Super clean polyisoprene polymer & latex for high performance medical devices

A comparison of the performance of various elastomers in medical stoppers and surgical gloves.

Dr. Philippe Henderson* and Dr. Bert Krutzer**

* Contact person[1]:
Global Innovation Mgr Cari*flex*™ Products
Kraton Polymers Nederland B.V.
John M. Keynesplein 10
NL-1066 EP Amsterdam

** Senior Scientist
Kraton Polymers Research B.V.

Presented at the Medtec Innovation Forum 2013.

Feb 27th, 2013

[1] Contact details: Kraton Polymers Belgium
Axis Parc, Building B, 2nd Floor
Rue Emile Francqui, 1
B-1435 Mont St. Guibert (Belgium)

Abstract

Manufacturers of healthcare goods are faced with increasing demands for the latest in rubber-based products: medical stoppers should be safe but convenient; surgical gloves should be strong, but tactile and kind to skin; protective equipment must meet rising safety standards, and increasing comfort expectations from users etc.

For applications where strength, comfort and protection are key, Cariflex™IR, with its non-allergenic character, transparency, lack of odor, softness, hysteresis and good consistency, offers the ideal alternative to existing material solutions.

For medical stoppers, a comparison of the chemistry and performance of four rubber products (Cariflex™IR, competitive Ziegler-Natta IR, chlorobutyl rubber; bromobutyl rubber) showed that our clean rubber delivers a unique combination of advantages including the absence of natural rubber proteins present in NR, an odor-free formulation with low residual metals and no residual catalysts, low needle insertion force, and minimal risk of rubber fragmentation (coring) and medication contamination due to needle insertion (leakage).

Kraton Polymers also offers Cariflex™IR Latex, a hypoallergenic water-based dispersion of this unique polyisoprene, that is used amongst others for the production of surgical gloves and condoms. A comparative study on commercially available surgical gloves made of various base materials demonstrated that gloves made of Cariflex™IR latex offer mechanical protection comparable to Natural Rubber Latex gloves while being better than other synthetics in terms of comfort and equal, or even superior, to NRL gloves. Mechanical properties evaluated included tensile strength, modulus, and puncture resistance.

Introduction

Rubber has been employed in a large span of medical applications such as gloves, condoms, gaskets, tubing, and stoppers. Amongst rubbers, natural rubber (NR) has been a cost effective and high performing answer to many of the demands of the medical device industry. But in the 1980ies, there was an increase in natural rubber latex (NRL) sensitization and allergic reactions among patients and health care professionals. In rare cases, these allergic reactions can be fatal.

Because of these reports, the medical device community has been working to implement alternatives to NR and NRL. The main candidates for replacing NR/NRL in medical devices are synthetic elastomers due to the absence of any proteins linked to the allergenic risks.

However, such replacement has not been an easy pursuit. For example, we estimate that over 85% of all surgical gloves consumed today globally are still made of NRL. We will see later in this paper that our Cari*flex*™ Isoprene Rubber Latex, offering the expected but delicate balance of protection and comfort, is now established as the best alternative to NRL in surgical gloves.
While NR replacement has been somewhat easier to achieve in medical stopper applications, the industry is faced with new issues, such as fragmentation upon needle insertion (coring), unfavorable interaction with sophisticated drugs, inability to meet challenges posed by new packaging designs, increasing safety standards and comfort requirements etc. The halo-butyl rubber and standard polyisoprene (of the Ziegler-Natta type) that are currently widely used for medical closures do not allow designers to meet all such new requirements. One synthetic rubber successfully used to meet such new requirements is anionic isoprene rubber. Such a rubber, as of today, is solely offered by Kraton Polymers under the trade name of Cari*flex*™ isoprene rubber, or Cari*flex*™IR.

Cis-1,4-polyisoprene types

There are currently two types of synthetic polyisoprene. The most widely used industrial process to produce high-cis polyisoprene is Ziegler-Natta (ZN) polymerization; this process can yield synthetic polyisoprene with cis contents above 96%. The alternative is anionic polymerization, which leads to cis contents above 90%. The latter process is uniquely employed by Kraton Polymers in its Belpre Ohio facility to produce Cari*flex*™IR. A unique feature of Cari*flex*™IR is its extreme purity and consistently high quality, which greatly simplifies manufacturing and quality control[2]. An overview of the different types of isoprene rubber is presented in Table 1.

[2] Ph. Henderson, "From Isoprene Monomer to Synthetic Polyisoprene Latex and its Uses", Presented at the Latex conference, 4–5 December, Munich (2001)

Table 1: Polyisoprene production: different processes give different products

Natural Rubber	Ziegler-Natta IR	Cari*flex*™ IR (Anionic IR or Li-IR)
No catalyst	Titanium/Aluminum Catalyst	Alkyl-lithium catalyst
Wide Molecular Weight Distribution	Wide Molecular Weight Distribution	Narrow Molecular Weight Distribution
98+ % cis content	96+ % cis content	90+ % cis content
High gel content	High gel content	Intrinsically NO gel
Contains natural impurities	Catalyst residuals	Low impurity level
Produced as emulsion	Produced in organic solution	Produced in organic solution

This anionic polymerization chemistry yields a cleaner and clearer rubber than most other synthetic rubbers (Figure 1) and with virtually no gels (Figure 2).

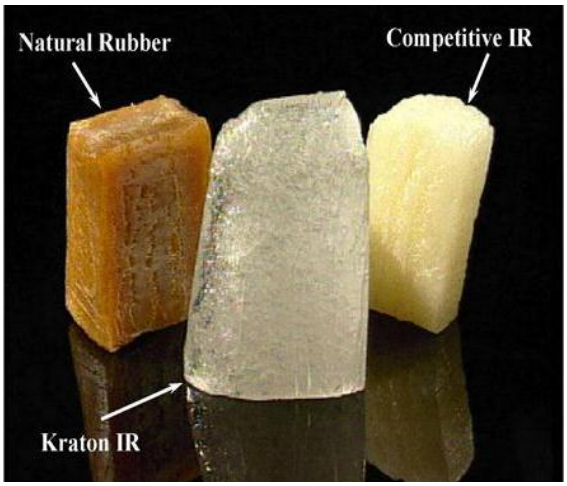


Figure 1: appearance of different rubbers

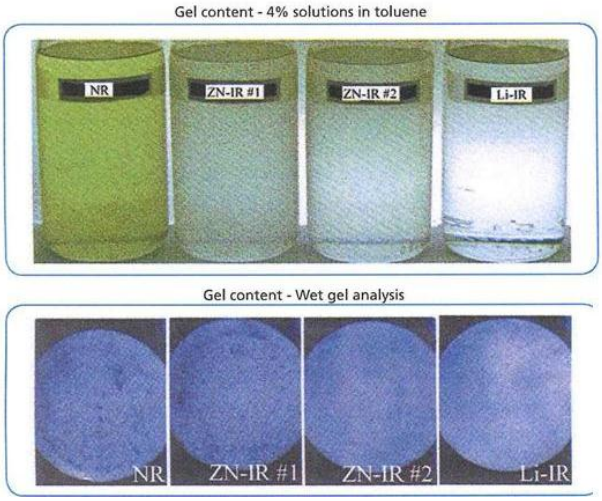


Figure 2: gel content of different rubbers

This paper compares anionic Isoprene Rubber to other synthetic rubbers by examining the materials through medical stopper and surgical glove application testing.

PART 1 - Performance in Medical Stoppers

In this section, we will compare the chemistry and performance of four rubber products that are currently used in medical stoppers, which include anionic IR, polymerized with an alkyl-lithium initiator; Ziegler-Natta IR, polymerized with titanium/aluminum catalyst; chlorobutyl rubber; and bromobutyl rubber. The criterion for the study was based on common medical stopper test protocols. The results will demonstrate that anionic isoprene rubber delivers a unique combination of advantages including the absence of natural rubber proteins present in NR, an odor-free formulation with low residual metals and no residual catalysts, low needle insertion force, and minimal risk of rubber fragmentation (coring) and medication contamination due to needle insertion.

Testing included Extractions (as measured by Turbidity, Foaming, Change in pH, Zinc, Potassium Permanganate-Reducing Substances, and Residue from Evaporation), Gas Permeability, Long term Aging, Gamma Ray Radiation, Needle Penetration Force, Leakage, and Coring.

Materials and Formulations

The types of rubbers and respective formulations selected in this testing represented a breadth of synthetic rubbers commonly used in the Medical Stoppers. All rubber samples had the necessary regulatory status for use in medical applications. The following is a general description of the rubbers and formulations tested:

Description	Designation
Anionic Isoprene	Cariflex™ IR0307
Anionic Isoprene	Cariflex™ IR0310
Ziegler-Natta Isoprene Rubber	ZN IR – A
Ziegler-Natta Isoprene Rubber	ZN IR – B
Ziegler-Natta Isoprene Rubber	ZN IR – C
Chloro-Butyl Rubber	Cl-IIR
Bromo-Butyl Rubber -A	Br-IIR-A
Bromo-Butyl Rubber –B	Br-IIR-B

Detailed formulations for the compounds can be found in Table 2. Target hardness was approximately 30 Shore A.

Table 2: Stopper formulations for the different rubbers evaluated

Formulations	IR0307 Control 1	IR0310	ZN-IR-A	ZN-IR-B	CL-IIR	Br-IIR-A	IR0307 Control 2	ZN-IR-C	Br-IIR-B
Cariflex™ IR0307	100						100		
Cariflex™ IR310		100							
ZN-IR-A			100						
ZN-IR-B				100					
ZN-IR-C								100	
Cl-IIR					100				
Br-IIR-A						100			
Br-IIR-B									100
Stearic Acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	
Carbon Black	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	
TiO2	3	3	3	3	3	3	4	4	4
Silica	10	10	10	10	10	10	10	10	
Calcined Clay	20	20	20	20	30	30	60	60	80
Perhexa-25B	2.9	2.9	2.9	2.9					
MgO					0.2	4			
ZnO					5				
n-butene-isobutylene copolymer									5
Perhexa-V							2.9	2.9	
Hexamethylene-diaminecarbamate									0.75
Zincdibutyl-dithiocarbamate					2				
Sulfur						0.7			
Total (phr)	136.7	136.7	136.7	136.7	151	148.5	177.7	177.7	189.8
Vulc. temp. (° C)	170	170	170	170	170	170	170	170	180
Vulc. time (min)	8	8	8	8	15	8	8	8	15
Hardness (JIS A)	30	29	31	32	33	36	34	32	43

Peroxides used in this study were 1) Perhexa-25A, n-Butyl 4,4-di (t-butylperoxy) valerate and 2) Perhexa-25B, 2,5-Dimethyl-2,5-di (t-butylperoxy) hexane. The curative for the Br-IIR was a combination of Sulfur/Mg and was selected because of its high rate of reaction. Stearic Acid was used as a co-agent for metal oxide to promote vulcanization. Carbon black and TiO_2 were used as coloring agent. Silica was used as reinforcement; wet silica (pH>7) works best for peroxide vulcanization. Calcinated clay was used as reinforcing filler and cost reduction. MgO, ZnO, Zincdibutyldithiocarbamate, Hexamethylenediaminecarbamate were used to accelerate vulcanization of Cl-IIR. N-Butene-isobutylene copolymer was suggested by a supplier for Br-IIR.

Extraction Testing

Extraction testing was used as a means to measure elements and other leachable materials that potentially come from the stopper and mix or even interact with medications. Extraction testing was applied per the Japanese Pharmacopeia 7-03 (XV revision 2006). The Japanese Pharmacopeia 7-03 was selected because it is considered the most stringent extraction test protocol in the medical device industry.

All stoppers made in each formulation (described in Table 2) were fully cross-linked, then washed in boiling water to remove releasing agents, degraded cross-linking byproducts, dust etc. and then dried to room temperature.

To make the Test Solution, the washed stoppers of a given formulation were placed in a glass container with water equal to 10 times the mass of the stoppers. The containers were sealed with suitable closures, then autoclaved at l21° C for 1 hour. After autoclaving, the glass containers were cooled to room temperature, removed from the Autoclave, opened, and the solution drained off and used as a *Test Solution*. This procedure was repeated with no rubber stoppers to create the *Blank Solution*.

The following tests were performed using these two "Test" and "Blank" solutions:

a) Turbidity:
The test solution was observed for clarity and colorlessness by ultraviolet-visible Spectrophotometer at wavelengths of 430 nm and 650 nm. Both the Test Solution and Blank Solution needed to be at least 99.0% clarity to "Pass".

b) Foam test:
5 ml of the Test Solution was placed in a glass-stoppered test tube (I.D. = 15 mm, length = 200 mm). The test tube was shaken vigorously for 3 minutes and foaming observed. If either a) foam did not occur or b) occurred, but disappeared within 3 minutes, the sample was deemed "Pass". Otherwise, it was considered a "Fail".

c) pH:
A Potassium Solution was prepared by dissolving 1.0 g of potassium chloride in 1000 ml of water. 1 ml of the Potassium Solution was added to 20 mL of both the Test Solution and the Blank Solution. The pH was measured for both solutions, the difference calculated, and reported. If the difference was greater than 1 pH point, then the sample was considered to have "Failed".

d) Zinc:
A Standard Zinc Solution (for Atomic Absorption Spectrophotometry) was prepared by taking 1.0ml of Standard Zinc Solution (Zn;0.01mg/mL,10ppm), and adding diluted nitric acid to make exactly 20 ml. The Zn content of this standard solution was 0.5 ppm. Then 10 ml of dilute nitric acid (1 in 3) was added for every 1 ml to make the Standard Zinc Solution.

The Zinc Sample Solution was made by measuring exactly 10 ml of a Standard Solution and adding water to make 20 mL of Zinc Sample Solution (one mL of this solution contained 0.01 mg of zinc).

Atomic Absorption Spectrophotometry was done on both the Zinc Sample Solution and the Standard Zinc Solution using the following conditions:

Gas:	Combustible gas-Acetylene.
Supporting gas:	Air.
Lamp:	Zinc hollow-cathode lamp.
Wavelength:	213.9 nm.

The absorbance of the Zinc sample solution was then compared to a Standard Zinc Solution for atomic absorption spectrophotometry. From this comparison the final Zinc level for the particular stopper was determined.

e) Potassium Permanganate-reducing Substances:

100 mL of the test solution was put in a glass-stoppered Erlenmeyer flask. 10.0mL of 0.002 mol/L potassium permanganate and 5 mL of dilute sulfuric acid were added and brought to a boil for 3 minutes. It was cooled and then had 0.10g of potassium iodide mix in shaken by hand. The flask was allowed to stand for 10 minutes and titrate with 0.01 mol/L sodium thiosulfate (indicator: 5 drops of starch). The test was repeated with the blank solution. Note: The difference of 0.002 mol/L potassium permanganate between the Test Solution and the Blank Solution had to be less than 2.0 mL for the rubber to pass the Standard.

f) Residue on Evaporation:

To measure Residue on Evaporation, 100 mL of the Test Solution and Blank Solution was evaporated on a water bath to dryness, and the residue dried at 105°C for l hour. The mass of the residue is required to exceed more than 2.0 mg for the Test Solution. If 2 mgs was not obtained for the Test Solution, then the preparation was repeated until a combined amount of 2.0 mg was obtained. There was no minimum required for the Blank Solution.

A UV spectrum from an Ultraviolet Visible Spectrophotometer was run on the residue from the Test Solution and the Blank Solution between 220 nm and 350 nm. Differences recorded and to be not more than 0.20.

The results of extraction testing are summarized in Table 3. Ziegler-Natta IR-A and Ziegler-Natta IR-C failed to meet the $KMnO_4$ reducing substance requirement (=< 2.0 ml). This makes these two formulations unsuitable for rubber stoppers under this protocol. Ziegler-Natta IR-B was at 1.7 ml, thus offering minimal safety margin versus the maximum 2.0 ml threshold. Though still passing the standard, this formulation may be considered by manufactures as a possible risk to failing this test at some later date.

Bromobutyl rubber Br-IIR-B gave the lowest level of extracts and passed JP specs.

Both IR0307 control 1 and IR0307 control 2 gave consistent results across all extraction testing and passed all of JP specifications. This performance by the anionic IR rubber is believed to be from the polymerization process itself, which has virtually no opportunity for residual catalyst. And from the lack of residual catalyst, low levels of extraction can be expected.

From this testing, both the anionic IR and Butyl rubbers are good candidates for medical stoppers falling under the Japanese pharmacopeia.

Table 3: Results of extraction testing

Test Parameter	Unit	Formulation								
		IR0307 Control 1	IR0310	ZN-IR-A	ZN-IR-B	CL-IIR	Br-IIR-A	IR0307 Control 2	ZN-IR-C	Br-IIR-B
Turbidity	Pass/Fail	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Foam test	No foam after 3min	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
pH delta	pH= +/-1.0	0.43	0.41	1	0.77	0.13	0.18	0.49	0.53	0.18
Zinc (mg/l)	< 1.0	ND*	ND*	ND*	ND*	0.11	ND*	ND*	ND*	ND*
$KMnO_4$ Reducing substance(ml)	=< 2.0	1.24	1.32	2.27	1.77	0.62	0.75	1.40	2.05	0.25
Residue on evaporation (mg)	=< 2.0	0.9	1.2	2.1	1.6	0.5	0.4	1.1	1.3	0.8
UV spectrum	Pass/Fail	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

* ND = Not Detectable

Gas Permeability

Oxygen and moisture vapor permeation for a stopper is critical when working with medications that are susceptible to degradation upon exposure to non-inert gases.
Although gas permeability is known to be lower in butyl rubbers than in polyisoprene rubbers, we have included such testing in our investigations for reference. Procedures used were JIS K6275-1 for Oxygen and JIS K7129 for Moisture Vapor transmission.

Of the three rubber types tested (Table 4), the Halogenated butyl rubber performed as predicted, having the lowest permeation of both oxygen and moisture. Butyl rubber is well known for its barrier properties, which come from the tight packing of its linear molecular structure.
There was no significant difference in gas permeability between the two other rubbers tested (IR307 and ZN-IR-C)
The significance of this testing is that when barrier properties for the stopper is critical, of the three rubbers tested, butyl rubber offers the best barrier properties by a significant margin.

Table 4: Gas permeability of 3 different rubbers

	Units	IR0307	ZN-IR-C	Br-IIR-B	Test Method
Oxygen Permeability	cm3/m2-day-atm	752	740	12.1	JIS K6275-1 @ 23 °C
	x 10^{-12} mol/m2-s-Pa	3.84	3.77	0.0617	
Moisture Vapor Transmission Rate (MVTR)	g/m^2-day	0.32	0.3	0.01>	JIS K7129 @ 23 °C, 85 %RH

Aging Test

In the design of Medical Stoppers, integrity of the rubber over time is an important part of design performance. A common method to investigate the performance of a stopper over time is to accelerate the aging by heating the sample and measure a property indicative of change and pertinent to the application. For this study, stoppers were heat cycled and subsequently tested for extractables to simulate and accelerate aging. Changes in extractable levels were viewed as indication of the stability of the rubber over the long-term.

The test procedure used for this study was to cycle the samples for 30 days from 12 hours at 0°C and 80%RH to 12 hours at 5° C and 30%RH (Table 5). Extractions were then made on the stoppers per JP 7-03 (XV revision, 2006) and tested for Foaming and Potassium Permanganate-Reducing Substances as per the above Extraction Testing.

The results of the $KMnO_4$ tests performed before and after aging are given in Table 5. Ziegler-Natta IR-A and Ziegler-Natta IR-C exceeded the limit again. This could be expected since extractables after aging are typically at the same or higher level than before aging. Ziegler-Natta IR-B, was now even closer to exceeding the =<2.0 ml limit, posing risk of high rejection rates to a manufacturer who would nevertheless consider using such material.
The butyl rubbers, though passing the test and still with the lowest extractables after aging, do show the largest increase in extractables of all rubbers tested. While absolute levels are low, the slow release of impurities over time is not desirable for the packaging of medicines.

IR0307 control 1 and IR0307 control 2 have low initial levels of extractables and change little in extractables in this accelerated aging. These data suggest good chemical integrity of the rubber over time and makes it a good candidate for the long term performance of a medical device.

Table 5: Test results after aging of different rubbers

Test	Parameter	IR0307 Control 1	ZN-IR-B	CL-IIR	IR0307 Control 2	ZN-IR-C	Br-IIR-B
Foam Test before and after 30 days heat aging	No foam after 3 min	Pass	Pass	Pass	Pass	Pass	Pass
$KMnO_4$ Reducing subs. (ml) : 0 day	=< 2.0	1.24	1.77	0.62	1.40	2.05	0.25
$KMnO_4$ Reducing subs. (ml) : 30 days	=< 2.0	1.38	1.95	1.1	1.45	2.15	0.85
% Change	%	11%	10%	77%	4%	5%	240%
Residue on evaporation (mg)	=< 2.0	0.8	0.8	1.2	1.1	1.1	0.9

Gamma Ray Radiation

Gamma Ray exposure is a common sterilization method for medical devices and is known to cause rubber in medical devices to lose properties with increased dosages. This is a concern for a stopper design. Testing in this study comprised of irradiating compression set buttons with gamma rays, then measuring changes in compression set as a function of dosage.

Though typical radiation levels for one round of sterilization is usually no more than 10-20 kGy, OEMs want the ability to re-sterilize product in case of a failed first cycle. Hence, gamma ray radiation testing is usually done in increments up to 50 kGy.

In this study, samples were exposed to gamma radiation levels of 10, 25, 50 kGy and then measured for Compression Set via JIS K6262 (Figure 3).

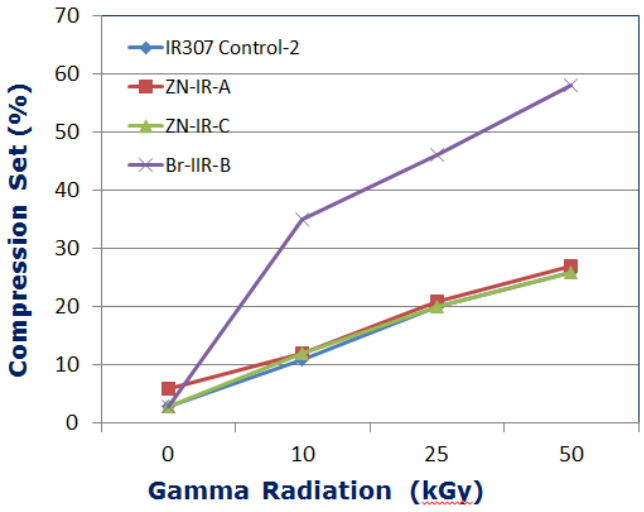


Figure 3: compression set as a function of radiation level for different rubbers

Results show that the bromobutyl rubber showed significant deterioration in compression set after gamma radiation, going from less than 5% to over 55%. All other rubbers (both anionic and Ziegler-Natta IR) showed less loss in compression set than the butyl rubber, only losing approximately 25% points (going from less than 5% to less than 30% compression set).

This loss in performance from Gamma Ray exposure by bromobutyl rubber poses a risk to any stopper made in this material. From this loss in properties, the stopper can potentially lose holding power in the vial should the vial be gamma sterilized. This would be a major concern to any designer for medical stoppers.

Mechanical Testing

Needle Penetration and Retraction Forces:
In the function of stoppers, the force needed to insert a needle is critical. If the force required is too high, the stopper will not find favor with the users from an ergonomic standpoint; it can also represent a safety risk. However, once inserted into the stopper, the force required to remove the needle shouldn't be too low to reduce the risk of a needle unwillingly slipping out (holding power).

In this testing, the forces were measured for two different needle designs (plastic and steel, Figure 4) as they penetrated the stoppers.

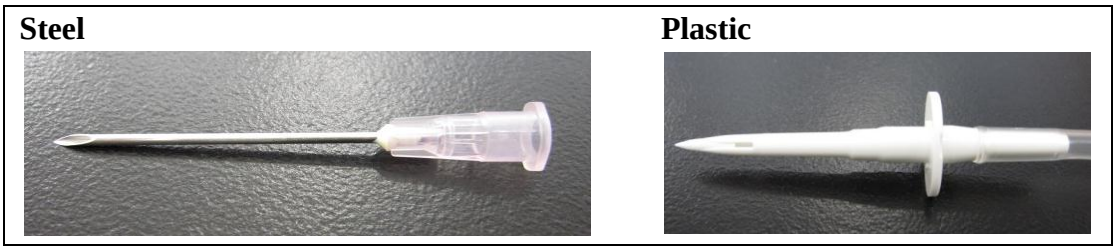


Figure 4: different needles employed to penetrate stoppers

To do this, stoppers were mounted on 50cc vials and then penetrated with the two different needles. The needles were 1) Steel (Terumo 18G x $1^{1/2}$) and 2) plastic (JMS b JY-A343L). Penetration speed was 200 mm/min. The forces were measured for both insertion and retraction.

Table 6: Insertion and extraction forces for two needles and different rubbers.

Needle Type	Type Force	Units	IR0307 Control-1	ZN-IR-B	Cl-IIR	Br-IIR-A	IR0307 Control 2	ZN-IR-C	Br-IIR-B
Steel	Insertion	Newton	4.3	3.9	6.5	9.1	5.5	7.4	7.2
	Retraction		3.3	3.4	5	5.7	1.2	5.1	5.3
Plastic	Insertion		43.3	39.8	44.2	98.7	46.1	51.3	71.3
	Retraction		23.2	42.5	35	83	38	60.5	52

Bromobutyl rubber stoppers require higher needle insertion forces than the chlorobutyl rubber and IR-based formulations (Table 6). In most cases, the retraction force is acceptable.

Leakage Test:

An important function of a stopper is to prevent leakage after inserting and retracting a needle. In this test, the stopper was 1) filled with water, 2) had a needle inserted, 3) the vial pressurized through the needle, 4) then de-pressurized through the needle, and 5) the stopper observed for any water leakage.

To do this, 10 cc vials were filled with 10 cc of water (Table 7). Then a steel (Terumo 18G x $1^{1/2}$) needle was penetrated through the stopper at 90 degree angle. 2 ml of water was then injected in the vial, and then 2ml of water draw out. The needle was extracted, and any water leakage observed and recorded.

All samples tested showed no leakage, indicating all re-sealed to test satisfaction. As leakage is a phenomenon with low incidence (but high potential consequences), it is not surprising that the test could not differentiate the various materials. The next test – coring – is more meaningful.

Table 7: Leakage testing of different stoppers

Needle	Test	Units	IR0307 Control-1	ZN-IR-B	Cl-IIR	Br-IIR-A	IR0307 Control 2	ZN-IR-C	Br-IIR-B
Steel	Liquid leaking	mg	0	0	0	0	0	0	0

Coring Test:

Coring is a term used when a needle is inserted into a cap and, while doing so, cuts and deposits rubber particulate from the stopper into the vial. This test was conducted in conjunction with the needle penetration test. Particulate from this action was then captured and photographed.

The test entailed filling 10 cc vials with 10 cc of water. Then a steel (Terumo 18G x $1^{1/2}$) needle was penetrated through the stopper 2 times at 45° and 90° angles (Table 8). The water was then filtered and fragments filtered off. The incisions and fragments were then photographed

In measuring the fragments from needle insertion, all stoppers had some rubber fragments from coring with the exception of IR0307 Control 1 and IR0307 IR Control 2. These two materials had "zero" rubber fragments.

This means that of all the formulations tested; only the anionic IR formulations stoppers would not contaminate the solution in the vial.

The pictures of the stoppers (see Figure 5) also show in a qualitative manner, yet very clearly, that the stoppers made from Cariflex™ polyisoprene rubber are significantly less damaged than the others, which is probably a manifestation of the legendary resealability of Cariflex™ IR.

Table 8: Coring of different stoppers

Testing Items	Units	IR0307 Control-1	ZN-IR-B	Cl-IIR	Br-IIR-A	IR0307 Control-2	ZN-IR-C	Br-IIR-B
Coring (90 deg.)	Number of Fragments	0	2	3	4	0	0	3
Coring (45 deg.)		0	4	7	7	0	3	5

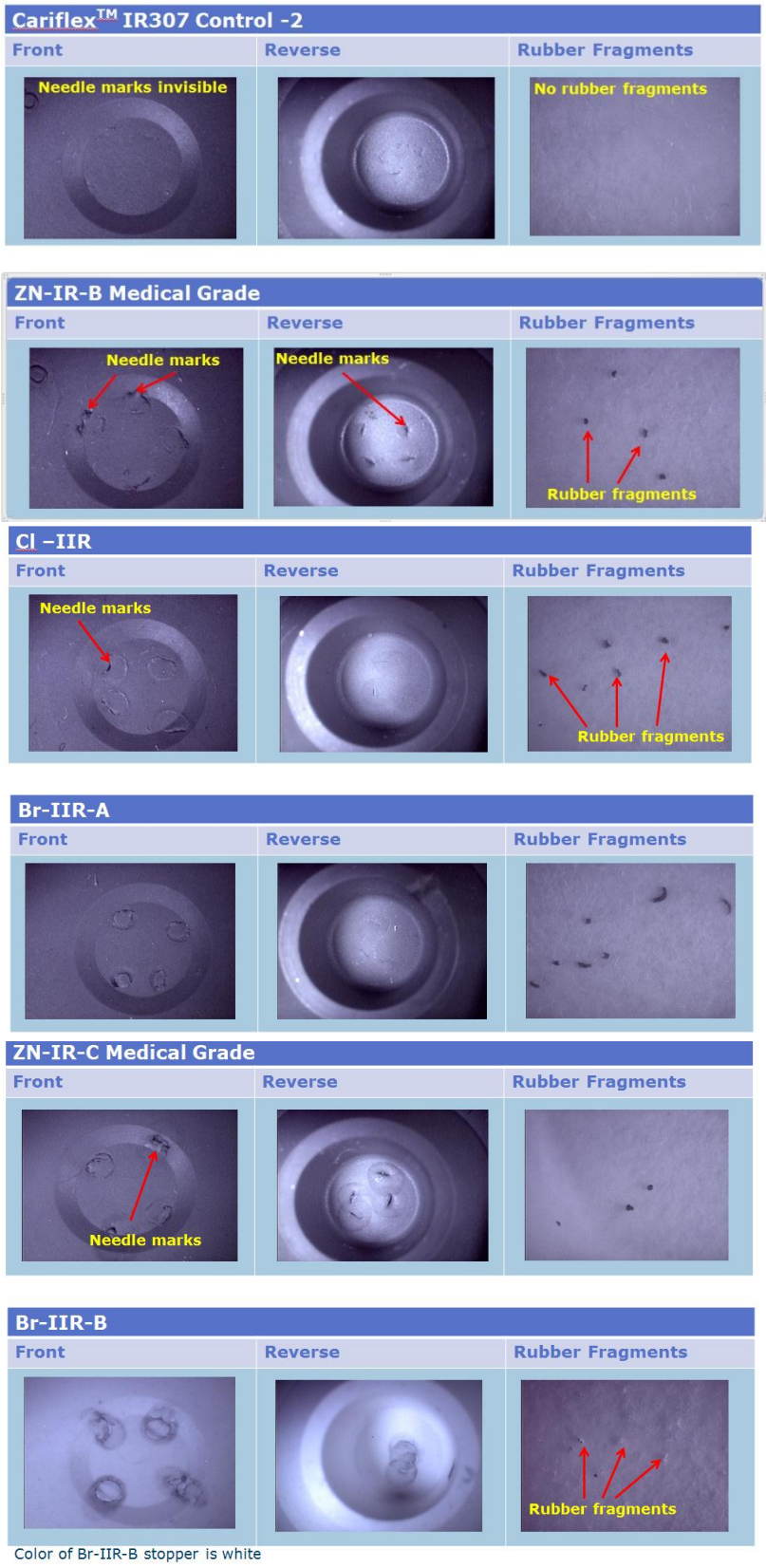


Figure 5: Examples of coring of different rubbers

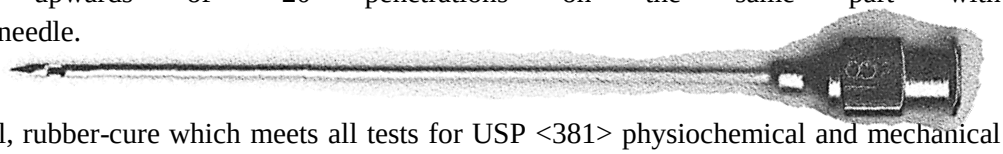
Specific example

One of Kraton's customers now exploits the unique features of our Cariflex™ polyisoprene products to manufacture a number of components used in a new medical device.

The new device has a locking mechanism that helps prevent the occurrence of drug leakage, a major industry concern, which has historically put both patients and health care workers at risk of inadvertent drug exposure. In some cases, certain drugs, in very small concentrations, can be hazardous to humans and animals. FDA approval is anticipated in the spring 2013 !

The new device offers the following features:

- Leak proof
- Compatible with chemotherapy drugs amongst others
- Resists coring and fragmentation and has raised the bar for this device. Withstands upwards of >20 penetrations on the same part with an 18 gauge needle.



- Conventional, rubber-cure which meets all tests for USP <381> physiochemical and mechanical testing (incl. penetration, fragmentation and self-sealing), which is twice as rigid as the Japanese Pharmacopeia
- User friendly
- Increases provider confidence while reducing anxiety levels
- Requires lighter-weight, less costly, protective gear
- Improves efficiency of medical providers – less preparation time

Conclusions about use in medical stoppers

There are several conclusions that can be reached from this study. There is no one rubber that is clearly better in all categories for a rubber stopper. One may have good performance in one area, but lack in another. So looking at each rubber:

Butyl rubber has the benefits of superior barrier properties and good chemical performance in chemical extraction, but it has poorer performance in stability from gamma sterilization and shows signs of decline in long term aging.

Ziegler-Natta Isoprene Rubber shows similar properties to Anionic rubber when exposed to gamma radiation and in Needle penetration forces (for some formulations). But Ziegler-Natta Isoprene Rubber formulations in this testing fail or come close to failing the Japanese standard for extractions. This rubber is, at best, a poor candidate for rubber stoppers and possibly all medical devices that are covered under this standard.

Anionic Isoprene rubber showed in this study to be 1) one of the cleanest rubber tested by way of extractables, had one of the best performances for long term aging 2) showed equal to or better retention of compression set from gamma sterilization, 3) and was superior to all other rubbers tested in not coring and causing rubber particles to be potentially introduced into the proposed solution. The pictures also show that stoppers based on Cariflex™ anionic polyisoprene are the least damaged by a needle puncture, which is a visual manifestation of the known resealability properties of Cariflex™ polyisoprene rubbers.

In summary, other than when barrier properties are a must in a stopper design, anionic Isoprene showed the best combination and, in some areas, superior properties in medical stoppers to the other rubbers in this study when tested under Japanese medical standards.

PART 2 - Performance in Surgical Gloves

The majority of surgical gloves are still manufactured from natural rubber latex. However, in the race to reduce patient and medical staff allergy risks, a growing number of hospitals aim to eliminate products made from natural rubber, including surgical gloves. Examples of the alternative synthetic materials used today in surgical gloves include polychloroprene (CRL) and polyisoprene.

However, replacement of natural rubber latex surgical gloves by synthetic alternatives has caused in the past some concerns regarding comfort and protection. Today, as high quality polyisoprene products are increasingly used in the healthcare world, such concerns are disappearing.

Introduction

For the manufacture of dipped goods, such as surgical gloves, the rubber needs to be available as an aqueous emulsion while IR production is solvent-based. Hence, for ZN-IR and Cariflex™ IR a secondary step is required which involves the emulsification of the rubber in solution into an oil-in-water system. A brief description of the process has been provided in a previous paper[3]. The so-called latex production process is designed to lead to synthetic lattices that mirror the key properties of NR latex, as is presented in Table 9 for Cariflex™ IR.

Table 9: Typical properties for Cariflex polyisoprene latex and NRL

Latex	Cariflex™ IR	NRL
Total solids content (wt.%)	65	Similar
Total rubber content (wt.%)	64	Similar
pH	11	Similar
Ammonia (wt.%)	0	0.2 – 0.8
Average particle size (micron)	1.1 -1.5	0.9
Mechanical stability (sec)	> 1500	> 900
Brookfield viscosity (mPa.s)	< 150	similar

Surgical gloves produced from either natural rubber or synthetic rubbers have different physical standards which they have to meet according to ASTM D3577-01a[4], summarized in Table 10. The physical properties are measured using ASTM D412[5].

[3] Ph. Henderson, "From Isoprene Monomer to Synthetic Polyisoprene Latex and its Uses", Presented at the Latex conference, 4–5 December, Munich (2001)
[4] ASTM D3577-01a, Standard specification for rubber surgical gloves
[5] ASTM D412, Standard test method for vulcanized rubber and thermoplastic elastomers - Tension

Table 10: Physical standards for surgical gloves according to ASTM D3577-01a. The physical properties are measured using ASTM D412.

Type	Before aging			After accelerated aging	
	Minimum tensile strength	Minimum ultimate elongation	Maximum stress at 500% elongation	Minimum tensile strength	Minimum ultimate elongation
	MPa	%	MPa	MPa	%
Natural Rubber	24	750	5.5	18	560
Synthetic Rubber	17	650	7.0	12	490

The ASTM requirements are mostly designed to guarantee sufficient protection of the surgeons and patients, but not so much to ensure comfort during use. An indication of comfort is given by the modulus at low elongation. Accordingly, in our study we have also investigated the moduli at lower elongation.

Replacement of natural rubber latex surgical gloves by synthetic alternatives has caused in the past some concerns regarding comfort and protection. For example, Thomas et al reported at the 2010 Annual Meeting of the American Academy of Orthopaedic Surgeons that latex-free gloves may be more likely to perforate than latex glove, especially in arthroplasty[6]. This was based on a field study involving only two different hospitals, two types of latex gloves, and three types of latex-free gloves.

The current study is aimed at systematically and quantitatively evaluating various types of commercial surgical gloves. It involves testing mechanical properties of four types of NR gloves, three types of anionic IR gloves, two types of ZN-IR gloves, and three types of polychloroprene gloves. Mechanical properties measured include those related to protection (tensile strength, tear strength and puncture resistance) and comfort (small deformation modulus, modulus at 500% elongation, and hysteresis).

Materials and Methods

Twelve different surgical gloves from different manufacturers were obtained, all size 7½. Four of these were manufactured from natural rubber (NR-A, NR-B, NR-C, and NR-D), three were prepared from Cariflex™ anionically polymerized polyisoprene IR401 latex (AnIR-A, AnIR-B, and AnIR-C), two were made from Ziegler-Natta poly-isoprene latex (ZN-IR-A, ZN-IR-B), and three from Chloroprene (CRL-A, CRL-B, and CRL-C).

Thickness of the gloves was determined according to ASTM-D3577, at the middle finger, at the palm, and at the cuff. Thicknesses were measured using a Marcator 1086 gage, equipped with a flat probe.
ASTM D412 was followed in measuring tensile strength, different moduli, and elongation at break. Dumbbells type C were cut from the gloves; one dumbbell from the palm, another one from the back of

[6] Thomas S, Aldlyami E, Gupta S, et al. Clinical performance of latex-free gloves: Is it safe for arthroplasty surgery? Paper #290. Presented at the 2010 Annual Meeting of the American Academy of Orthopaedic Surgeons. March 9-13, 2010. New Orleans

the hand, both in the direction of the fingers. For all tests an Instron type 3365 tensile bench was used, either with or without a long-range travelling extensometer.

Because for this type of elastomeric articles it is impossible to determine the real Young's modulus reproducibly, we measured the modulus in the range of 5 to 15 %extension by linear regression over this region and called this value small deformation modulus. In this way it was possible to obtain a reproducible measure for the modulus at small strains, which seems to be a valuable measure for the use of surgical gloves (important e.g. for finger movements).

The different polymers used to prepare the surgical gloves will have different strain induced crystallization behavior. When a material crystallizes and melts during a cyclic deformation, the material produces a substantial hysteresis loop: the hardening induced by crystallization during stretching is recovered during unloading. The area inside the loop represents the crystallization energy. Hysteresis curves were recorded by measuring the stress-strain curve up to a certain deformation at 500 mm/min, and subsequently recording the same curve when returning to zero strain, again at 500 mm/min. This procedure was repeated on the same sample for increasing maximum strains in sequential loops.

Tear strength of the samples was measured according to ASTM-D624[7]. Because it is known that use of the trouser shaped die often results in so-called knotty tearing, only the V-shaped specimen was analyzed. Samples were cut from a glove in the same way as was done for the tensile measurements: one from the palm of the hand, the other from its back. Tear strengths were measured at a grip separation speed of 500 mm/min.

Puncture resistance was determined according to ASTM F1342[8], and according to ASNZL 4179[9]. In the first test a puncture probe as given on the left side of Figure 6 was used, in the second the probe shown on the right side of Figure 6. The samples were kept between two metal plates, with chamfered holes. In case of ASTM F1342 the diameter of the holes was 6.4 mm, for ASNZL 4179 it was 10 mm.

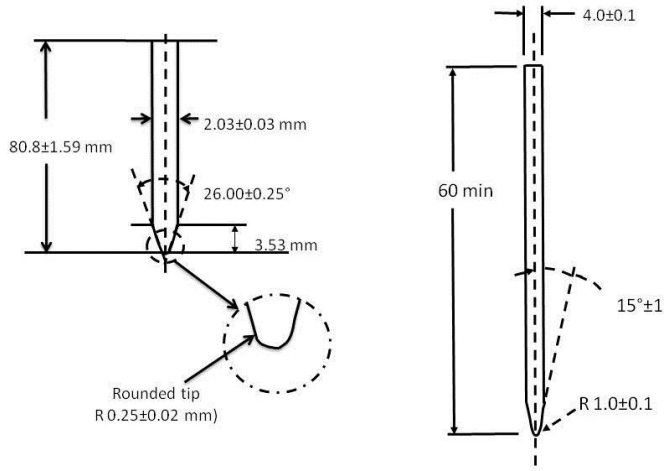


Figure 6: dimensions of the probes used to test puncture resistance. The left graph shows the probe used in ASTM F1342, the right one the probe of ASNZL 4179

[7] ASTM D624, Standard test method for tear strength of conventional vulcanized rubber and thermoplastic elastomers

[8] ASTM F1342, Standard test method for protective clothing material resistance to puncture

[9] ASNZL 4179, Single-use sterile surgical rubber gloves – Specification. Appendix YY, Requirement and test method for glove cuff rupture resistance

Results

Except for three types, thickness of all gloves was in the order of 200 micrometer. AnIR-B and ZN-IR-B were in the order of 250 micrometer, CRL-A was about 175 micrometer. All gloves were thickest at the finger, and thinnest at the cuff.

An impression of the crosslink density was obtained by swelling a small circular disk in toluene. The average molecular mass between two crosslinks was found to be between 6500 and 8500 for all samples. The degree of swelling decreases as the crosslink density increases, and at values as measured for the gloves, it is experimentally almost impossible to determine statistically significant differences[10]. The conclusion that can be drawn from the results is that all gloves are well cross-linked.

Tensile strength, moduli, and elongation at break:

Tensile measurements were made following the ASTM D412 standard cited in the surgical glove standard. Figure 7 contains typical example tensile curves of four of the gloves tested. As can be seen the tensile forces are all of the same order of magnitude for all samples (later in this report the NR sample will be discussed). The anionically polymerized polyisoprene has the highest elongation at break, the natural rubber sample the lowest. The curves indicate that the modulus at small strain is lowest for the anionically polymerized polyisoprene, followed by Ziegler-Natta polyisoprene and natural rubber. Chloroprene has a higher modulus. We will look at this aspect in more detail later in this section.

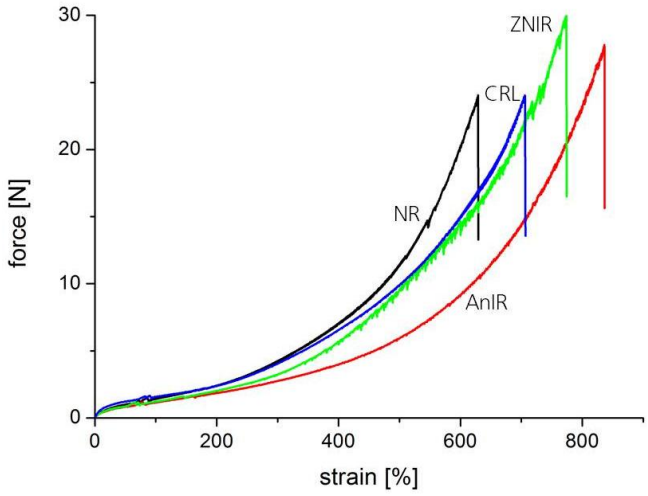


Figure 7: examples for tensile force vs. strain curves for four different types of gloves. (Strain was measured using the extensometer)

[10] J.L. Valentin, J. Carretero-Gonzalez, I. Mora-Barrantes, W. Chasse, K. Saalwachter, *Macromolecules*, **41**, 4714 (2008)

The tensile strengths of the different gloves are shown in Figure 8. The left columns give the results as measured using the long travelling extensometer to record the stress-strain curve. It is remarkable that the tensile strength of the NR gloves all were quite low, below the specification for unaged samples. The standard deviation of the NR results was also significantly larger as compared to the other types. The AnIR, ZN-IR and CRL glove types were all well within the specification for unaged synthetic surgical gloves.

It turned out that the reason for the unexpectedly low figures for the NR gloves was in the use of the extensometer. The right columns in Figure 8 represent the tensile strengths as measured without the extensometer. As can be seen from the comparison of the results obtained with and without the extensometer, only the NR samples are influenced by its use! This may indicate that NR gloves are susceptible to small disturbances while under stress.

For the AnIR gloves sample AnIR-B is somewhat stronger than the other two, which correlates with their thickness. For the chloroprene gloves CRL-A is stronger than the others, but this glove is the thinnest of the three.

When tested without the extensometer, all of the surgical gloves tested met the minimum tensile strength criteria for unaged samples set forth in ASTM standard: 24 MPa for NR, 17 MPa for synthetic gloves.

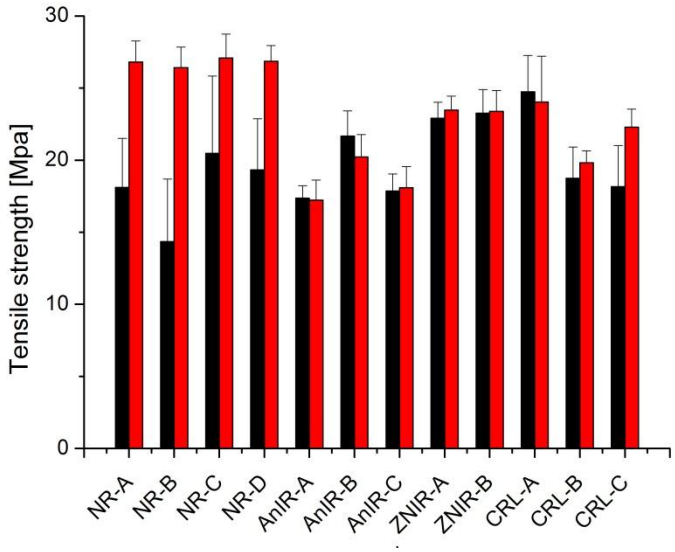


Figure 8: Left bars (black) indicate results obtained while using the extensometer, right bars (red) represent the results obtained without the extensometer. Error bars indicate one standard deviation

It was remarkable to observe that the break pattern of the NR and ZN-IR gloves was different than the pattern of the AnIR or the CRL types. This is shown in Figure 9. It is clear that the NR and ZN-IR types show an irregular break pattern, whereas the other types give a rather straight cut, perpendicular to the

direction of strain. The difference in break pattern for NR and ZN-IR can be an indication for that their tearing behavior is different than AnIR and CRL. The tearing propagation of the latter two may be faster.

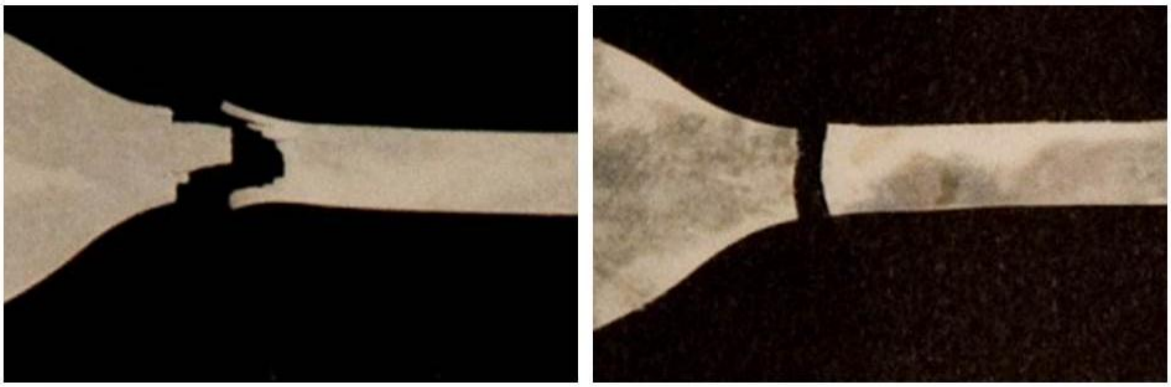


Figure 9: The left picture shows the break pattern of a NR sample, the right picture is a typical one for an AnIR gloves. ZN-IR showed the same pattern as NR, the CRL samples showed an identical pattern as AnIR. All samples were retained after stress-strain recovery

The other properties of the unaged gloves tested for, complying to ASTM D3577, are the modulus at 500% and the elongation at break. The elongation at break is also influenced by the use of the extensometer (Figure 10): with the extensometer the elongation at break is smaller. This can be explained by the fact that dumbbell broadens into a shoulder in the neighborhood of the grip, so here it can more than proportionally elongate.

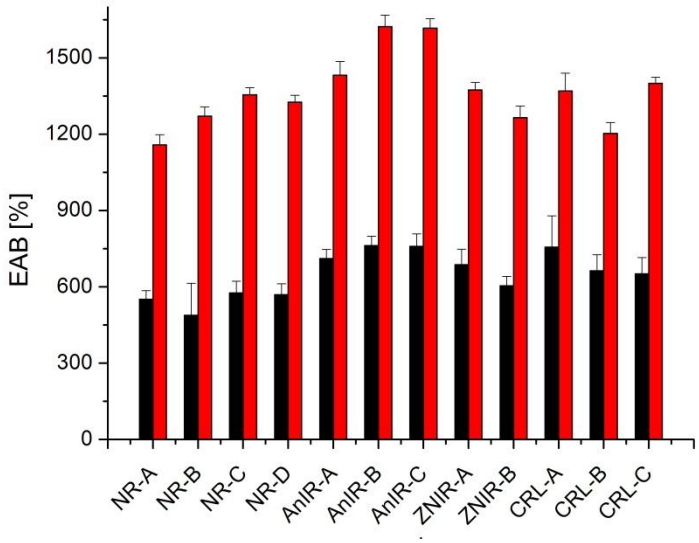


Figure 10: Elongation at break as measured with (left columns, black), and without (right columns, red) extensometer

When comparing stress-strain curves measured with and without extensometer, the latter seems to be extended towards higher strains, as compared with the former.

The modulus at 500% is shown inFigure 11, both using the extensometer and without. When looking at the results obtained using the extensometer, all the NR gloves fail the criterion of modulus500%<5.5 MPa. Of the synthetic gloves ZN-IR-B and CRL-B fail the specification for synthetic gloves <7 MPa. The results obtained without using the extensometer indicate that both NR and synthetic gloves are within their specifications.

The difference in modulus 500% as obtained with or without extensometer can be explained by the effect described above. The stress-strain curve appears to be extended towards larger strain values when using the extensometer. Therefore, the stress at 500% deformation as indicated by the measurement without extensometer is actually the stress at a lower deformation when using the extensometer.

The fact that the modulus 500% for NR is so much higher when measured with extensometer than without it can be explained by looking at 13 again. From this graph it is clear that NR and CRL show lower values for the elongation at break than AnIR. This implies that the stress-strain curve shows the steep increase already at lower elongations at break. In this steep region a small difference in elongation can make a large difference in force (and therefore modulus).

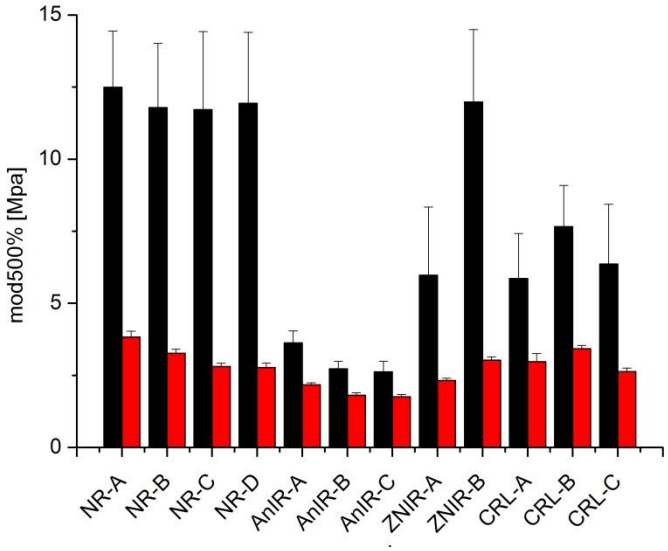


Figure 11: Modulus at 500% elongation as measured with (left columns, black), and without (right columns, red) extensometer

The question is which are the best/more accurate data, with or without extensometer? In principle the ones measured with the extensometer would be more reliable, because with this device only the isotropically deforming part of the dumbbell is taken into account. However, because the extensometer is attached to the dumbbell mechanically, by a tiny force, it may disturb the measurement of the tensile strength. So moduli are more accurately determined with the use of the extensometer, tensile strength may

be measured more reliably without it. Elongation at break is in principle more accurate using the extensometer, but for natural rubber its use may induce premature break.

It is important to note that, except when he is slipping his hands into the glove, a surgeon will probably never reach during common use the 17 or 24 MPa tensile strengths required for synthetic and natural rubber based gloves, respectively. The maximum stress at 500% elongation may also never be realized as typical use (bending fingers) only elongates the glove by 50 to maybe 100% (use region will be defined as the properties up to approximately 100%). Thus while the physical properties dictated by the ASTM standard are required for a glove to be labeled and used as a surgical glove, these are not indicative of glove comfort.

In general the comfort of a glove seems to be associated with its stiffness. Since the feel of a glove involves small deformations, the most likely parameter to characterize softness is the stiffness at small elongations. Ideally the Young's modulus would be the measure of choice to compare materials. Figure 12 gives the stress-strain curve at low deformations for the four types of material. From this graph it becomes clear that it is almost impossible to obtain a reliable value for the Young's modulus. Therefore we decided to compare moduli at small deformations (between 5 and 15 %) and call this the small deformation modulus.

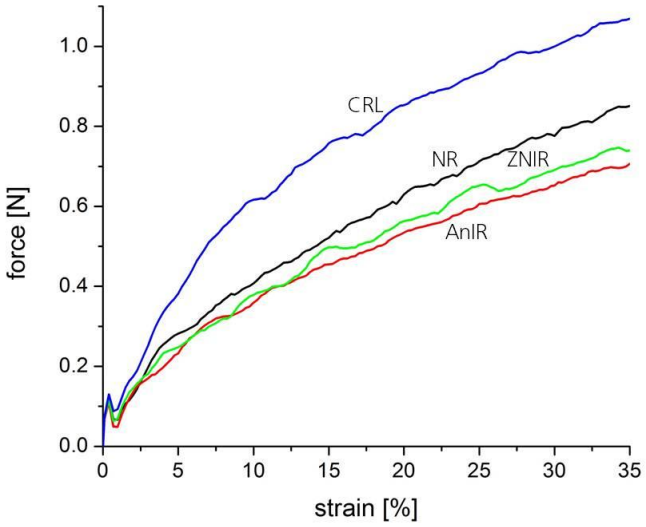


Figure 12: stress-strain curve at low deformation. The black curve is a NR sample, the red one an AnIR, the green one a ZN-IR, and blue the a CRL one

The moduli at very small deformation, at 25 and at 100% deformation are shown in Figure 13. The results in Figure 13 show that anionic polyisoprene is softer than natural rubber and Ziegler-Natta polyisoprene. Conversely chloroprene is the stiffest (highest Young's Modulus) and is generally considered the least comfortable.

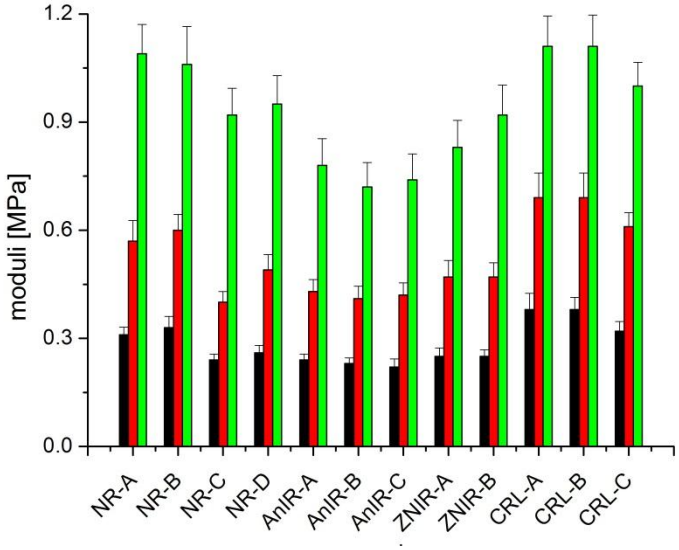


Figure 13: Small deformation modulus (black), 25% (red), and 100% (green) modulus

The degree of strain-induced crystallization of the glove in tension was measured via a hysteresis method. When a material crystallizes and melts during a cyclic deformation, the material produces a substantial hysteresis loop (see Figure 14 for raw plots). During the first cycle there is typically both non-recoverable and recoverable hysteresis, however, during the second and subsequent cycles most hysteresis is due to crystallization during stretching followed by melting during retraction. In other words, the hardening induced by crystallization is recovered during unloading. The area inside the loop represents the crystallization energy. Thus hysteresis experiments can be used as a measure of crystallinity during stretching, and to identify the strain at which crystallization begins.

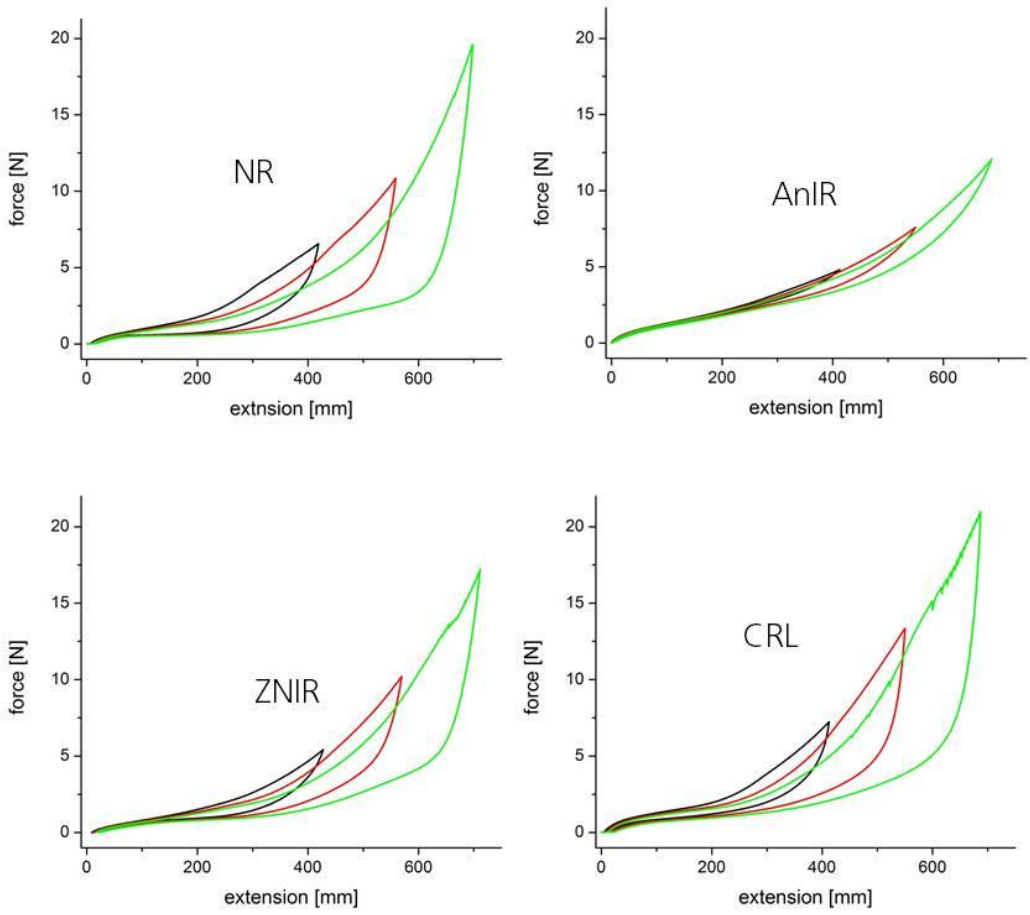


Figure 14: examples of hysteresis measurements. First loop was elongated 420 mm (black), the second 600 (red), and the final 700 mm (green).

Figure 14 shows typical examples of the hysteresis curves for the four glove types. It is clear that NR and CRL materials show the largest crystallization energy, with ZN-IR at an almost equal value. The gloves prepared from AnIR show the least hysteresis. This is in accordance with the cis contents of the materials: anionically polymerized polyisoprene typically shows cis percentages in the low 90's, whereas NR and ZN-IR have percentages in the upper nineties. The microstructure of the CRL polymer will mainly be trans.

Figure 15 shows the hysteresis loss values for the anionically polymerized polyisoprene gloves as well as gloves manufactured from NR, Ziegler Natta polyisoprene and chloroprene rubber at different elongations (based on grip to grip displacement). The data shown are based on the plots of the hysteresis data. This experiment differentiates the materials clearly by their base polymer type. The CRL and NR gloves show the most hysteresis, the ZN-IR gloves less, and then the AnIR. The curves for the AnIR gloves show only a small crystallization induced hysteresis loop. Furthermore, this loop only becomes visible at higher elongations as compared to other materials.

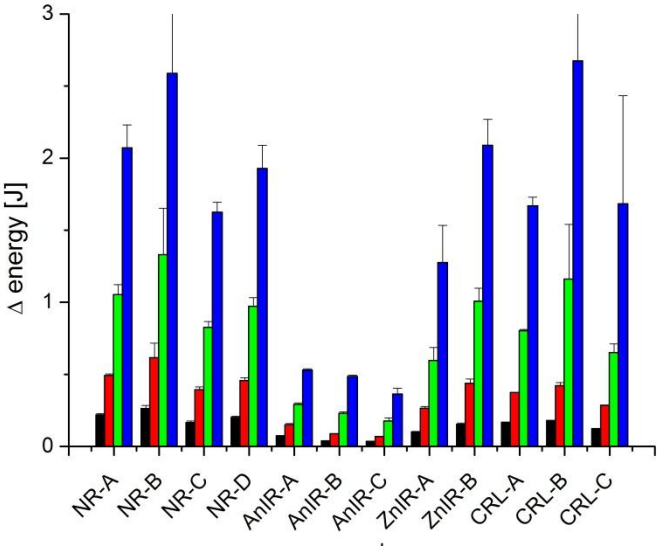


Figure 15: Energy loss due to hysteresis at 500 (black), 750 (red), 1000 (green), and 1250% (blue) deformation

At elongations of 50-100% AnIR is the only material not showing strain-induced crystallization. Thus the graphs suggest that only for AnIR the danger is absent that local crystallization in a glove during use negatively affects comfort.

Tear strength:

Tear strength of the gloves was measured according to ASTM D624, using the V-shaped die. Results are shown in Figure 16. For the NR samples the results seem to be very similar: all four have values around 50 kN/m, allbeit that NR-C is somewhat lower. The AnIR all three show consistently values of about 25 kN/m. For the ZN-IR samples the variation is larger: ZN-IR-B shows a tear strength of about 50 kN/m, very similar to NR, whereas the value obtained for ZN-IR-A is considerably lower. Because the microstructure of ZN-IR is very similar to that of NR, on beforehand it was expected that mechanical properties including tear strength, would be very similar as well.

The CRL samples also show a somewhat mixed picture, with CRL-A on the same level as the AnIR samples, and CRL-B and CRL-C having lower tear strength values of about 20 kN/m.

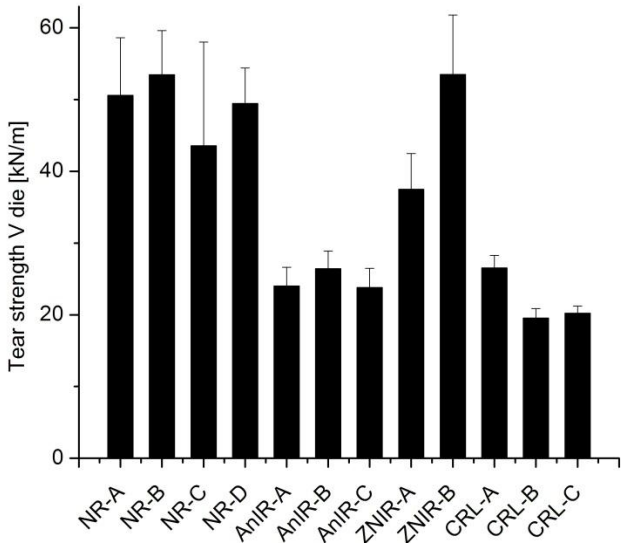


Figure 16: Tear strength using the V-shaped (type C) die

Bueche[11] states that tear strength is not dependent on tensile strength as such, but it is the energy furnished to the rubber in extending it to its maximum elongation that is important. So not only the strength of the material but also its modulus and elongation are involved. However, calculating energies from the stress-strain curves revealed that they are very similar for all glove types. The AnIR types even gave slightly higher values than the others.

Tear strength is a complicated phenomenon, which consists of tear initiation and tear propagation. A tear may be initiated by a small hole created by a puncturing force. The tear measurements as described here only measure tear propagation. The lower value measured for AnIR and CRL is consistent with the break pattern observed during the tensile strength measurement (Figure 9).

Puncture resistance:

The puncture resistance of the gloves were tested in two ways, using two differently shaped tips, and two holes having different diameters.

Results from the ASTM F1342 tests are shown in Figure 17. All puncture forces measured are between 3.7 and 5.5 N and vary within all product groups. According to the ASTM F1342 when the elongation exceeds 20 mm the test should be stopped to prevent damage to the test setup. However, because we took precautions for this, we recorded the puncture force at puncture.

The elongation at which puncture occurs is very similar for almost all gloves, except for two AnIR ones, which show a larger elongation at puncture.

[11] F. Bueche, "Physical properties of polymers", Interscience Publishers (1962)

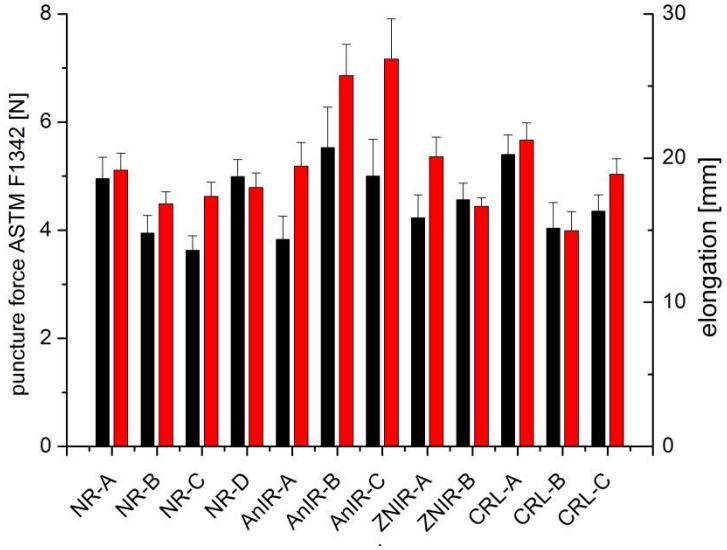


Figure 17: Puncture resistance according to ASTM F1342. Bars on the left (black) represent the puncture force, bars on the right (red) represent the elongation at puncture.

The best way to look at puncture resistance may be to compare the energy it takes to puncture the material. Below the values for the two types of puncture tests carried out are given. From these results it is clear that two out of three of the AnIR and one of the CRL gloves are able to absorb most energy before they become punctured. The results of Figure 18 indicate that it is possible to manufacture gloves from Cariflex™ IR401 having better possibility to adsorb puncture energy.

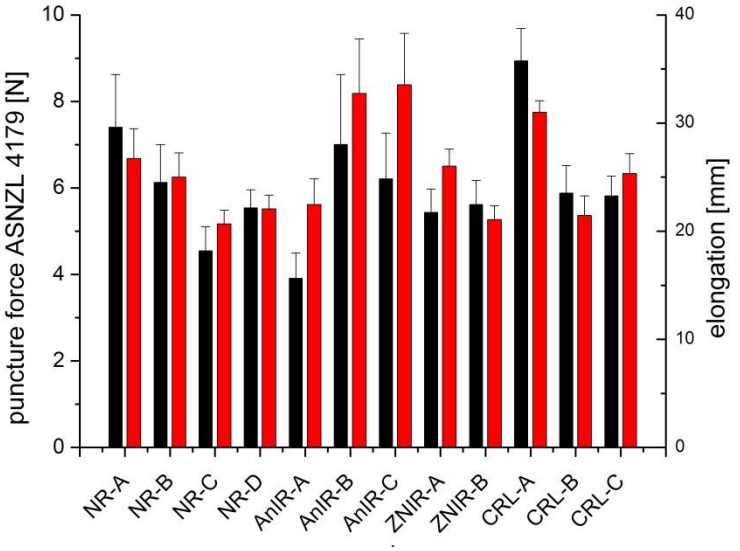


Figure 18: Puncture energy as determined according to ASTM F1342 (black) and ASNZL 4179 (red)

Conclusions about use in surgical gloves

Twelve different gloves, produced from four different types of material were evaluated with respect to their mechanical behavior.

It was shown that all gloves met the ASTM standard for surgical gloves. However, when the extensometer was used, tensile strength of the Natural Rubber gloves was below the specification for all four samples. Thus, NR seems to be susceptible to small disturbances when under stress. AnIR and CRL suffer from easier tearing propagation than NR and ZN-IR, but sustain higher or equivalent puncture energy, which may be related to tear initiation. Basis these data we infer that all glove types studied offer comparable mechanical protection.

All four types of material show hysteresis when cycling through force-extension loops. For the anionically polymerized polyisoprene the hysteresis is the least, indicating strain induced crystallization is less. The hysteresis graphs suggest that only for AnIR the danger is absent that local crystallization in a glove during use negatively affects comfort. Small strain modulus is lowest for AnIR, medium for NR and ZN-IR, and highest for CRL. Summarized, we infer that gloves prepared from AnIR offer better comfort.

Acknowledgements

- **The Kraton Innovation Center of Tsukuba, Japan, and Advantage Science, 3rd party laboratory in Japan, for driving and performing the medical stopper study.**

- **The Kraton Innovation Center of Amsterdam for driving and performing the surgical glove study.**