.5%
Udel® PSU	< 1.3%
Veradel® PPSU	< 1.1%
Radel® PSU	< 0.7%
Avaspire® PAEK	< 1.2%
Avaspire® GF PAEK	Re-analysis required

To ensure there was no chemical interaction between the chlorine dioxide and polymer chains we analyzed each sample after exposure for changes in molecular weight. A significant shift in molecular weight would indicate sections of the polymer were chemically reacting with the chlorine dioxide The analysis was performed using gel permeation chromatography (GPC) technology, and the results showed there was an insignificant shift in the molecular weight of the samples during each exposure method. The percent changes are listed below for reference. The 50,000 ppm-hour exposure always deviated from the control the most, so that is the value used to calculate the percent change.



Syensqo glass-filled, crystalline materials maintained a similar tensile modulus throughout the different exposures.

Testing:

Four Delrin grades – SC655, SC631, PC652, SC698

Properties Evaluated:

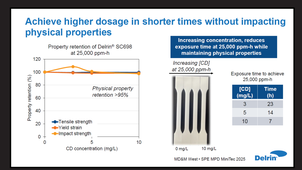
Tensile properties

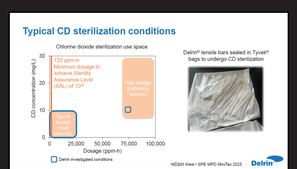
Notched Charpy impact

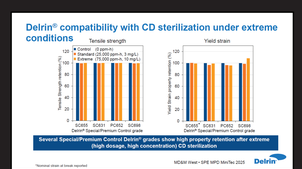
Color change

Weight change

Delrin grade	Grade description
SC655 NC010	Medium viscosity acetal homopolymer
SC631 NC010	Medium-high viscosity, nucleated, acetal homopolymer
PC652 NC010	Medium viscosity, lubricated acetal homopolymer
SC698 NC010	Low viscosity, lubricated acetal homopolymer (with improved processing and surface finish)







Packaging Testing after Chlorine Dioxide Exposure

Oliver

Test outline:

ClorDiSys sterilized Oliver Packaging's proprietary films used in pouch configuration to determine compatibility of the packaging after exposure to chlorine dioxide gas sterilization and vacuum levels as deep as 5 kPa

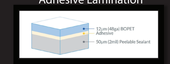
Cycle Parameters:

3500 ppm-hour chlorine dioxide gas setpoint
1 mg/L chlorine dioxide gas concentration setpoint
70% relative humidity for 60 minutes

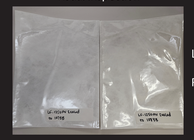
Product	Type/Format	Material Description	Quantity
UT73 / LF-1250AV	Pouch	Uncoated 1073B Tyvek sealed to peelable PET/PE film **(adhesive lam)**	200
ST7382C / LF-1250AV	Pouch	Coated 1073B Tyvek sealed to PET/PE film **(adhesive lam)**	150
UT73 / LF-2550AV	Pouch	Uncoated 1073B Tyvek sealed to peelable Nylon/PE film **(adhesive lam)**	200
UT73 / LF-2550	Pouch	Uncoated 1073B Tyvek sealed to peelable Nylon/PE film **(extrusion lam)**	200
ST7382C / PETG	Coated Tyvek sealed to PETG strip	Water-based adhesive coated 1073B Tyvek lidding sealed to PETG strip	50
X7139NP34 / PETG	Coated Tyvek sealed to PETG strip	Hot melt adhesive coated 1073B Tyvek lidding sealed to PETG strip	50
HDPE/CleanCut Cards	HDPE Card	28mil HDPE	50

Sample Test Report from Study

(Below) LF-1250AV
Biaxially Oriented Peelable PET Film
Adhesive Lamination



Visual Inspection



Left: Unsterilized Control Sample

Right: Sterilized Sample

Elongation %

MD	Non-sterile	ClO2
	Initial	Initial
	%	%
1	125	129
2	123	120
3	124	116
4	118	111
5	142	113
6	123	105
Avg	126	116
CD	Non-sterile	ClO2
	Initial	Initial
	%	%
1	84	114
2	87	106
3	87	116
4	87	117
5	96	106
6	100	110
Avg	90	111

Tensile Strength

MD	Non-sterile	ClO2
	Initial	Initial
	lb f	lb f
1	16.42	17.0
2	16.38	16.5
3	16.52	15.9
4	16.38	16.8
5	17.18	16.1
Avg	16.6	16.4
	PSI	PSI
	6568	6792
	6552	6596
	6608	6352
	6552	6700
	6872	6448
Avg	6630	6578
CD	Non-sterile	ClO2
	Initial	Initial
	lb f	lb f
1	17.41	18.9
2	17.82	19.1
3	17.70	19.5
4	18.10	19.6
5	18.30	18.8
6	18.09	19.4
Avg	17.90	19.2
	PSI	PSI
	6964	7564
	7128	7564
	7080	7640
	7240	7792
	7320	7852
	7236	7528
Avg	7161	7657

Peel Strength

Non-sterile	ClO2
Initial	Initial
1.94	2.41
2.63	2.88
2.31	2.49
2.49	2.35
2.12	2.67
2.90	2.74
2.55	2.63
2.71	2.61
2.08	3.24
3.11	2.79
2.00	1.82
1.57	2.78
1.68	1.79
1.94	2.72
2.97	2.39
1.80	2.03
1.42	2.01
1.92	2.56
1.74	2.15
1.40	2.31
1.34	3.07
1.84	2.95
2.06	2.43
1.84	2.20
2.02	3.14
2.25	2.91
1.99	2.26
2.23	2.01
1.98	2.00
1.57	2.28
2.65	3.48
2.41	2.85
3.47	3.37
2.07	3.10
1.97	3.12
2.38	2.43
2.32	2.50
1.94	3.72
2.89	2.30
3.08	2.58
2.63	2.61

Puncture Resistance

	Non-sterile	ClO2
Thru PET	Initial	Initial
1	6.27	6.52
2	6.43	6.55
3	6.31	6.50
4	6.3	6.35
5	5.74	6.46
AVG	6.21	6.38

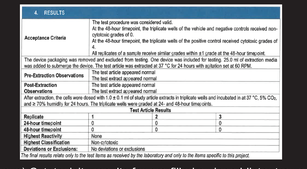
Summary of Results

Property	Non-Sterile	ClO_2
Elongation	MD: 126% CD: 90%	MD: 116% CD: 111%
Puncture Resistance	6.21lbf	6.38 lbf
Tensile Strength	MD: 6,630 psi CD: 7,161 psi	MD: 6,578 psi CD: 7,657 psi
Peel Strength	2.63 lb/in	2.61 lb/in

Result: no loss in physical performance properties

Cytotoxicity Testing

A study included variety of products and packaging have been tested for cytotoxicity. Packaging is to be tested for cytotoxicity to comply with ASTM F2475-20. All devices and packaging were determined to by non-cytotoxic after sterilization.



4. RESULTS

Acceptance Criteria	The test procedure was considered valid. At the 48-hour timepoint, the triplicate wells of the vehicle and negative controls received non-cytotoxic grades of 0. At the 48-hour timepoint, the triplicate wells of the positive control received cytotoxic grades of 4. All replicates of a sample receive similar grades within ±1 grade at the 48-hour timepoint.
Pre-Extraction Observations	The device packaging was removed and excluded from testing. One device was included for testing. 25.0 ml of extraction media was added to submerge the device. The test article was extracted at 37 °C for 24 hours with agitation set at 60 RPM.
Post-Extraction Observations	The test article appeared normal The test article appeared normal The test extract appeared normal

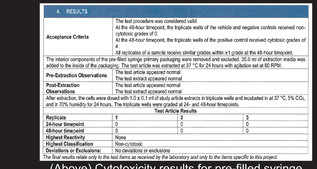
After extraction, the cells were dosed with 1.0 ± 0.1 ml of study article extracts in triplicate wells and incubated in at 37 °C, 5% CO_2, and ≥ 70% humidity for 24 hours. The triplicate wells were graded at 24- and 48-hour timepoints.

Test Article Results

Replicate	1	2	3
24-hour timepoint	0	0	0
48-hour timepoint	0	0	0
Highest Reactivity	None		
Highest Classification	Non-cytotoxic		
Deviations or Exclusions:	No deviations or exclusions		

*The final results relate only to the test items as received by the laboratory and only to the items specific to this project

(Above) Cytotoxicity results for pre-filled syringe blister tray and Tyvek® lid, concluding that it is non-cytotoxic after sterilization



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Pre-Extraction Observations	The interior components of the pre-filled syringe primary packaging were removed and excluded. 35.0 ml of extraction media was added to the inside of the packaging. The test article was extracted at 37 °C for 24 hours with agitation set at 60 RPM.
Post-Extraction Observations	The test article appeared normal The test article appeared normal The test extract appeared normal

After extraction, the cells were dosed with 1.0 ± 0.1 ml of study article extracts in triplicate wells and incubated in at 37 °C, 5% CO_2, and ≥ 70% humidity for 24 hours. The triplicate wells were graded at 24- and 48-hour timepoints.

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