

Report

Identification of Phenolic Antioxidants in Elastomers for Pharmaceutical and Medical Use

Charles B. Airaud, ¹⁻³ André Gayte-Sorbier, ² Roland Creusevau, ¹ and Régine Dumont ¹

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Phenolic antioxidants were identified by thin-layer chromatography (TLC) in 102 samples of pharmaceutical and medical rubber articles. Despite the large number of antioxidants proposed for elastomers, only eight compounds were found in the articles analyzed. The choice of antioxidants apparently does not depend on the sterilizing processes or on the use or brand of articles.

KEY WORDS: phenolic antioxidants; thin-layer chromatographic (TLC) analysis of elastomers.

INTRODUCTION

Rubbers are used in drug packaging and administration and in nursing. Our aim was to identify phenolic antioxidants in such rubber articles. The first purpose of the study was to propose an analytical method to the manufacturers of elastomeric articles to verify the identity of antioxidants and for use in quality control. The second purpose was to provide a method of control for the pharmaceutical industry and hospital pharmacists to evaluate any problems with the compatibility of rubbers in contact with drugs and the body (1-4). Our third goal was to discover which compounds among the wide existing range (5) are actually used, for application in forensic toxicology as an example. The fact that formulations of rubbers are usually not divulged by manufacturers must be emphasized in order to explain the last two purposes.

MATERIALS AND METHODS

The 102 articles analyzed were junctions in infusion sets for plasma, blood, and solutions, plunger seals of disposable syringes, surgeon's gloves, stoppers and plunger seals in blood-collection devices, balloon urological catheters, rubber nipples, baby pacifiers, stoppers of injection vials, and plunger seals of injection cartridges. Each of them was represented by several brands and sometimes by several types of a given brand. The rubber articles were ground to powder after having been frozen in liquid nitrogen. The different parts of balloon urological catheters were tested independently, as several elastomers are used in the same article. Samples (20 g) were extracted with acetone (250 ml) for 8 hr in a Soxhlet apparatus and the extracts were concentrated to 10 ml. Extracts (20 μ l) were spotted on silica gel

plates with a concentrating zone (Merck 11845). The chromatograms were developed in benzene under an extraction hood and sprayed with an aqueous solution containing 2.34% (w/v) sodium tetraborate and 0.33% (w/v) sodium hydroxide, then with a freshly prepared 0.1% (w/v) methanolic solution of *N*-chlorodichloro-2,6-*p*-benzoquinone monimine. The R_f values and the colors were compared with those reported in one of our previous works (5). Following this, one or, at most, two antioxidants were assumed to be those present. Rubber extracts were then spotted on three plates of the same type, side by side with 0.5% (w/v) acetonitrile reference solutions of the assumed antioxidants and with mixtures of the two. The plates were developed together in petroleum ether (boiling range, 40-60°C) within 1 cm of the upper edge. When dry, each plate was developed in one of the solvents, (a) benzene, (b) benzene:hexane (75:25), and (c) benzene:ethyl acetate:acetone (100:5:1), then sprayed as above. If, in the three solvents, the R_f values and color are identical for the samples and the reference solutions, and if the corresponding spots for the mixtures are not deformed or divided, then the antioxidants present in the rubbers are assumed to be identical to the spotted reference compounds.

RESULTS AND DISCUSSION

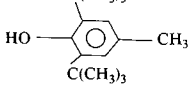
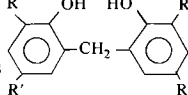
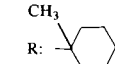
The results are presented in Table I. The brands (columns 1-9) and laboratories (columns 10 and 11) are designated with capital letters. The numbers following these letters indicate, for each brand or each laboratory, the number of different types of articles in which a given antioxidant has been found. Parentheses mean that several antioxidants are used in the same article. Only the eight compounds listed have been found in current use, *a priori* for toxicological reasons. However, the numerous articles studied came from various countries, some of which have no regulations governing this question. In such cases, compounds approved for alimentary contact are generally used. But the 57 phenols previously analyzed (5) are approved for

¹ Département de Pharmacie, Centre Hospitalier Spécialisé Valvert, Bd des Libérateurs, 13391 Marseille Cédex 11, France.

² Département d'Analyse Appliquée à l'Expertise, Faculté de Pharmacie, 27, Bd Jean Moulin, 13385 Marseille Cédex 5, France.

³ To whom correspondence should be addressed.

Table I. Results

Article, brand, number of different types ^a											Compound	Trade name (manufacturer) (supplier)	Formula	Approximate R_f value, petrol ether, then solvents			Color
1	2	3	4	5	6	7	8	9	10	11				a	b	c	
(A 4) (C 2) (C 2)	H 1 (H 1) (I 1) (J 2) (K 1)			M 2 (N 1)	M 2 (N 1)		P 1 T 2 U 1		(B' 1)	(E' 2)	I	Antioxidant BHT (Bakelite) (Göbel Pfrengle GmbH)		0.86	0.86	0.85	Yellow
(C 2)		H 1 Q 1	W 2			M 2 P 2	P 1 S 1 U 1	S 2 V 1			II	Cyanox 2246 (Cyanamid) (Devineau) Antioxidant OMB (Bakelite) (Göbel Pfrengle GmbH)		0.65	0.48	0.72	Yellow
B 4 C 1 D 3 F 1 G 1 (A 4) (C 2)	(H 1) (I 1) (J 2) (K 1)		X 4	O 2	O 2	O 2					III	Cyanox 425 (Cyanamid) (Devineau)	R: -C(CH ₃) ₃ R': -C ₂ H ₅	0.70	0.53	0.73	Yellow, green edge
							N 2		A' 2 B' 5 (B' 1)	C' 4 D' 9 E' 6 (E' 2)	IV	Permanax WSP (Vulnax International Ltd.)		0.74	0.55	0.76	Yellow
				P 2	P 2						V	Naugawhite (Uniroyal) (Chevassus)	R: -(CH ₂) ₈ -CH ₃ ^b R': -CH ₃	0.70	0.53	0.82	Yellow, green edge
		R 1									VI	Wingstay T (Goodyear Chemicals) (Compagnie Française Goodyear)	Mixture of hindered phenols	0.63 ^c 0.72 0.89	0.48 ^c 0.64 0.90	0.68 ^c 0.75 0.91	Purple Violet Pink
	L 1			N 1 (N 1)	N 1 (N 1)						VII	Naugard SP (Uniroyal) (Chevassus)	Undefined formula	0.36 0.71 0.72	0.18 0.56	0.57 0.61 0.81	Blue Grey Violet blue
B 1 D 1 E 2 H 1											VIII	Vulkanox CS (Bayer AG) (Bayer- France)	Undefined formula	0.23	0.11	0.49	Cream

^a Column 1, junctions in infusion sets for plasma, blood, and solutions; column 2, plunger seals of disposable syringes; column 3, surgeon's gloves; column 4, stoppers and plunger seals in blood-collection devices; column 5, tubes of urological catheters; column 6, balloons of urological catheters; column 7, valves of urological catheters; column 8, baby-bottle nipples; column 9, baby pacifiers; column 10, stoppers of injection vials; column 11, plunger seals of injection cartridges. See text for the meaning of letters, numbers, and parentheses.

^b Formula deduced from the chemical name given by the manufacturer, but these names are sometimes unduly simplified when the chains are branched.

^c These spots appear only after heating the plates at 100°C in an oven.

contact with food and thus toxicity does not explain the very limited choice of antioxidants.

In addition to the absence of toxicity, one might assume that the nature and the use of an article (and any sterilizing process) would affect the choice of antioxidant. However, Table I shows that the same antioxidants are used in very different articles. For instance, compounds I, II, and III were found in numerous items. Thus, the nature and the use of an article have no or little effect on the manufacturer's choice of antioxidant. Compounds other than I and IV, however, were not found in rubber stoppers for injection vials or in plunger seals of injection cartridges in spite of the large number of these samples.

Surgeon's gloves sterilized with ethylene oxide (brand H) or by irradiation (brand Q) contain the same antioxidant (compound II). Similarly, plunger seals of brand L syringes and tubes of brand N urological catheters contain compound VII; junctions in brand G infusion sets and brand N catheter valves contain compound IV. However, the first articles

quoted in each of these sets are sterilized with ethylene oxide, and the second ones by irradiation. The analyzed baby-bottle nipples and baby pacifiers, the only articles sterilized by boiling water or autoclaving at the moment of use, contain only compounds I and II, like articles sterilized with ethylene oxide or by irradiation. Thus, the sterilizing processes do not govern the choice of antioxidants.

Furthermore, the nature of the antioxidant does not depend on the brand, given that different articles of the same brand do not contain the same phenolic compound (for instance, brand H gloves and syringe plunger seals or brand P nipples and urological catheters). In the case of different types of the same article of the same brand, such as the junctions of the different types of infusion sets of brands B, C, and D, different compounds were also found. In urological catheters, the same antioxidant was found in the tubes and in the balloons, but another one in the valves, brand O excepted.

Rubbers are sometimes composed of mixtures of sev-

eral elastomeric polymers in very different proportions, each of these elastomers having a different antioxidant. Some cases where two antioxidants were found may correspond to such mixtures.

Thus, most of the antioxidants identified are sterically hindered molecules, which results in their very low volatility (6), but their choice does not depend on the sterilizing processes or on the use or brand of articles.

The first chromatographic development in petrol ether was used to carry oils from rubbers near the front of solvent, as they cause streaking of the spots (7). Furthermore, antioxidant R_f values were lower for rubber extracts, compared to pure-compound values, and the preliminary development in petrol ether avoids this artifact. Specifically, if this development is not done, antioxidant IV in a rubber extract has a R_f value of 0.65, instead of 0.74, thus equal to that of antioxidant II, spotted as the reference, which produces a similar color with the spray reagent. With the other antioxi-

dants present, predevelopment with petrol ether may be omitted.

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