

Comparison of Two Distinct Phenolic Antioxidants in γ -Sterilized NR Compounds Used as Rubber Pistons in Syringes for Single Use

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SYNOPSIS

The effects of γ -irradiation and aging on pharmaceutical NR compounds have been studied mainly by DSC. The extent of aging was measured quantitatively by enthalpy changes and peak temperature shifts of the primary oxidation exotherm. Quantitative thermal evaluations were supplemented by extraction tests and mechanical testing. The NR compound formula has been kept constant and only the type and concentration of antioxidant was varied. Two distinct phenolic antioxidants, BHT and Wingstay-L at four different concentration levels, have been employed for this purpose. The most effective antioxidant package for a given elastomeric compound, subjected to γ -irradiation and aging, giving the lowest changes in physical properties, is evaluated. © 1992 John Wiley & Sons, Inc.

INTRODUCTION

Elastomeric compounds are complex mixtures of polymer, carbon black, and/or mineral filler, curatives, plasticizers, and miscellaneous additional ingredients. The elastomeric materials are currently widely used for medical and paramedical applications subject to ionizing radiation. Little is known about the effects of γ -irradiation on the many additives that are present in these polymeric materials, which might come in contact with a medicine. It has been postulated that undesirable sideproducts may be formed, which could subsequently migrate into the medicine and present a hazard.¹

In the present study, investigation was focused on NR compounds being used as rubber pistons in syringes for single use. The observation was made that syringes, irradiated three months after production, exhibited intense yellowing in the vicinity of rubber pistons. This discoloration became less in-

tense as the concentration level of the antioxidant was reduced. Samples from the same batch, that have been irradiated shortly after production, showed no yellowing. Also, antioxidant-free samples, following the same procedure, yielded no discoloration at all. This fact suggested that the investigation should be concentrated on the type and level of the antioxidant itself.

The above observations indicated a possible exudation of the antioxidant to the surface of the material. It is well known that, in addition to antioxidant depletion by chemical consumption, polymer antioxidants may be lost by physical processes. There is a large number of well-established techniques for testing antioxidant diffusion in polymers.²⁻⁸

The present study employed Differential Scanning Calorimetry (DSC) to describe the effects of γ -irradiation and aging on NR compounds. Quantitative thermal evaluations were supplemented by extraction tests and mechanical testing. The NR compound formula has been kept constant and only the type and concentration of antioxidant was varied. Two types of commercially available phenolic

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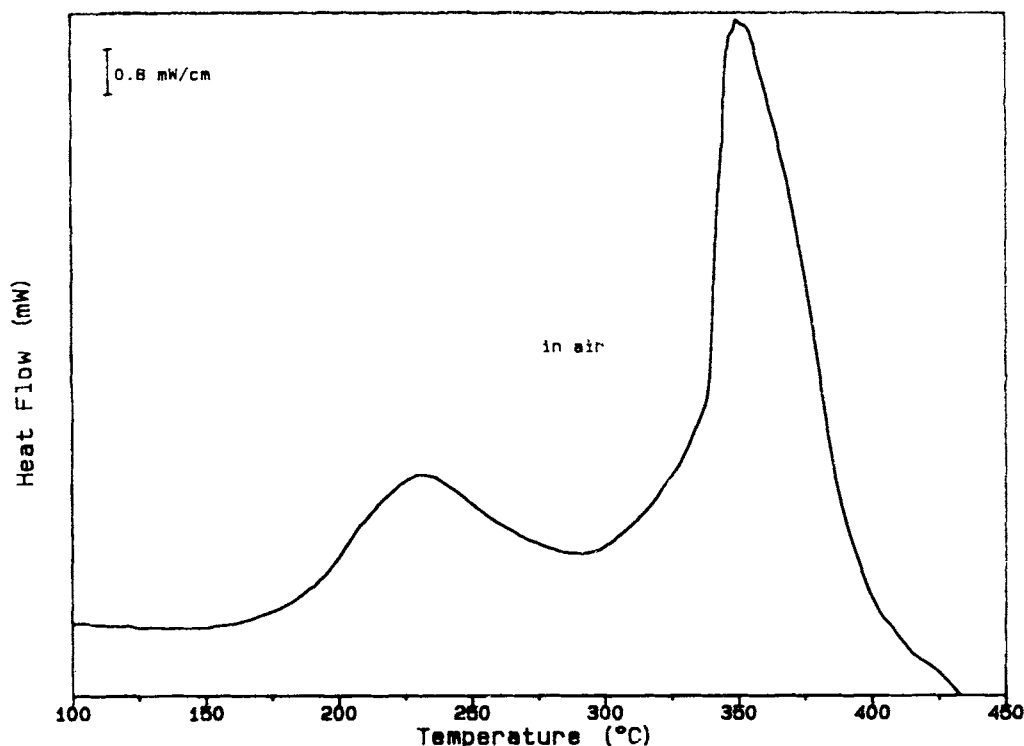


Figure 1 Characteristic DSC degradation exotherms of an NR compound in air atmosphere.

antioxidants, at four different concentration levels, have been employed for this purpose. The most effective antioxidant package for a given elastomeric compound subject to γ -irradiation and aging, yielding the lowest changes in physical properties, is determined.

Several studies have appeared in the literature demonstrating the utility of DSC (or DTA) in the study of rubber oxidation.⁹⁻¹² There are two methods

for studying the thermal oxidation by DSC: the isothermal and the continuous scanning methods. In the former, the sample is maintained at a constant temperature throughout the experiment, and in the latter, the material is degraded at a programmed heating rate. The isothermal method was not applied in the present study, due to the fact that competitive thermal events altered or masked the oxidation behavior of the materials.

Table I The Effect of Two Distinct Phenolic Antioxidants at Various Concentrations on the Oxidation Peak Temperature, T_p , of NR Compounds

Antiox. Type	Antiox. Con ⁿ (phr)	As-Molded "Surface"	As-Molded "Bulk"	Irradiated	Aged "Surface"	Aged "Bulk"
Antiox. free	0.00	212.8	212.9	216.2	210.0	210.0
	0.10	223.8	224.2	218.1	216.9	216.7
	0.25	224.9	225.5	222.4	218.6	219.0
	0.50	233.2	234.3	225.7	225.0	225.5
	1.00	232.5	233.0	232.1	228.5	228.5
BHT	0.10	213.4	213.5	212.4	212.1	213.6
	0.25	214.5	214.9	214.7	213.3	213.8
	0.50	214.3	214.7	214.1	213.3	213.8
	1.00	218.0	218.3	215.0	214.3	215.0

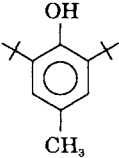
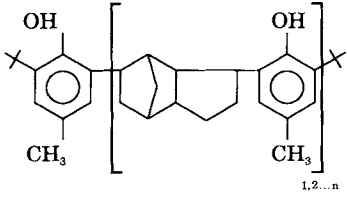
Oxidation peak temperature (°C).

In an oxidizing atmosphere, two exotherms are evident in the DSC thermogram of an NR compound, as illustrated in Figure 1. The initial exotherm occurs in the 175–275°C region. In nitrogen atmosphere, no exotherm was detected in that region; thus the initial exotherm (in oxygen or air) was attributed to oxidation of the sample. The second exotherm, which occurs in the 300–400°C region, was attributed to polymer decomposition. The interest was focused on the primary oxidation exotherm.

The degradation that is observed results from two types of reaction: (1) chain scission, which weakens and softens the material, and (2) crosslinking, which stiffens and hardens the rubber. The relative importance of the two processes varies with the nature of the material and conditions. Shelton et al.¹³ have shown that NR tends to get softer upon aging, while synthetic SBR hardens. Hydroperoxides, formed in autoxidation, decompose to produce oxy and peroxy radicals, which abstract allylic hydrogen from unsaturated rubbers to form carbon-free radicals on the polymer chain. If oxygen is available, the radicals combine to initiate autoxidation. If the oxygen concentration is low, as in the interior of rubber, the carbon radicals may combine to form a crosslink.

MATERIALS

The chemical structures of the sterically hindered phenols, whose thermoanalytical behavior was examined in the present work, are as follows:

Chemical Structure	Trade Name
2,6-ditertiary butyl- <i>p</i> -cresol (butylated hydroxy toluene) 	BHT (Ciba-Geigy)
Reaction product of butylated <i>p</i> -cresol and di-cyclopentadiene 	Wingstay-L (Goodyear)

These antioxidants will be referred to, hereafter, using their commercial names.

The samples have been provided by Seal Line S.p.A., Italy. All the ingredients of the compound were kept constant, while the type and level of antioxidant was varied. The elastomeric compounds investigated were suitable for rubber pistons in syringes for single use.

EXPERIMENTAL

A Du Pont 9000 Thermal Analyzer, fitted with a D.S.C. module, was used to obtain the thermograms. The heating rate was 10°C/min and the oxygen flow was kept at 150 mL/min. The sample size was about 15 mg. Areas were determined with a planimeter and were divided by the sample weight in milligrams. The cell was calibrated for quantitative measurements using indium and tin standards. The specimens were shavings, cut from the surface and the bulk of the material. It was necessary to control strictly the details of cutting and placing samples in the DSC pans in order to obtain reproducible results.

Samples were irradiated in air, using a cobalt 60 source, to yield a minimum dose of 2.5 Mrad with an average dose rate of 0.13 Mrad/h. The irradiated samples were then aged in an air-circulating oven at 100°C for 22 h. Samples of the same level and type of antioxidant were left to age separately in order to avoid undesirable effects due to migration and diffusion-induced phenomena.

Irradiated and aged specimens were subjected to tensile properties characterization. The resistance of a compound to γ -irradiation and aging was measured by the percent change in various physical properties measured, that is, tensile strength, elongation at break, and 50% modulus. The measurements were carried out with an Instron tester, model 1011, at room temperature, at a crosshead speed of 500 mm/min.

For the extraction test, the reagent used was cyclohexane. The procedure was as follows: In 50 mL of cyclohexane were placed, at the same time, 13 pistons of total surface area $A = 54.34 \text{ cm}^2$, used in 2.5 mL syringes, 8 pistons of total surface area $A = 55.20 \text{ cm}^2$, used in 5.0 mL syringes, 5 pistons of total surface area $A = 53.25 \text{ cm}^2$, used in 10.0 mL syringes, 3 pistons of total surface area $A = 55.20 \text{ cm}^2$, used in 20.0 mL syringes. Reflux was followed for 15 min and the solutions were then cooled in water bath. The absorbance at 450 nm of each ex-

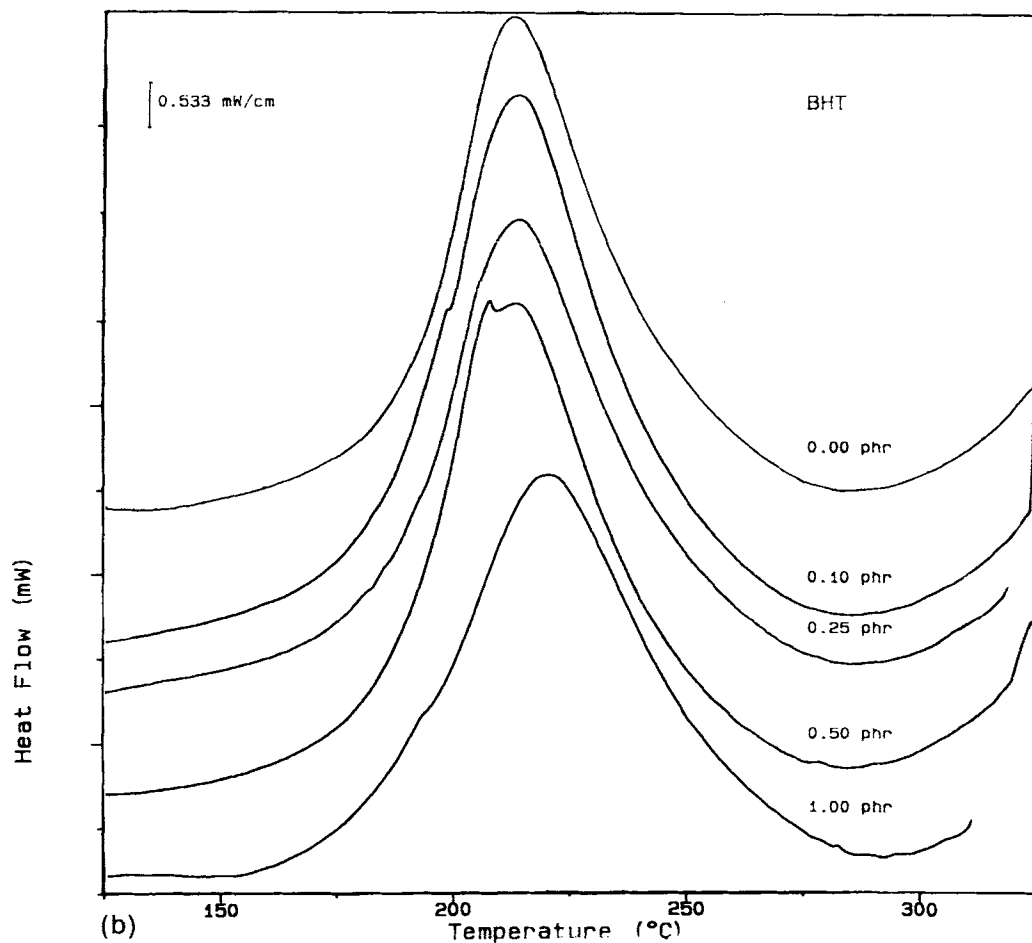
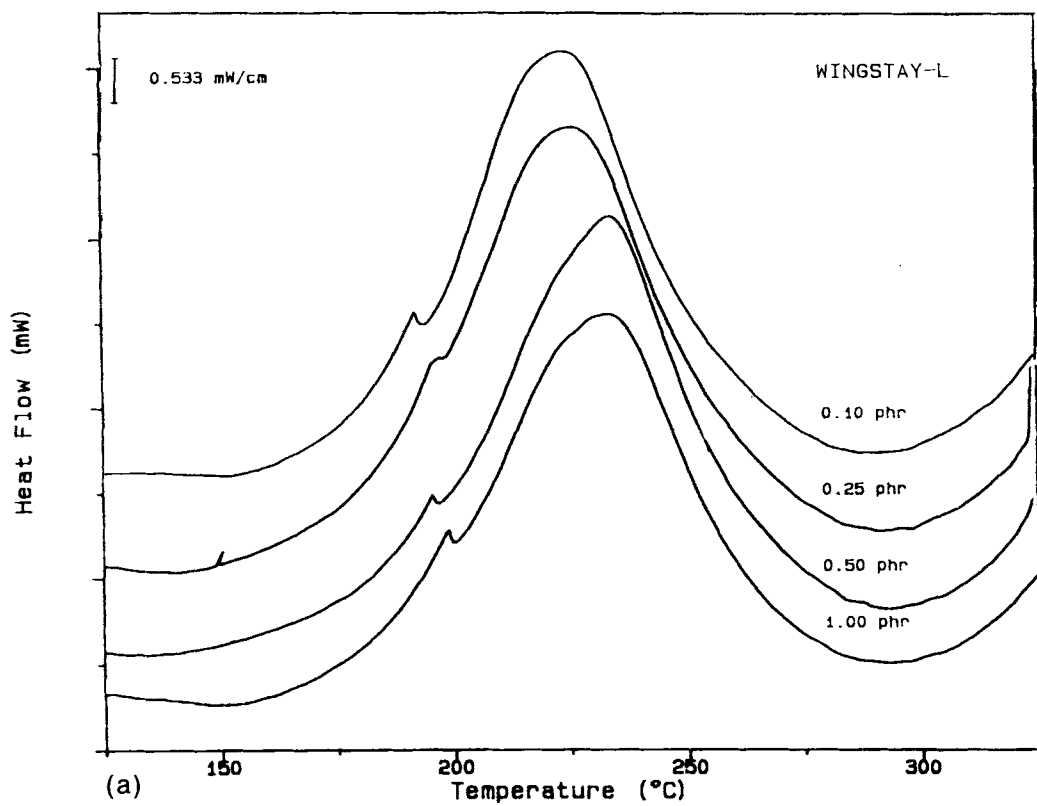


Figure 2 Influence of antioxidant concentration (phr) on DSC thermograms of NR compounds in O₂ atmosphere (Heating rate = 10°C/min).

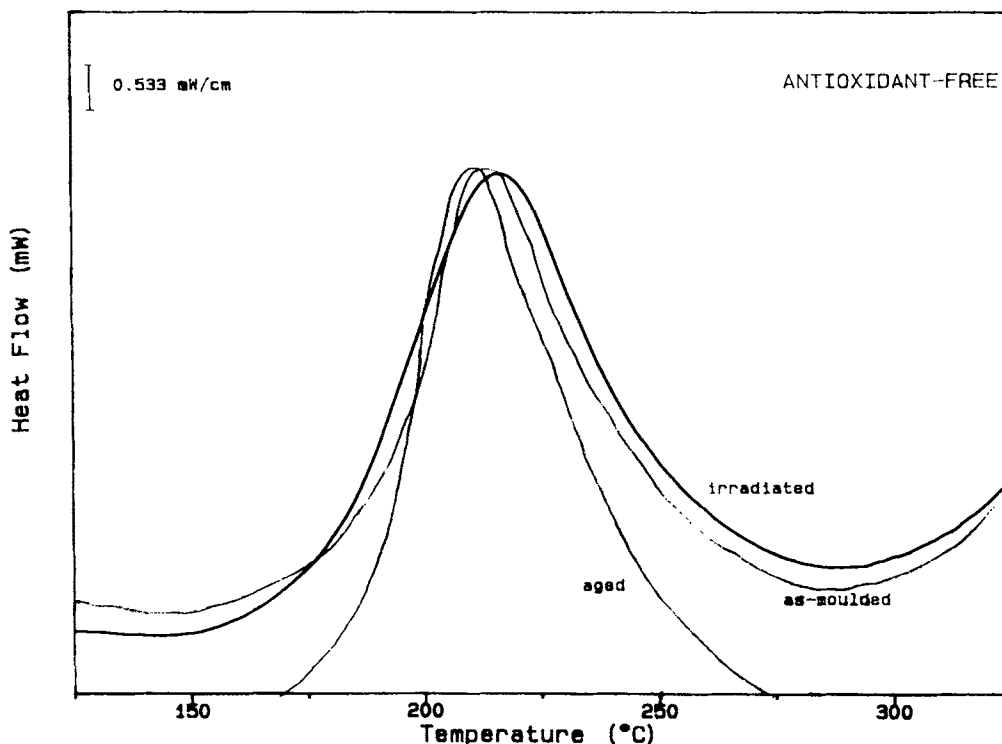


Figure 3 Effect of aging and γ -irradiation on the oxidation exotherm of an antioxidant-free NR compound.

traction solution was measured, using a Shimadzu UV-110 spectrophotometer.

RESULTS AND DISCUSSION

The DSC continuous scanning method was employed to evaluate the antioxidant efficiency. The

effectiveness of the antioxidant was estimated by: (a) the peak temperature of the primary oxidation exotherm, (b) the overall enthalpy of oxidation, and (c) the activation energy calculated from a given kinetic model.

The sample with the highest oxidation peak temperature is presumed to be the most effective stabilized system, at least at elevated temperatures.⁹

Table II UV Absorbance Values (450 nm) of the Extracted Solutions of NR Compounds Obtained at Different Periods of Time

NR Compound	phr	Shortly after Production		One Month after Production		Two Months after Production		Three Months after Production	
		Nonirrad.	Irrad.	Nonirrad.	Irrad.	Nonirrad.	Irrad.	Nonirrad.	Irrad.
Antioxidant-free	0.00	0.023	0.022	0.024	0.022	0.023	0.022	0.025	0.024
Wingstay-L	0.10	0.022	0.022	0.025	0.023	0.024	0.024	0.025	0.025
Wingstay-L	0.25	0.024	0.022	0.024	0.025	0.026	0.025	0.027	0.025
Wingstay-L	0.50	0.028	0.022	0.028	0.027	0.028	0.028	0.028	0.026
Wingstay-L	1.00	0.025	0.024	0.033	0.026	0.033	0.030	0.033	0.030
BHT	0.10	0.028	0.022	0.032	0.026	0.031	0.029	0.031	0.030
BHT	0.25	0.035	0.023	0.041	0.034	0.045	0.042	0.047	0.046
BHT	0.50	0.043	0.025	0.065	0.056	0.070	0.067	0.089	0.082
BHT	1.00	0.068	0.025	0.080	0.068	0.084	0.083	0.086	0.092

Table III Thermal Oxidation Enthalpies (ΔH , J/g) of NR Compounds on Samples Taken from the Bulk and Surface of the Materials

Antiox. Type	Antiox. Con ⁿ (phr)	As-Molded "Surface"	As-Molded "Bulk"	Irradiated	Aged "Surface"	Aged "Bulk"
Antiox. free	0.00	114	120	131	123	142
Wingstay-L	0.10	100	111	109	118	134
	0.25	105	113	112	112	126
	0.50	100	107	95	114	127
	1.00	94	102	95	103	118
	BHT	0.10	117	123	117	121
BHT	0.25	108	116	109	121	145
	0.50	98	107	100	126	138
	1.00	103	116	102	118	135

Samples' wt: 15 mg.

The effect of antioxidant type and concentration on the peak temperature for NR compounds is given in Table I.

Figure 2(a) presents the thermograms of the NR compound at various levels of Wingstay-L. A noticeable temperature shift to the right was observed as the antioxidant concentration level was increased. However, for antioxidant concentrations above 0.5 phr, this shift to the right was minimized if not reversed. This means that an optimum antioxidant

level had been reached at 0.50 phr, above which a superabundant situation existed. Figure 2(b) presents the corresponding thermograms of BHT. As can be seen, this antioxidant contributes to a negligible increase in the peak temperature, as compared to the antioxidant-free compound, at least up to 0.5 phr. This is attributed to the high volatility and migration rate of BHT, which can lead to substantial losses, and consequently contributes insufficiently to NR stabilization.

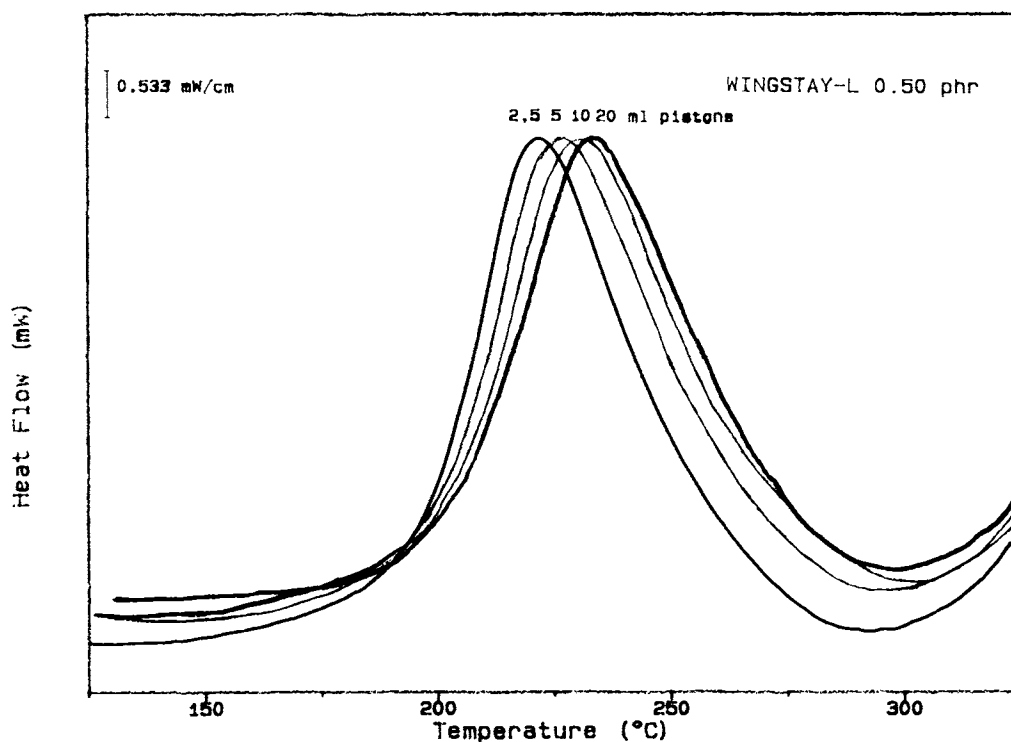


Figure 4 Effect of piston size on the oxidation behavior of an NR compound.

Table IV Oxidation Peak Temperatures, T_p , Obtained at Different Heating Rates, ϕ

No.	Heating Rate ϕ ($^{\circ}\text{C}/\text{min}$)	Wingstay-L (0.50 phr) T_p ($^{\circ}\text{C}$)	BHT
1	2.5	200.9	186.2
2	5	213.3	200.0
3	10	234.3	214.7
4	20	241.2	234.5
5	30	254.3	244.0
6	50	270.9	261.4

Activation energies E : (Wingstay-L) 87.2 kJ/mol, (BHT) 72.2 kJ/mol. Activation Energies were calculated from the slope of the "best" straight line of the plot of $\log \phi$ vs. $1/T$ (K^{-1}).

Changes induced by γ -irradiation (2.5 Mrad) on specimens containing Wingstay-L caused a shift of the peak temperature to the left (see Table I). However, no such shift was detected at 1 phr. As far as

BHT is concerned, negligible shifts to the left are observed for concentration levels up to 0.50 phr, but at 1 phr, a noticeable shift to the left occurs. Additionally, the effect of γ -irradiation on the antioxidant-free sample caused, comparatively, a significant shift to the right (see Fig. 3). These results can be explained as follows: one of the first results of the reaction of γ -irradiation with polymers is the formation of free radicals or excited molecular fragments. The resultant changes in the molecular structure of polymeric materials by irradiation are dependent on the respective rate of recombination, crosslinking, or cleavage of the molecular fragments. The shift to the left, as far as the antioxidants are concerned, is attributed to the predominance of chain scission reactions on irradiation. Indeed, the primary antioxidants used, known to function as radical scavengers, trap the radicals as soon as they are formed and, thus, reduce in this way the corresponding rates of recombination and crosslinking

Table V Changes in the Values of Tensile Strength and 50% Modulus of NR Compounds Caused by Aging and γ -Irradiation

Tensile Strength (N/mm^2)				
Antiox. Type	Antiox. Con ⁿ (phr)	As-Molded	Irradiated	Aged
Antiox. free Wingstay-L	0.00	15.0	15.0	7.5
	0.10	14.9	14.3	10.5
	0.25	13.8	13.8	11.5
	0.50	13.2	13.1	12.6
	1.00	12.8	12.8	12.6
BHT	0.10	15.1	13.8	7.7
	0.25	15.0	14.0	8.5
	0.50	14.9	14.2	10.5
	1.00	—	—	—
50% Modulus (N/mm^2)				
Antiox. Type	Antiox. Con ⁿ (phr)	As-Molded	Irradiated	Aged
Antiox. free Wingstay-L	0.00	1.85	1.90	0.93
	0.10	1.60	1.48	1.06
	0.25	1.54	1.40	1.12
	0.50	1.57	1.42	1.20
	1.00	1.30	1.32	1.25
BHT	0.10	1.80	1.77	0.90
	0.25	1.73	1.64	0.87
	0.50	1.60	1.67	0.95
	1.00	—	—	—

Measurements were obtained at a crosshead speed of 500 mm/min.

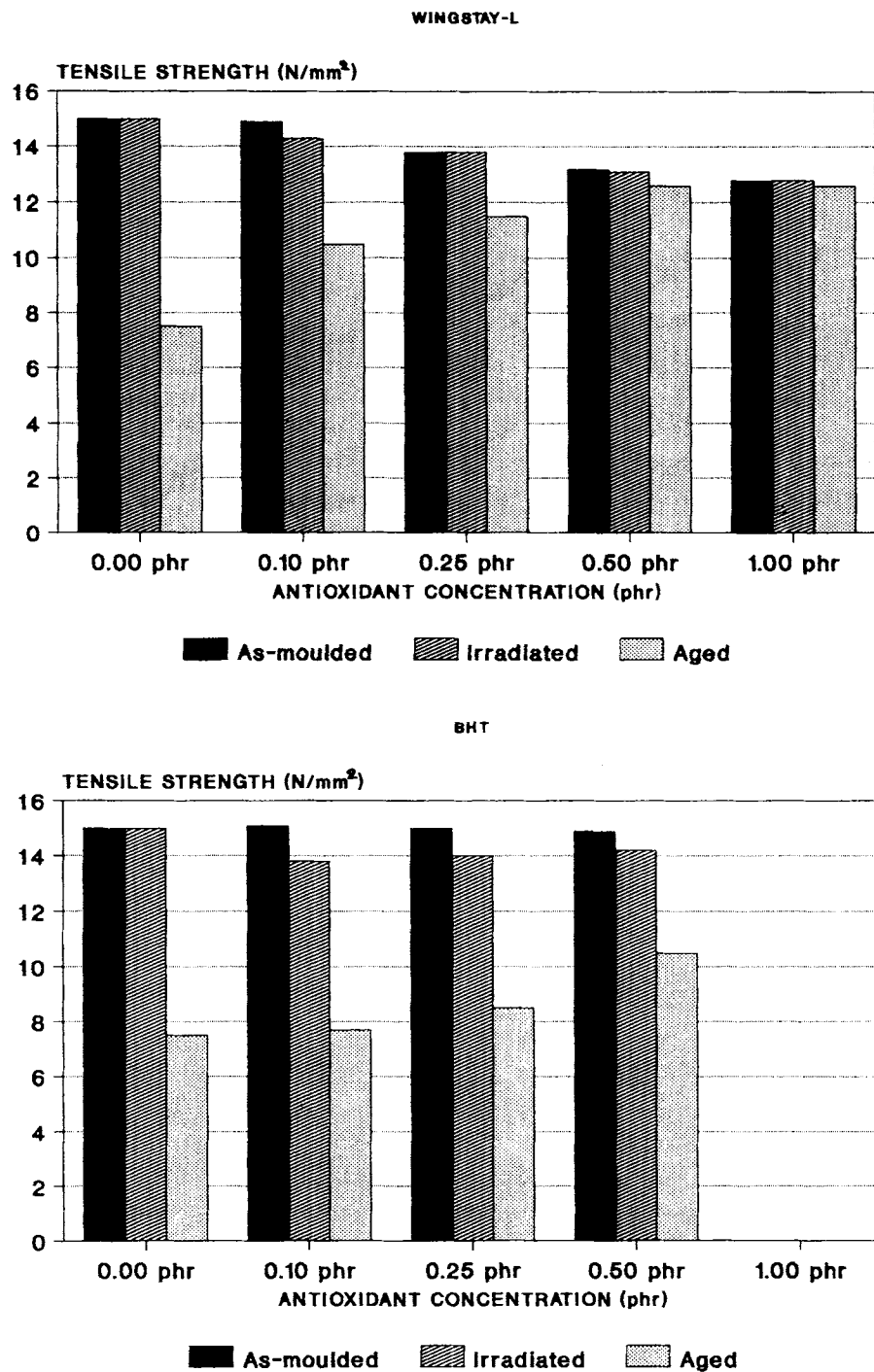


Figure 5 Changes in the values of tensile strength and 50% modulus of NR compounds caused by aging and γ -irradiation. Measurements obtained at a crossed speed of 500 mm/min.

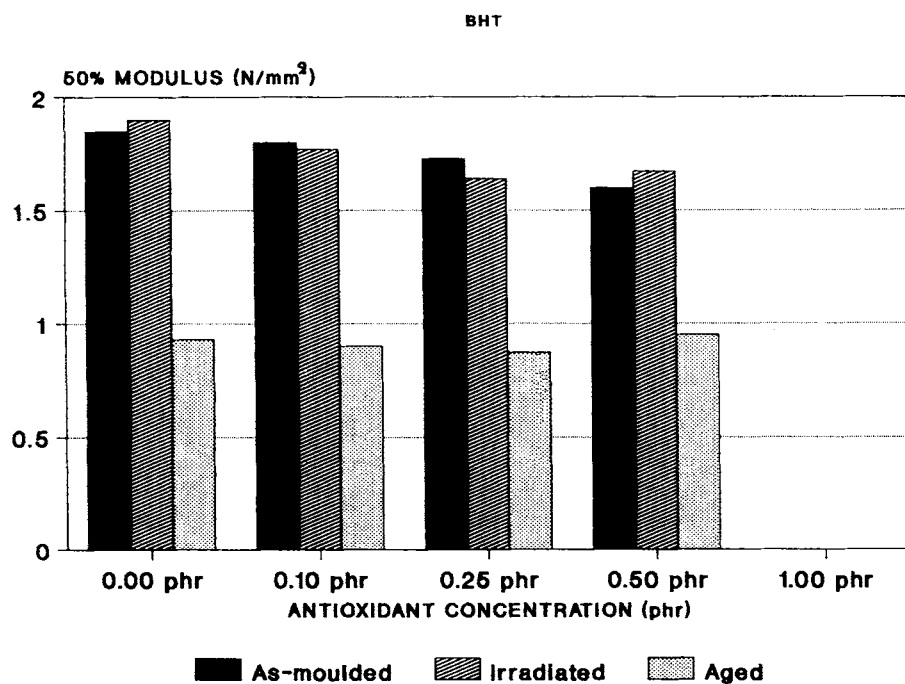
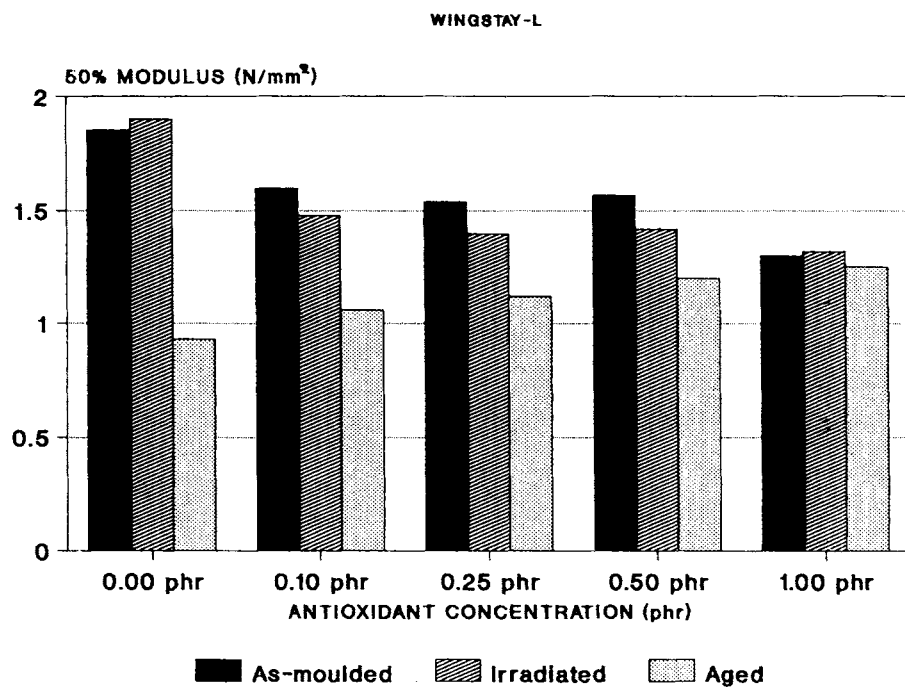


Figure 5 (Continued from the previous page)

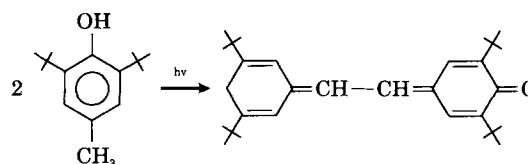
reactions. On the contrary, the shift to the right, which occurred in the antioxidant-free compound, is attributed to the predominance of crosslinking and recombination reactions.

The aging test (100°C, 22 h) caused a significant decrease in the oxidation peak temperature, T_p , of all the samples, the extent of which is dependent on the antioxidant system used (see Table I). The resultant changes reflect the net effect of softening, which results from chain scission.

The above results suggest that the Wingstay-L is a more powerful antioxidant as compared to BHT at any concentration level. This is attributed to the enhanced electroaffinity of the substituent present in the ortho position of Wingstay-L, which is known to be related to the efficiency of the homolytic splitting of the OH bond and the transfer of the hydrogen atom to an alkoxy or peroxy radical.¹⁴ Additionally, due to its inherently immobile structure (high mol wt), Wingstay-L remains incorporated into the polymer, contributing in this way to improved antioxidant stability. This has also been proved with extraction tests.

As is shown in Table II, the UV absorbance (at 450 nm) generally increases with antioxidant concentration. This increase becomes more obvious in the case of BHT. Table II also shows that the UV absorbance of BHT extraction solution is drastically increased when the extraction test is performed at successively prolonged periods of time after compounding. This extractability can be directly related to the high migration rate BHT has, compared to Wingstay-L, which shows a negligible migration trend, since the UV absorbance of its extracted solutions sustain low values. Here the effect of γ -irradiation on migration is also shown: the UV absorbance values of samples taken shortly after production are the same or even less than the corresponding, nonirradiated ones. This is because hinderphenol antioxidants do not give rise to degradation products extracted from the irradiated polymer, because it is suspected that such products are becoming covalently bound to the polymer as a result of radical coupling process. Gamma irradiation of polyolefins is known to give rise to macroalkyl radicals, and hence the trapping of antioxidant degradation products is probable.¹ Nevertheless, UV absorbance values are always higher in the case of BHT-based compounds. On the contrary, samples, with BHT irradiated 2–3 months after production, gave intense yellowing with high UV absorbance values, especially at high concentration levels, as compared to the nonirradiated ones. This behavior was not observed with Wingstay-L based compounds. This discoloration is attributed to the con-

version of the migrated BHT to stilbenequinone by high energy irradiation, according to the following reaction¹⁵:



The presence of stilbenequinone on irradiated yellow BHT samples was detected by FTIR spectroscopy.

The enthalpy of oxidation, ΔH , is related to the area under the initial exotherm of the DSC thermogram of an NR compound. It is sufficient to say that the greater the area under the curve, the more the oxidation products there are. The enthalpy of oxidation, in correlation with the peak temperature, define the optimum antioxidant level to be used. There are, though, certain factors that substantially influence the enthalpy of oxidation of NR, namely, sample mass, size, and geometry.¹⁶ Therefore, special care was taken for the DSC samples to have these factors constant. Substantial differences in the exothermic area of the oxidation exotherm were observed between specimens cut from the bulk and from the surface of the aged NR compounds. On the contrary, no distinct differences were found between specimens cut from the bulk and from the surface of the as-molded compounds (see Table III). The reduced area of the surface samples was attributed to the counter-effect phenomenon (i.e., endotherms), caused by the sublimation and volatilization of the various additives of the material, which have migrated to the surface of the compound during the aging process.

Differences were also found between specimens cut from the bulk of 2.5, 5, 10, and 20 mL pistons (see Fig. 4). The specimens from the smaller pistons exhibited lower peak temperatures. This is due to the fact that, during the compounding process, the thinner sheets (used for the production of the smaller sizes) were more susceptible to oxidation. This could mean that either higher antioxidant levels or milder processing conditions should be used for the smaller size pistons.

The peak exotherm temperature is known to be related to the activation energy (E_a) of oxidation of NR. For the determination of the activation energy, Kissinger and Ozawa's method was employed.^{17,18}

$$E_a = \frac{-R}{0.457} \frac{\Delta \log \phi}{\Delta(1/T_p)}$$

where E_a is the activation energy in kJ/mol, ϕ is the heating rate in K/min, T_p is the peak exotherm temperature in K, and R is the universal constant of gases.

This method is independent of the reaction order and, in addition, the mass does not present a considerable influence on the E_a values obtained. This method is valuable to analyze the curing kinetics of systems with multiple exotherms or unreliable baselines.

Six heating rates (2.5, 5, 10, 20, 30, and 50°C/min) were used. The results are presented in Table IV. The activation energy of the Wingstay-L-based compound was found to be higher than the corresponding BHT one. Representative activation energy values of as-molded compounds are also given in Table IV.

Slight differences were observed in the mechanical properties of the as-molded samples with different antioxidants, which became more evident at higher concentration levels. More particularly, as can also be seen in Table V, the modulus of the Wingstay-L-based compound was lower than that of BHT. This decrease in modulus, that is, decrease in the crosslinking density, is due to the interference of Wingstay-L in the vulcanization process. These results were supported by rheometric measurements during the compounding process where it was found that the viscosity of the Wingstay-L-based compound was lower than that of BHT.

The resultant changes in the mechanical properties of the NR compounds caused by γ -irradiation (2.5 Mrad) are also given in Table V. As can be seen in Figure 5, the sample with the high mol wt antioxidant (Wingstay-L) retained to a great extent its original mechanical properties, as compared to BHT. Moreover, as the antioxidant concentration increased, the percentage decrease of the mechanical properties is reduced and, in the case of Wingstay-L, is minimized, if not eliminated.

The aging test (100°C, 22 h) caused significant decreases in tensile modulus and ultimate tensile strength, the extent of which are dependent on the antioxidant system used. The results are shown in Figure 5. The observed changes reflect the net effect of softening, which result from chain scission. The decay in tensile properties is reduced as the concentration level of each antioxidant is raised.

CONCLUSIONS

Since rubber pharmaceutical products need to maintain their properties for a period of 3 to 5 years

after being subjected to γ -sterilization and postirradiation processes, an effective antioxidant system is necessary to provide stabilization to the compound.

The selection of an effective antioxidant system is an important task, since the choice, for instance, of a volatile antioxidant with a high migrating rate, can give rise to undesirable side effects (such as discoloration), not only for the product itself, but the side effects might also be potential health hazards.

The results show that polymeric-type antioxidants seem to be a suitable selection for such products, since they give the lowest changes in physical properties after accelerated tests (irradiation and aging). These results are attributed to the fact that, due to their high mol wt, the antioxidants are inherently immobile, hence remaining in the compound and providing the necessary stabilization. Moreover, the high intrinsic antioxidant activity of Wingstay-L can be explained by the ease of transfer of the hydrogen atom, as compared to BHT.

Another point to be considered is the optimization of the concentration level of the antioxidant to be used. On a cost-performance basis, it is generally impractical to use antioxidants above their optimal level. Furthermore, high levels of antioxidant can have adverse effects, such as retardation of the vulcanization process and acceleration of the oxidative degradation due to the pro-oxidant effect.

Finally, the DSC results seem to correlate well with the mechanical property measurements, and this is another proof that DSC is a useful tool in assessing the effectiveness of an antioxidant system.

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