

exposed to 20-w. cool white fluorescent light in the presence of air, for a period of 2 or 3 days. In the course of this investigation it has been found that when an aqueous solution of promethazine hydrochloride of similar concentration is exposed to sunlight for longer periods of time, phenothiazine is one of the major degradation products. After extraction of the aqueous solution, this compound was identified by thin-layer chromatography and by its infrared spectrum.

SUMMARY

A procedure has been developed for the analysis

of promethazine hydrochloride in syrups. Column chromatography is combined with extraction to separate the active ingredient from interfering degradation products and excipients. Phenothiazine has been identified as one of the degradation products of promethazine.

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—Technical Articles—

Evaluation of the Suitability of Butadiene-Acrylonitrile Rubbers as Closures for Parenteral Solutions

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The sorption, leaching, tensile, and other properties of a series of butadiene-acrylonitrile rubbers from the medium-high acrylonitrile group were evaluated to determine the suitability of this copolymer system as elastomer closures for multiple-dose vial injectable preparations. These elastomers were found to exhibit considerable sorption of antibacterial preservatives from solution and leaching of extractives to the solutions when compared with a butyl rubber control. Partial identification of the leached materials was possible by chemical analysis. By reducing the amount of accelerator in one of the elastomer formulations by 25 per cent, a 35 per cent reduction in the amount of extractive leached from the elastomer resulted. This rubber formulation also exhibited a lower tensile strength and greater ultimate elongation. The butadiene-acrylonitrile elastomers possessed very low porosity and exhibited a low degree of water vapor transmission.

THERE HAS been considerable development in elastomer chemistry and technology during the last two decades, and a variety of synthetic elastomers are now in common use. A few of the more important uses of elastomers by the pharmaceutical industry are as packaging materials, surgical gloves, tubing for medical use, and vial closures.

These materials make excellent closures for multidose vials containing parenteral solutions because of their unique combination of prop-

erties—namely, pierceability and resealability (1). Unfortunately, the favorable qualities are also accompanied by various undesirable characteristics. It has long been known that rubber closures may yield substances to the preparation for which it is used as a stopper, a property known as leaching (2, 3). The closure can also sorb components from the preparation (3). In addition, it has been reported that materials can be lost by vapor transmission through the closure, chemical incompatibility between the product and closure could take place, physical instability of the elastomer could result, and coring or cutting away of rubber particles by the hypodermic needle is a frequent occurrence (1, 4, 5-7).

It is evident from the foregoing brief literature review that most of the studies appearing in the

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TABLE I.—COMPOSITION OF BUTADIENE-ACRYLONITRILE COPOLYMERS^a

1002	1022	1032	1042
Butadiene	Butadiene	Butadiene	Butadiene
Acrylonitrile	Acrylonitrile	Acrylonitrile	Acrylonitrile
Mono and dioctylated diphenyl- amines mixture	DTBPC ^b	DTBPC ^b	Mono and dioctylated diphenyl- amines mixtures
Sodium salt of a fatty acid	Sodium salt of a fatty acid	Rosin acid soap	Alkyl aryl sulfonic acid salt

^a In addition to the components listed above, sodium and potassium salts, mercaptans, sulfates, peroxides, fatty acids, amines, and disproportionated rosins are present in these copolymers in amounts of 1% or less. ^b 2,6-Ditertiary butyl *p*-cresol.

literature to date have dealt with factors affecting sorption, leaching, and various other properties of several natural and synthetic elastomeric products (1–12). Recently, some information has been presented concerning the influence of mylar, silicone, and epoxy linings on the sorption and leaching tendencies of closures (1, 13). However, except for these reports, there has been very little information presented in the literature regarding the development of rubber closures that would meet the broad and diversified requirements of the pharmaceutical industry.

The present study was undertaken to evaluate the sorption, leaching, and physical properties of a group of elastomers not commonly used as closures for parenteral multiple-dose containers. It was also the intent of this study to explore ways to improve the properties of these elastomers by formulation modification, if the results indicated certain shortcomings for use as closures for multiple-dose vials. The long-range objective of the investigational program is to develop a closure which will possess the major characteristics demanded by the pharmaceutical industry, namely, be nonadditive, nonsorptive, non-reactive, and yet possess the requisite physical properties needed for satisfactory use as a closure for multiple-dose parenteral preparations.

EXPERIMENTAL

Materials

Elastomers.—The elastomers selected belong to the nitrile rubber group and are butadiene-acrylonitrile copolymers.¹ Four of these formulations, coded 1008, 1009, 1010, and 1011, were employed. These were identical in composition, except for the antioxidants and emulsifying agents which are different in each case (Table I). A representative formula is as follows: butadiene-acrylonitrile copolymer, zinc oxide, sulfur, channel black, di-(2-ethyl hexyl)phthalate, diethylene glycol, tetraethylthiuram disulfide,² tetramethylthiuram disulfide,³ stearic acid.

¹ Marketed as Hycar by the B. F. Goodrich Chemical Co., Cleveland, Ohio.

² Marketed as Ethyl Tuads by the R. T. Vanderbilt Co., New York, N. Y.

³ Marketed as Methyl Tuads by the R. T. Vanderbilt Co., New York, N. Y.

The respective nitrile rubber present in each elastomer compound is as follows:

Elastomer Compd.	Nitrile Rubber No.
1008.....	1022
1009.....	1032
1010.....	1042
1011.....	1002
1008' ⁴	1022

The nitrile rubber constitutes the bulk of the elastomer compound. The other ingredients which act as reinforcing agents, colorants, accelerators, plasticizers, and fillers are present in much smaller amounts.

Butadiene-Acrylonitrile Copolymers.—The nitrile rubbers are the basic crude polymers. They are spongy, yellowish-white solid materials. The composition of each polymer is recorded in Table I.

Solvents.—Alcohol U.S.P.; chloroform, certified reagent (Fisher Scientific Co.); petroleum ether (40–60) (Sargent and Co.), double distilled before use; polyethylene glycol 300 (Ruger Chemical Co.).

Components of Elastomer Compounds.—Butadiene-acrylonitrile rubber and di-(2-ethyl hexyl) phthalate (B. F. Goodrich Chemical Co.), a mono- and dioctylated diphenylamines mixture,⁵ tetraethylthiuram disulfide, tetramethylthiuram disulfide; sulfur (Olin Mathieson Chemical Corp.); channel black (J. M. Huber, Inc.); diethylene glycol (Carbide and Carbon Co.); stearic acid and zinc oxide (National Bureau of Standards).

Miscellaneous Reagents and Chemicals.—Benzyl alcohol, certified reagent and anhydrous sodium sulfate, certified reagent (Fisher Scientific Co.); *p*-chloro- β -phenylethyl alcohol (Ciba Pharmaceutical Co.); zinc diethyldithiocarbamate⁶ and zinc dimethyldithiocarbamate;⁷ anhydrous calcium sulfate;⁸ epoxy adhesive sealant.⁹

Standard Solutions.—Benzyl alcohol 1.0% (w/v solution) in standard citrate-phosphate buffer (0.275 *M*), pH 4; *p*-chloro- β -phenylethyl alcohol 0.3% (w/v solution) in standard citrate-phosphate buffer (0.275 *M*), pH 4; standard phosphate buffer solutions (0.2 *M*), pH 4–9.

Equipment.—Micro Kjeldahl steam distillation

⁴ Elastomer 1008' is a modified form of 1008. It contains 25% less of tetraethylthiuram disulfide and tetramethylthiuram disulfide, respectively.

⁵ Marketed as Age Rite Stalite by the R. T. Vanderbilt Co., New York, N. Y.

⁶ Marketed as Ethyl Zimate by the R. T. Vanderbilt Co., New York, N. Y.

⁷ Marketed as Methyl Zimate by the R. T. Vanderbilt Co., New York, N. Y.

⁸ Marketed as Drierite by the W. A. Hammond Drierite Co., Xenia, Ohio.

⁹ Marketed as Hysol by the Hysol Corp., Olean, N. Y.

unit; Beckman ultraviolet spectrophotometer, model DB; Perkin Elmer infrared spectrophotometer, model 421; Beckman pH meter, model Zeromatic; Instron Universal Testing Equipment, model TM; Aminco Winslow Mercury Porosimeter; Hotpack constant humidity chambers; hydraulic cutting press for ASTM tensile studies.

Sorption of Preservatives

Preparation of Samples.—The vulcanizates were obtained in sheets of uniform thickness (0.4 cm.). These were cut into small pieces of uniform dimensions ($0.4 \times 0.5 \times 1.0$ cm.³) using a paper cutter. The cut pieces were washed by immersion in a 1% solution of sodium lauryl sulfate using continuous agitation for 10 min. The detergent solution was decanted and the sample was washed repeatedly with fresh warm water. Fifteen to 20 washings were used. The sample was finally washed with 10 successive quantities of distilled water. The washed samples were dried in a hot air oven between 60–70° and stored at room temperature.

Sorption Properties.—Sorption of *p*-chloro- β -phenylethyl alcohol (0.3% solution in citrate-phosphate buffer) and benzyl alcohol (1.0% solution in citrate-phosphate buffer) was investigated. An amount of the prepared vulcanized samples (elastomer compounds 1008, 1009, 1010, 1011, and butyl rubber stoppers¹⁰) equal to 2.5 Gm. was transferred to a 25-ml. conical flask containing 10 ml. of the preservative solution. Triplicate samples of each elastomer compound were prepared for each preservative solution, and control solutions were run simultaneously. The samples were stored at room temperature and shaken once or twice daily to remove the air bubbles which settle on the elastomer samples. At the end of the experimental period (1–3 weeks) solutions from all the samples were withdrawn. The preservative content was ascertained by spectrophotometric absorbance measurement at 257 $m\mu$ and 267 $m\mu$ for benzyl alcohol and *p*-chloro- β -phenylethyl alcohol, respectively.

Direct absorbance measurement was not possible due to the presence of leached materials from the several samples. A reasonable degree of purification was obtained by steam distillation of the solutions using a micro Kjeldahl distillation unit. One or 2 ml. of solution was transferred to the distillation unit. The distillate was collected directly in a 25-ml. volumetric flask. About 20 ml. of the distillate was collected each time and the final volume was adjusted to 25 ml. with distilled water. The butyl rubber was found to possess some steam volatile materials, and a correction factor was applied according to the method suggested by Lachman *et al.* (14).

Leaching of Extractives

Leaching behavior of the samples was investigated by allowing the prepared elastomer samples to stand in contact with the selected solvents. Duplicate samples of each of the elastomer compounds and their basic nitrile rubber polymers were prepared by transferring 2.5 Gm. of the sample in a 25-ml. conical flask. To each flask, 10 ml. of distilled water, 10% ethyl alcohol, or 50% aqueous polyethylene gly-

col 300 were added. The flasks were sealed and stored at room temperature (23–28°) and shaken once or twice daily. At the end of the experimental period (1–6 weeks) solutions containing the leached materials were withdrawn and filtered through a sintered-glass funnel of medium porosity. Their absorbance was checked in the visible and ultraviolet range.

Effect of Surface Area.—Since elastomer compounds 1008, 1009, 1010, and 1011 were found to be less porous than the butyl rubber, it was considered of interest to investigate the effect of surface area on the leaching behavior. Sample 1008 was selected for the study. The investigation was conducted in two ways. In one set of experiments, the weight of the samples was kept constant at 2.0 Gm. and they were cut into large, small, and very small pieces to obtain a small (6.5 cm.²), medium (8.9 cm.²), and large (10.2 cm.²) surface area, respectively. In the other set of experiments, samples weighing 1 Gm., 1.5 Gm., and 2 Gm., respectively, were cut in calculated sizes to obtain the same surface area. All the samples were tested in distilled water at room temperature in accordance with the procedure described earlier.

Effect of pH.—In order to evaluate the effect of pH on the leaching properties of the nitrile rubber vulcanizates, two of the samples which showed the lowest degree of leaching were selected. Butyl rubber was used for comparison. The procedure followed was identical to that in the determination of leaching in the pure solvents. The pure solvent was replaced with the same amount of standard phosphate buffer solution (0.2 *M*) at pH 4, 5, 6, 7, 8, and 9, respectively.

Identification of the Leached Materials

Spectrophotometric Analysis.—Ultraviolet absorption spectra of all the materials used in the synthesis of the basic nitrile rubber polymers and in the several elastomer formulations were obtained in distilled water, 10% ethyl alcohol, and 50% aqueous polyethylene glycol 300. Most of the ingredients are only sparingly soluble in these solvents. Consequently, saturated solutions were prepared by allowing 5 Gm. or 5 ml. of the compound to stand with 25 ml. of the solvent for 48 hr. with occasional shaking. The solutions were filtered through a medium porosity sintered-glass funnel and diluted wherever necessary. The ultraviolet absorption spectra of these solutions was compared with the absorption spectra of the leached material from the basic nitrile polymers and vulcanized elastomer formulations.

Chemical Analysis.—One-hundred grams of elastomer compound 1008 was cut in small pieces. It was washed and dried according to the procedure described previously. The dried sample was transferred to a glass refluxing assembly and refluxed for 2 hr. with 400 ml. of distilled water. The aqueous extract so obtained was transferred, while still hot, to a 1-L. beaker. The remaining elastomer compound was washed twice with 50-ml. portions of hot distilled water. The washings were combined with the first portion. The combined aqueous extract appeared milky with a white colloidal material dispersed in it. The extract was allowed to cool to room temperature. A portion of the extract settled

¹⁰ Butyl Rubber Stoppers manufactured by West and Co., Inc., were used for comparative evaluation.

out as a thin white precipitate, but the rest of it remained suspended. The dispersed material was not retained on ordinary filter paper.

The aqueous extract was transferred to a 1-L. separator. It was extracted with successive 100-ml. portions of petroleum ether by shaking for 25 min. each time. The extraction was continued until 1 ml. of the petroleum ether portion did not leave any observable residue on evaporation to dryness. A total of five extractions was required. All the petroleum ether portions were combined and washed twice by shaking with 50-ml. portions of distilled water. The petroleum ether extract was then dried by allowing it to stand in contact with 50 Gm. of anhydrous sodium sulfate for 24 hr. with occasional shaking. The dried extract was filtered through filter paper, and the solvent was distilled off. The residual solvent was removed by keeping the extract in a vacuum desiccator for 24 hr. The final residue weighed 15 mg. and was a pale viscous liquid. An infrared absorption spectrum of the material was obtained.

The aqueous extract left after extraction with petroleum ether was heated at 80° to remove the residual petroleum ether. It was allowed to cool to room temperature and was extracted repeatedly with 100-ml. portions of chloroform until 1 ml. of the chloroform portion left no residue on evaporation to dryness. A total of four extractions was sufficient. The chloroform extract was washed, dried, and the solvent was removed as described above for the petroleum ether extraction.

The final residue weighed 17 mg. and occurred as a brownish amorphous mass. This was redissolved in a small amount of fresh chloroform. Most of the material dissolved, but a small portion of the insoluble brown residue separated out. Infrared absorption spectrum of the insoluble residue was taken in liquid petrolatum¹¹ and that of the soluble portion in chloroform.

The aqueous extract left after extraction with petroleum ether and chloroform was distilled under reduced pressure to approximately 50 ml. This was evaporated to dryness and heated strongly on a direct flame. The residue did not decompose or char, indicating that it was an inorganic material. This residue was further analyzed for inorganic components according to standard semimicro techniques.

Physical Testing of Rubber Samples

Water Vapor Transmission and Sorption.—

Preparation of Samples.—The vulcanized elastomer compounds were cut into circular disks of uniform diameter (1.8 cm.) from sheets of uniform thickness (0.4 cm.) using an electric cork borer. These disks were washed by immersing them in a 1% solution of sodium lauryl sulfate and stirring for 10 min. The detergent solution was decanted and the sample washed repeatedly with fresh warm water. Final washing was performed with 10 successive quantities of deionized water. The washed samples were air dried (25–28°) and stored at room temperature in a desiccator.

Evaluation of Moisture Sorption.—The prepared disks were individually tied with a thin copper wire

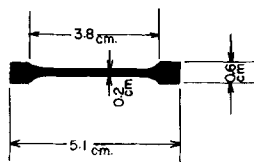


Fig. 1.—Dimensions of dumbbell samples used for the determination of tensile properties.

and with a portion of the wire, a hook was formed by which the disks were hung in a 90% ± 3% relative humidity cabinet set at 26°. The individual samples were removed from the relative humidity chamber after 1, 2, 3, and 4 hr. and 3, 5, 7, 11, and 71 days and weighed.

Evaluation of Water Vapor Transmission.—To 10-ml. glass vials, approximately 5 Gm. of anhydrous calcium sulfate was added. The disks of the elastomer formulations were sealed along the top rim of the vials with an epoxy adhesive sealant and allowed to set for 20 min. The vials were then crimped with three-piece aluminum vial caps. The outer and center portions of the aluminum seal were detached, exposing a uniform surface area of rubber beneath the cap. The sample vials were weighed (0 time sample) and placed into a 90% relative humidity chamber at 26°. Another set of 10-ml. glass vials, which did not contain calcium sulfate, was sealed in the same manner with the four different rubber disks and placed into the relative humidity chamber as controls. Samples with and without anhydrous calcium sulfate were removed from the relative humidity chambers at 1, 2, 3, and 4 hr. and 3, 5, 7, 11, and 71 days and weighed.

Tensile Properties.—The vulcanized sheets were cut into uniform "dumbbell" shaped samples having the dimensions shown in Fig. 1, by use of a hydraulic cutting press. These were tested for tensile strength, ultimate elongation, and tensile set in accordance with modified ASTM procedures (15). The modification consisted of altering the minimum distance between grips (bench marks) at the start of the test from that recommended by the ASTM. For all samples with the exception of 1008', a 2-cm. distance was used, while for 1008' 0.5 cm. was employed. Using the recommended bench mark distances of the ASTM with the model TM Instron which has a maximum travel of 60 cm. for its tensile fixture, no break could be obtained with any of the samples. Consequently, it was necessary to reduce bench mark distances until a point of rupture within the travel distance of the equipment was obtained. The rate of jaw separation for each of these measurements was 50 cm./min.

The *tensile strength* of a material may be defined as the force required to rupture a dumbbell sample of unit area. It may be calculated as follows:

$$\text{tensile strength} = \frac{\text{force at rupture } (F)}{\text{cross sectional area of unstretched sample } (A)}$$

The *ultimate elongation* (E) of a sample can be defined as the maximum elongation immediately prior to sample rupture and is expressed as follows:

$$E(\%) = \frac{L - L_0}{L_0} \times 100$$

¹¹ Marketed as Nujol by Plough Laboratories, Memphis, Tenn.

where L = observed distance between stretched bench marks at point of rupture,
 L_0 = original distance between unstretched bench marks.

The bench mark for the rubber dumbbell samples is the distance between the jaws clamping the sample.

The *tension set* is determined by stretching the sample at a uniform rate of speed (0.6 cm./sec.) for 15 sec. The sample is held in this stretched position for 10 min. At the end of the 10-min. period, the sample is released and allowed to rest for an additional 10 min. with no external force applied. At the end of the rest period, the distance between the bench marks is again measured. *Tension set* is defined as the extension remaining after a sample has been stretched and allowed to retract in a specified manner, expressed as a percentage of original length.

Porosity Studies.—The vulcanized samples of the butadiene-acrylonitrile copolymer compounds were cut into small cubical pieces (0.4 cm. \times 0.4 cm. \times 0.4 cm.) and the porosity determined by mercury diffusion using the Aminco-Winslow porosimeter (16).

Each sample is placed in the penetrometer which is in turn attached to the porosimeter. A vacuum pump evacuates the system and fills the penetrometer with mercury. Pore sizes of 17μ or larger in diameter can be determined under these conditions.

TABLE II.—SORPTION OF *p*-CHLORO- β -PHENYLETHYL ALCOHOL

Sample	Preservative Absorbed, %		
	1 Wk.	2 Wk.	3 Wk.
Butyl	14.5	15.6	16.9
1008	78.0	78.3	78.3
1009	75.5	76.4	76.5
1010	76.5	78.2	78.7
1011	75.1	75.8	76.0
1008'	77.8	78.4	78.5

TABLE III.—SORPTION OF BENZYL ALCOHOL

Sample	Preservative Absorbed, %		
	1 Wk.	2 Wk.	3 Wk.
Butyl ^a	5.6	7.1	8.9
1008	32.1	34.8	35.2
1009	32.5	35.2	35.5
1010	33.0	35.8	36.1
1011	31.9	35.5	36.2
1008'	34.5	35.0	35.0

^a The values were obtained after applying correction for the steam volatile impurities leached by the butyl rubber. Corrected absorbance, $A_c = A_{257} - (A_{253} - A_{263})(14)$.

The penetrometer is then transferred to the pressure chamber of the porosimeter where pressures up to 5000 p.s.i. can be applied to the mercury and where pore sizes down to 0.035μ in diameter can be measured. As the pressure is increased, mercury is forced into smaller and smaller pores, the volumes of which are continuously indicated by the level of mercury in the graduated stem of the penetrometer.

RESULTS AND DISCUSSION

Sorption of Preservatives.—The results of the sorption study are presented in Tables II and III. All the butadiene-acrylonitrile copolymer compounds show considerable sorption of *p*-chloro- β -phenylethyl alcohol and benzyl alcohol from buffered aqueous solutions of the preservatives. There is very little difference in the loss of preservative after 2 or 3 weeks, indicating equilibrium has been attained at 2 weeks or sooner. The amount of *p*-chloro- β -phenylethyl alcohol sorbed is almost twice the amount of benzyl alcohol during the same period of time. Elastomer compound 1008', the modified sample, showed a degree of sorption similar to that of the rest of the samples belonging to the acrylonitrile group. In comparison to the butyl rubber, the formulations under investigation caused considerably more sorption of the preservatives.

The sorption properties of elastomers is a direct consequence of their ability to "dissolve" other materials. The extent to which a preservative would be sorbed from an aqueous solution would thus depend on the partitioning tendencies of the preservative between water and the elastomer. The long chain, high molecular weight organic molecules of the elastomers preferentially sorb hydrophobic organic materials from aqueous systems. A nonpolar substance, with a limited water solubility, would usually be more soluble in the elastomer composition than in water. Thus, it is reasonable to expect greater sorption of *p*-chloro- β -phenylethyl alcohol than benzyl alcohol which is more polar than the former and has greater water solubility.

It has been proposed that sorption is a function of the basic polymer and is not influenced by the fillers to any considerable extent (17). All the samples evaluated in this investigation showed a remarkably similar degree of sorption as would be expected with acrylonitrile-butadiene ratios in the same relative range. This similar degree of sorption displayed by these formulations suggests that the difference in the molecular structure of the particular

TABLE IV.—ULTRAVIOLET ABSORPTION MAXIMA OF THE LEACHED MATERIALS FROM POLYMER SAMPLES

Sample		Wavelength, $m\mu$		
		Distilled Water	10% Ethyl Alcohol	50% Polyethylene Glycol
Nitrile rubber	1002	244	244	280; 208
Nitrile rubber	1022	244	224	277; 207
Nitrile rubber	1032	275; 266; 246	275; 266; 246	274; 266; 248; 212
Nitrile rubber	1042	224	224	288; 224-208
Elastomer compn.	1008	244	244	248; 208
Elastomer compn.	1009	244	244	248; 208
Elastomer compn.	1010	244	244	248; 208
Elastomer compn.	1011	244	244	248; 208
Elastomer compn.	1008'	244	244	248; 208

TABLE V.—ULTRAVIOLET ABSORPTION MAXIMA OF THE SOLUTION OF INGREDIENTS USED IN THE ELASTOMER FORMULATIONS

Ingredient ^a	Wavelength, m μ		
	Distilled Water	10% Ethyl Alcohol	50% Polyethylene Glycol 300
Acrylonitrile	260	260	292
	220	220	222
Mono- and dioctylated diphenylamines	280	280	284
	244	244	208
DTBPC	275	275	276
			207
Rosin acid soap	275	275	275
	266	266	266
	260	260	212
Alkyl aryl sulfonic acid salt	261	261	262
	255	255	256
	223	223	223
Diethylene glycol Di-(2-ethyl hexyl) phthalate	262	262	264
	276	276	284
Tetraethyl thiuram disulfide			232
			210
Tetramethyl thiuram disulfide	268	269	275
	250	250	246
	206	206	210

^a Only those ingredients are listed whose solutions had well-defined maxima. Others (zinc oxide, sulfur, stearic acid, etc.) either did not absorb or had no maxima.

TABLE VI.—LEACHED COMPONENTS IDENTIFIED IN 50% POLYETHYLENE GLYCOL 300

Butadiene-Acrylonitrile Copolymer Sample	Leached Component
1002	Mono- and dioctylated diphenylamines mixture ^a
1022	2,6-Ditertiary butyl <i>p</i> -cresol
1032	Rosin acid soap ^a
1042	Mono- and dioctylated diphenylamines mixture

^a These were also identified to be the components present in distilled water and 10% ethyl alcohol extractives.

basic nitrile rubber polymers is not large enough to alter significantly their affinity for the preservative molecules.

Leaching of Extractives.—The polymers show a considerable degree of leaching at room temperature in distilled water, 10% ethyl alcohol, and 50% aqueous polyethylene glycol 300. Leaching was observed both from the basic polymers (*i.e.*, the butadiene-acrylonitrile copolymers) and the finished elastomer formulations. The absorption patterns of the leached materials from the butadiene-acrylonitrile copolymers differed from one another as is evident from the ultraviolet absorption maxima presented in Table IV.

The leached materials from the various vulcanized elastomer compounds, unlike the material leached from the butadiene-acrylonitrile copolymers, had identical absorption patterns in all three solvents (Table IV). The degree of absorbance, however, was different with sample 1008 exhibiting the least leaching.

The leached materials from the butadiene-acrylonitrile copolymers could be identified by a comparison of their ultraviolet absorption spectra with that of the component ingredients. The leached materials from all four samples were found to be single ingredients and their identification was relatively simple. A comparison with the wavelengths of maximum absorbance of the component ingredients, presented in Table V, led to the identification of the leached materials. These are recorded in Table VI. The materials leached in distilled water and 10% ethyl alcohol were found to be the same as in 50% polyethylene glycol 300 in the case of basic nitrile rubber polymers 1002 and 1032. In the case of basic nitrile rubber polymers 1022 and 1042, the materials leached in 50% ethyl alcohol and in water could not be identified.

Although the absorption pattern of the leached materials from the various vulcanized elastomer compounds was identical in all three solvents, it was not similar to the absorption pattern of any of the pure component ingredients, and no identification was possible by their comparison. A bulk extract was, therefore, prepared and fractionated into different solubility groups by solvent-solvent extraction. Three different fractions were obtained, namely, a petroleum ether extract, a chloroform extract, and an inorganic portion. The residue from the petroleum ether extract was examined for its infrared absorption in its original form. This gave an indication of the presence of phenyl groups (at 702, 740, 1575, and 1595 cm^{-1}) and ester groups (at 1710–1720 cm^{-1}). The only component in the elastomer formulations containing these groups is di-(2-ethyl hexyl) phthalate. Its presence was confirmed by taking an infrared spectrum of the pure compound which was found to coincide with the petroleum ether extractive.

The residue from the chloroform extract occurred as a brownish mass and appeared to be impure as it did not go into solution completely upon the addition of chloroform. The insoluble residue did not show any identifiable group on the infrared spectrum besides a hydrocarbon chain and could not be identified. The chloroform soluble portion gave an indication of the presence of —C=S groups. One source of these could be the thiuram-type accelerators, *i.e.*, the tetraethyl thiuram disulfide and the tetramethyl thiuram disulfide. However, an infrared spectrum of the pure compound did not resemble that of the extract. It was, therefore,

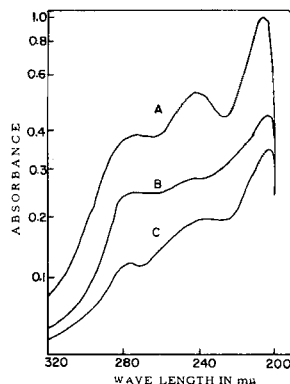


Fig. 2. — Ultraviolet absorption spectra of the aqueous extract of elastomer 1008 and zinc diethyldithiocarbamate. Key: A, aqueous extract diluted with 50% aqueous polyethylene glycol 300; B, saturated solution of zinc diethyldithiocarbamate in distilled water; C, aqueous extract diluted with distilled water.

suspected to be a reaction product of these materials and was identified as a mixture of zinc diethyl/methyl dithiocarbamate. These products are known to be formed during vulcanization process (18). These appear to be the primary leached components responsible for strong absorbance in the ultraviolet region. An ultraviolet absorption spectrum of the aqueous extract obtained after large dilution was in excellent agreement with the absorption spectrum of the dithiocarbamates (Fig. 2). The inorganic portion was identified to be zinc sulfide which is also formed during the vulcanization process.

Based on these findings, elastomer formulation 1008 was modified by reducing the concentration of tetraethyl and tetramethyl thiuram disulfide 25%. This sample, now called 1008', demonstrated a 35% reduction in the degree of leaching. Figures 3, 4, and 5 represent the results of the leaching study over a period of 6 weeks in distilled water, 10% ethyl alcohol, and 50% aqueous polyethylene glycol 300, respectively. As is evident from the figures, the degree of leaching of the acrylonitrile rubbers is much higher than the butyl rubber samples. Furthermore, the degree of leaching in 50% aqueous polyethylene glycol 300 was much higher than in distilled water or 10% ethyl alcohol.

Leaching of extractives by the elastomers is much more complex than might appear initially. Attempts to prevent or reduce leaching by modification of the formulation most likely has received considerable attention by the rubber stopper manufacturers, but since this has not been reported in the literature, it is difficult to assess the progress made. The degree of reduction in leaching achieved by the modification of the formulation in the present investigation is by no means adequate; nevertheless, the results are quite encouraging, particularly in view of the fact that a reduction of the tetraethyl and tetramethyl thiuram disulfides alone brought about a 35% reduction in leaching. It may be possible to further reduce leaching by decreasing the di-(2-ethyl hexyl) phthalate and zinc oxide which have also been found to be leached from the rubber. There is, however, a finite limitation to the extent of reduction beyond which the physical

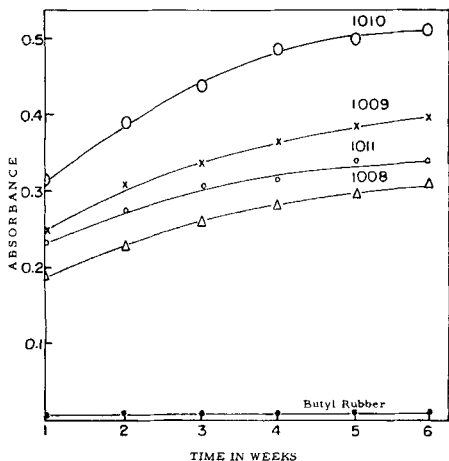


Fig. 3.—Relative leaching from elastomer samples in water at room temperature.

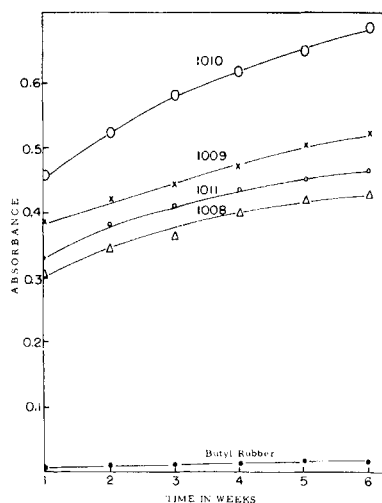


Fig. 4.—Relative leaching from elastomer samples in 10% aqueous ethyl alcohol at room temperature.

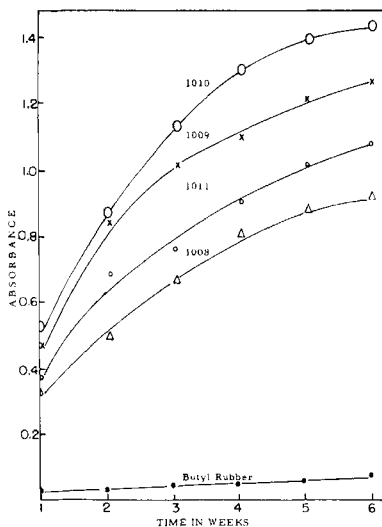


Fig. 5.—Relative leaching from elastomer samples in 50% aqueous polyethylene glycol 300 at room temperature.

properties of the elastomer may be adversely affected.

Effect of Surface Area and pH on Leaching.—The amount of leaching was found to be directly proportional to the surface area and completely independent of weight as illustrated by the graphs in Fig. 6. The leaching increased as the surface area of rubber exposed to the solvent was increased, even though the weight of the sample was maintained constant. On the other hand, samples with the same surface area, but of different weights, had the same degree of leaching. An increase in the surface area of the samples allows greater contact with the solvent, resulting in a faster rate of dissolution. The fact that leaching was not a function of the mass employed indicates that the leaching process in the butadiene-acrylonitrile copolymer compounds is essentially a surface phenomenon.

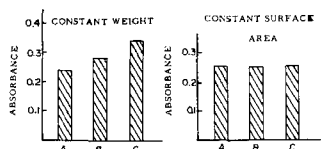


Fig. 6.—Effect of surface area on leaching. Weight: A, 1.0 Gm.; B, 1.5 Gm.; C, 2.0 Gm. Surface area: A, 6.5 cm.²; B, 8.9 cm.²; C, 10.2 cm.².

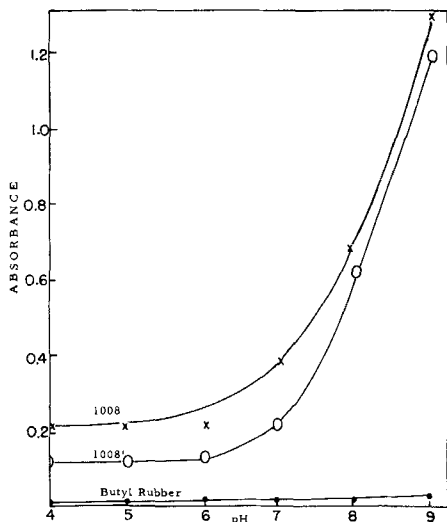


Fig. 7.—Effect of pH on leaching.

This may be a consequence of the low porosity of the samples.

The pH of the solvent had a profound effect on leaching. In the acidic range, the degree of leaching is relatively low. As the pH value increases, an increase in the degree of leaching is observed (Fig. 7).

Water Vapor Transmission.—The data summarized in Table VII indicate that for the storage period of the test, elastomer formulation 1011 shows the greatest tendency for water vapor permeation, while elastomer formulation 1008' the least.

Water Sorption.—The results from the water sorption studies are summarized in Table VIII. It is evident from these data that the five elastomer formulations show sorption of about the same magnitude. However, it would appear that the relationship found for the water vapor transmission

studies exists here too, but the magnitude of the differences are not so great.

Tensile Properties.—It is evident from the data in Table IX that a reduction in the tetraethyl and tetramethyl thiuram disulfide concentration by 25% in formulation 1008' over formulation 1008 results in a considerably less tight cure (undercure) as evidenced by the lower tensile strength and greater ultimate elongation. From the curves in Fig. 8, illustrating the Hooke's law relationship of the five rubber formulations, this is further substantiated by the lower slope of the curve for formulation 1008' as compared to formulation 1008. It would be expected that elastomer formulation 1008' would exhibit higher coring, could be more difficult to insert into vials, and possibly exhibit greater seizure with the glass wall of the vial, and very objectionable compression set.

Porosity Studies.—Porosity measurements performed on the five rubber formulations using the mercury porosimeter at a maximum of 5000 p.s.i. showed essentially no porosity down to 0.035 μ in diameter. This can possibly explain why low water vapor transmission was found for these rubber samples in the water vapor transmission studies discussed earlier. In addition, this low porosity could also be the reason why leaching was found essentially to be a surface phenomenon and not influenced by the weight of the rubber sample.

TABLE VIII.—WATER VAPOR SORPTION OF ELASTOMER FORMULATIONS, mg.

Time	1008'	1008	1009	1010	1011
1 hr.	1.3	1.8	1.6	1.3	1.5
2 hr.	1.5	2.1	1.9	1.5	1.8
3 hr.	2.4	3.0	2.8	2.8	2.7
4 hr.	3.0	3.8	3.5	3.7	3.6
3 days	5.0	5.3	6.5	6.1	7.6
5 days	7.4	7.5	8.2	9.7	10.1
7 days	9.4	10.7	9.2	11.9	11.2
11 days	10.3	11.5	9.7	12.7	12.2
71 days	10.3	11.9	9.9	13.7	13.8

TABLE IX.—TENSILE CHARACTERISTICS OF ACRYLONITRILE RUBBER SAMPLES

Formulation	Tensile Strength, lb./sq. in.	Ultimate Elongation, %	Tension Set, %
1008'	875	5180	4.0
1008	1250	1570	12.5
1009	2090	1600	10.0
1010	1700	1289	7.5
1011	1640	1014	5.0

TABLE VII.—WATER VAPOR TRANSMISSION THROUGH ELASTOMER FORMULATIONS, mg.

Time	1008'		1008		1009		1010		1011	
	Sample ^a	Control ^b	Sample	Control	Sample	Control	Sample	Control	Sample	Control
1 hr.	0.6	0.3	0.5	0.7	0.9	0.6	0.7	0.5	0.9	0.5
2 hr.	0.7	0.4	0.6	0.8	1.1	0.7	0.8	0.5	1.1	0.6
3 hr.	0.9	0.7	1.2	1.1	1.5	1.2	1.5	1.1	1.8	1.0
4 hr.	1.4	1.2	2.6	1.6	2.0	1.6	2.1	1.6	2.3	1.6
3 days	4.7	3.8	4.2	4.2	5.1	4.5	5.6	5.0	6.1	5.0
5 days	5.0	4.6	5.3	4.9	6.5	5.5	6.1	6.1	7.6	6.3
7 days	7.4	8.7	7.5	7.0	8.2	7.7	9.7	8.4	10.1	8.5
11 days	9.4	10.5	9.4	9.0	10.0	9.5	12.0	10.5	11.8	10.4
71 days	28.1	16.8	32.2	15.2	32.4	14.4	36.0	17.7	39.7	16.9

^a Sample = sample with anhydrous calcium sulfate. (See Footnote 8.) ^b Control = no anhydrous calcium sulfate. (See Footnote 8.)

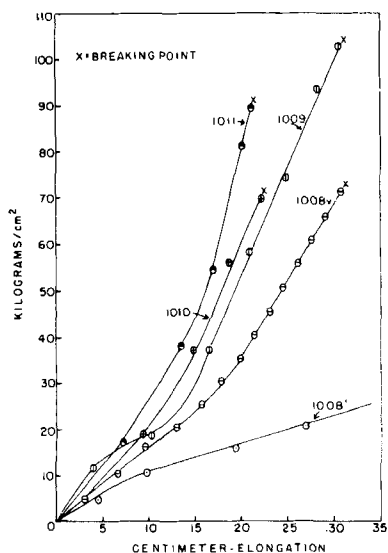


Fig. 8.—Hooke's law relationship for various elastomers.

SUMMARY AND CONCLUSIONS

The information gained from this study may be summarized as follows.

1. Considerable sorption of preservative was found to take place for each of the five elastomer formulations evaluated.

2. The magnitude of the loss of preservative was found approximately the same for the several formulations.

3. Significant extractive was leached from each of the formulations and were identified.

4. A reduction of 25% in the concentration of tetraethyl and tetramethyl thiuram disulfides in elastomer formulation 1008 resulted in a 35% reduction in extractives leached from the elastomer.

5. Water vapor transmission and sorption studies indicated that elastomer formulation 1008' gave the best results and formulation 1011 the poorest.

6. A reduction of 25% in concentration of tetraethyl and tetramethyl thiuram disulfides in formulation 1008 gave a rubber formulation which exhibited two-thirds the tensile strength and about three and a half times the ultimate elongation. It would be anticipated that closures made from this formulation would not function satisfactorily because of probable undercure.

7. All the elastomer formulations in the study exhibited a very low degree of porosity and small pore size.

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