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Analysis of tablets containing acetylsalicylic acid and phenylephrine by high-performance liquid chromatography*

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Abstract: A high-performance liquid chromatographic method permitted the quantitation of acetylsalicylic acid, phenylephrine, caffeine and phenacetin in tablets, and of the main impurities, salicylic acid and mono- and diacetyl derivatives of phenylephrine. A C8 reversed-phase column was used with a mobile phase containing methanol–1 M phosphoric acid–water 34:5:61 v/v/v.

Keywords: *Acetylsalicylic acid; reversed-phase high-performance liquid chromatography; phenylephrine; analgesic tablet formulation.*

Introduction

The solid-state acetylation of phenylephrine by acetylsalicylic acid was first reported by Troup and Mitchner [1] and later by Brown and Portmann [2]. Transacetylation by acetylsalicylic acid of other compounds in tablet formulations such as acetaminophen [3–5], codeine [6, 7] and homatropine [8] has also been reported. Early work on the stability and methods of analysis for phenylephrine has been reviewed [9]. More recently, oxidation products of phenylephrine have been identified [10] and more spectrometric assay methods described [11–13]. Column chromatography on XAD-2 was used to assay phenylephrine in syrups [14]. This paper describes the analysis of acetylsalicylic acid and phenylephrine in tablets by high-performance liquid chromatography (HPLC). The method is used to compare tablets containing acetylsalicylic acid, phenylephrine and other components, from two plants of the same manufacturer. This is apparently the first method allowing the simultaneous determination of the active components and the degradation products.

Experimental

Samples and storage conditions

The composition of the tablets used is listed in Table 1. The phenacetin in the old

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Table 1
Composition of tablets

	Plant A		Plant B
	Formulation AA (old) (mg)	Formulation AB (new) (mg)	Formulation B (mg)
Core			
Acetylsalicylic acid	230	388.8	388.8
Phenacetin	160	—	—
Caffeine anhydrous	27.5	32.4	32.4
Monocalciumphosphate monohydrate	–	+	+
Starch	+	+	+
Talc	–	+	+
Outer layer			
Chlorpheniramine maleate	2.0	2.0	2.0
Phenylephrine	10	12.18*	12.18*
Magnesium stearate	+	–	–
Tricalcium phosphate	+	+	+
Talc	+	+	+
Calcium sulphate dihydrate	–	+	+
Starch	+	+	+
Titanium dioxide	+	+	+
Saccharose	+	+	+
Coating (methylcellulose)	–	–	+

* As the hydrochloride.

formulation AA from plant A is replaced by acetylsalicylic acid in the new formulation AB from the same plant. Another difference between AA and AB is the absence of magnesium stearate in the latter. Both types are sugar coated. The absence of a pellicular coating distinguishes AB from tablet type B, made in another plant. In tablet types AB and B phenylephrine base has been replaced by the hydrochloride. To compare tablets AA with tablets B, eight normally aged batches of each were available, covering periods of 14–65 months. Only one batch of the new formulation AB was available. To compare formulations AB and B, tablets were stored in stressed conditions at 37°C, 50°C and 70°C, for up to 250 days. Fresh samples (three tablets) of a particular batch of AB and B, packed in capped vials, were put in ovens at regular intervals. The bulk of each batch was kept in a closed container in a desiccator at about 6°C. When the experiment started these batches were 10 months old.

Reagents and chemicals

Phenylephrine hydrochloride, acetylsalicylic acid, salicylic acid, phenacetin, chlorpheniramine maleate, methylphenobarbital and caffeine were of pharmacopoeial quality. Acetylsalicylic acid was further purified by crystallization from acetone. Methylphenobarbital, used as the internal standard, was further purified by column

chromatography on silica gel with methylene chloride–acetone 95:5. Water was doubly distilled. Organic solvents were of reagent grade (Aldrich Europe, Beerse, Belgium) and were distilled in glass before use. Phosphoric acid was of *pro analysi* quality, and all other reagents were of reagent grade (E. Merck, Darmstadt, FRG).

Phenylephrine derivatives were obtained by synthesis. Phenylephrine base was precipitated from an aqueous solution of the hydrochloride by addition of ammonia. The dried base was acetylated with acetic anhydride in pyridine by standing overnight at room temperature. The solution was evaporated and the residue purified by repeated column chromatography on silica gel with methylene chloride–acetone 50:50 and 75:25 v/v. The purification was followed by thin-layer chromatography (TLC) on silica gel F 254 (E. Merck, Darmstadt, FRG) with benzene–acetone–formic acid 70:29:1 v/v/v as the mobile phase. R_f values for the phenylephrine derivatives and tablet components were: phenylephrine hydrochloride, 0.0; chlorpheniramine maleate 0.0; N-monoacetylphenylephrine [N-(3,β-dihydroxyphenethyl)-N-methylacetamide] (I), 0.12; caffeine, 0.17; N,O^3-diacetylphenylephrine [N-(3-acetoxy-β-hydroxyphenethyl)-N-methylacetamide] (IIa), 0.23; N,O^β-diacetylphenylephrine [N-(3-hydroxy-β-acetoxyphenethyl)-N-methylacetamide] (IIb), 0.29; triacetylphenylephrine [N-(3,β-diacetoxyphenethyl)-N-methylacetamide] (III), 0.36; phenacetin, 0.39; aspirin, 0.53; salicylic acid, 0.59. Detection was by UV light at 254 nm and by spraying with diazotized *p*-nitroaniline [1, 2]. After evaporation of the column fractions, I was crystallized from ether, and IIa from ether-*n*-pentane 1:1 v/v. IIb and III gave oily residues. I, IIa and III were shown to have the structures reported previously [1]. Compound IIb was characterized by IR and mass spectrometry. The oily products IIb and III were unstable.

Apparatus and operating conditions

A high-pressure pump (Model M 6000A, Waters, Milford, MA, USA) was connected to a 20-μl loop injector (Model CV-6-UHPa-N60 Valco, Houston, TX, USA), a LiChrosorb RP8 Hibar column, particle size 10 μm, 250 × 4 mm (E. Merck, Darmstadt, FRG), a 254-nm fixed wavelength detector (Model 440 Waters, Milford, MA, USA), an integrator (Model DP88 Pye-Unicam, Cambridge, UK) used in the peak height mode, and a recorder (Model BD 40 Kipp and Zonen, Delft, The Netherlands). The mobile phase was prepared from 340 ml methanol and 50 ml phosphoric acid (1 M); the mixture was diluted to 1000 ml with water and degassed by sonication. The flow rate was 1 ml/min. The detector was set at 0.005 a.u.f.s. The chart speed was 5 mm/min. The column was kept at room temperature (*ca* 20°C).

Preparation of sample solutions

When present, the pellicular coating was removed from the tablets. After crushing in a mortar, 110.0 mg homogeneous powder was transferred to a 50.0-ml volumetric flask, and 15.0 ml 0.05% (m/v) solution of methylphenobarbital was added as the internal standard (IS), followed by 2.0 ml methanol and 2.5 ml phosphoric acid (1 M). The flask was sonicated for 5 min and the mixture diluted to 50.0 ml with water. Again the flask was sonicated for 5 min and the mixture filtered. The first few milliliters were discarded and the filtrate injected immediately. Tablets heated at 70°C could not be crushed as described above, since they formed a sticky mass in the vial. The vial content was dried over sodium hydroxide in a vacuum, then suspended in methylene chloride which was immediately evaporated under vacuum. The resulting powder was homogenized and analysed, a correction being made for the difference between the initial and final masses.

Chromatographic analysis

Regression lines (y = concentration in mg/50 ml; x = peak height ratio) were obtained for standard solutions containing phenylephrine ($y = 2.517x - 0.069$), I ($y = 3.226x - 0.023$), IIa ($y = 12.594x - 0.071$), caffeine ($y = 0.305x - 0.109$), phenacetin ($y = 0.211x - 0.039$), acetylsalicylic acid ($y = 2.403x - 0.731$), salicylic acid in the absence of phenacetin ($y = 3.732x - 0.002$), and salicylic acid in the presence of phenacetin ($y = 3.532x + 0.093$). Calibration curves for the unstable derivatives IIb and III were not prepared: concentrations of IIb were calculated using the regression line for I, corrected for differences in molecular mass and retention time. III was not detected even in greatly decomposed tablet samples. Correlation coefficients were at least 0.999 except for phenylephrine (0.998). When immediate analysis was impossible, standard solutions were kept at 5°C.

The reproducibility of the extraction and the chromatographic system was examined using a homogeneous mixture of powdered AA tablets 14 months old. The results are shown in Table 2. The figures reported in the table for the active components express the

Table 2
Reproducibility of the analytical method

		Tablet components						
	Parameter	Phenylephrine	I	IIa	Acetylsalicylic acid	Salicylic acid	Caffeine	Phenacetin
Chromatographic reproducibility								
8 injections of the same extract	x	98.7	18.3	18.6	94.3	4.5	110.0	99.5
	RSD	3.8	3.2	11.0	1.2	13.1	1.4	0.5
Extraction reproducibility								
1 injection of each of 10 extracts of a homogeneous tablet mixture	x	101.0	18.4	20.7	95.9	3.2	109.6	99.2
	RSD	6.3	4.8	10.7	0.7	10.1	1.3	0.6

x = mean. RSD = relative standard deviation. I = N-(3,β-dihydroxyphenethyl)-N-methylacetamide. IIa = N-(3-acetoxy-β-hydroxyphenethyl)-N-methylacetamide. Results expressed as percentages of the claimed content for active constituents (see text).

percentage of the label claim. Impurities are reported as percentages of the label content of the corresponding active component: this facilitates comparison with pharmacopoeial limits, but means that the sum of the percentages for a component and the corresponding impurities does not equal 100. The results show good chromatographic and extraction reproducibilities. The relative standard deviation (RSD) on values are largest for the small peaks (e.g. phenylephrine, decomposition products). The RSDs in the chromatography of salicylic acid and acetylsalicylic acid are higher than those for the extraction of these compounds because of the slow decomposition of the samples during eight consecutive analyses. For an acetylsalicylic acid extract at room temperature this loss was calculated to be about 0.1%/h.

Results and Discussion

Typical chromatograms, obtained for 16-month-old AA and B tablets, are shown in Fig. 1. The main components were well separated. Phenylephrine was not completely separated from small unknown components (cf. the high RSDs in Table 2), but I, IIa and IIb were adequately separated. Compound IIb has not previously been found in acetylsalicylic acid–phenylephrine mixtures. The fact that product III was not separated from phenacetin is not really a problem since in B tablets which do not contain phenacetin, III was not detected even after storage at 70°C. In previously reported TLC studies trace amounts of III were detected [1, 2]. Figure 1 clearly shows a difference in quality between AA and B tablets. In the conditions described, chlorpheniramine was not eluted from the column, but it could be determined using a mobile phase containing an increased amount of methanol. In such conditions the other components are not separated.

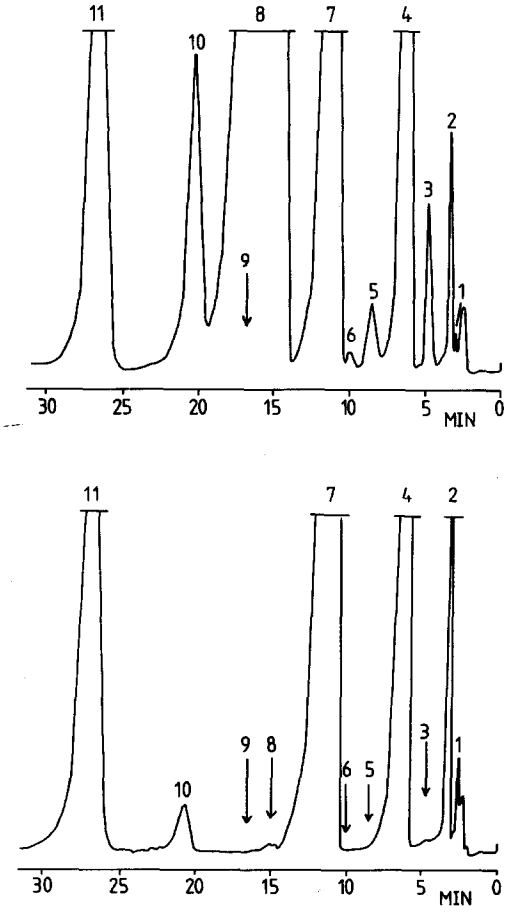

Figure 1
HPLC of 16-month-old tablets of type AA (a) and type B (b). 1, Maleic acid (from chlorpheniramine maleate); 2, phenylephrine; 3, N-(3,β-dihydroxyphenethyl)-N-methylacetamide (I); 4, caffeine; 5, N-(3-acetoxy-β-hydroxyphenethyl)-N-methylacetamide (IIa); 6, N-(3-hydroxy-β-acetoxyphenethyl)-N-methylacetamide (IIb); 7, acetylsalicylic acid; 8, phenacetin; 9, N-(3,β-diacetoxyphenethyl)-N-methylacetamide (III); 10, salicylic acid; 11, methylphenobarbital, internal standard (IS).

Figure 2 shows the influence of the methanol content of the mobile phase on the capacity factor of the tablet components. For the packing material used a methanol content of 34% provided the best compromise between speed and resolution. Table 3 lists the results obtained from the analysis of naturally aged batches of types AA and B. Each figure is the mean of two analyses each using a fresh extract of the same powder mixture. A single tablet analysis (S) was compared with the analysis of a homogenized mixture of 10 tablets (M). To correct any influence of nonuniformity of weight, the single tablet results were corrected for the mean tablet weight. For formulation AA a striking difference was observed between the S and M analyses (see below). The acetylation of phenylephrine was very irregular, but fast for all batches. Some batches have clearly been incorrectly overdosed as reflected by differences in the total content of phenylephrine and its derivatives. Important batch-to-batch differences in stability were demonstrated. For example, a 16-month-old batch had a lower phenylephrine content than a 65-month-old batch, although the total content of phenylephrine plus derivatives was much higher in the former. It is clear that a decrease in phenylephrine levels corresponded to an increase in the amount of I. IIa was present in the newer samples but absent in the older ones. Since IIb was found in the older samples but not in the newest, there is some evidence that IIa was transformed into IIb. Acetylsalicylic acid decomposed rapidly, 10% being lost in *ca* 2 years, while a corresponding amount of salicylic acid was formed. The 3.0% limit of the USP XX [15] for buffered tablets was exceeded in about 1 year and the BP 1980 [16] 0.15% limit was exceeded in all the batches examined. Several batches contained excessive caffeine and possibly phenacetin.

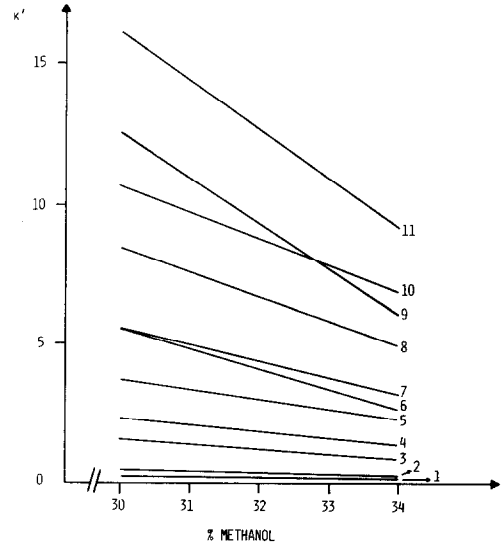

Figure 2
Effect of methanol content of the mobile phase on the capacity factor of tablet components. 1, Maleic acid; 2, phenylephrine; 3, N-(3,β-dihydroxy-phenethyl)-N-methylacetamide (I); 4, caffeine; 5, N-(3-acetoxy-β-hydroxyphenethyl)-N-methylacetamide (IIa); 6, N-(3-hydroxy-β-acetoxyphenethyl)-N-methylacetamide (IIb); 7, acetylsalicylic acid; 8, phenacetin; 9, N-(3,β-diacetoxyphenethyl)-N-methylacetamide (III); 10, salicylic acid; 11, methylphenobarbital, internal standard (IS).

For formulation B the differences between S and M analyses were small; the tablets were much more stable. Up to 5% excess phenylephrine was present, but the content never dropped significantly below the specified level. On storage a slight increase in the level of I was observed but IIa and IIb were never detected in significant amounts: detection limits were 2% (IIa) and 4% (IIb). In all batches the salicylic acid content was far below the USP XX limits, but the BP 1980 limit was always exceeded. The detection limit for salicylic acid was 0.05%. The caffeine content was about 5% below the label claim: it is possible that the monohydrate was used instead of the anhydrous form.

Table 3
Analysis of naturally aged tablets

Formulation AA																
Batch age	65 months		65 months		50 months		38 months		31 months		25 months		16 months		14 months	
Type of analysis	S	M	S	M	S	M	S	M	S	M	S	M	S	M	S	M
Components																
Phenylephrine	28	19	35	63	32	30	60	77	25	33	90	66	57	46	178	109
I	40	30	44	28	41	40	29	31	52	57	30	51	63	66	10	22
IIa	ND	ND	ND	ND	ND	ND	21	45	16	18	15	20	12	20	15	21
IIb	55	90	46	21	58	54	8	11	51	54	4	26	11	ND	ND	ND
Acetylsalicylic acid	75.0	78.7	78.0	97.8	81.7	84.5	92.7	98.6	80.0	81.5	91.3	93.3	94.8	93.2	101.8	98.6
Salicylic acid	12.7	12.3	11.5	6.0	15.8	11.0	5.3	4.4	12.7	11.0	5.4	6.7	7.3	7.0	2.9	1.8
Caffeine	108.5	113.2	111.8	115.0	105.1	108.0	103.2	110.8	107.3	111.6	96.7	108.5	104.9	101.8	107.0	96.5
Phenacetin	90.3	104.6	93.3	108.0	100.7	106.9	96.8	106.5	98.0	107.2	94.2	105.0	97.0	106.8	103.5	102.2
Formulation B																
Batch age	65 months		58 months		50 months		49 months		37 months		24 months		16 months		15 months	
Type of analysis	S	M	S	M	S	M	S	M	S	M	S	M	S	M	S	M
Components																
Phenylephrine	107	100	104	108	105	104	97	107	105	98	108	100	107	103	103	99
I	16	8	10	9	12	11	8	11	4	4	6	6	5	4	4	5
IIa	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
IIb	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Acetylsalicylic acid	93.7	98.3	92.6	100.4	95.6	97.9	97.1	99.5	95.3	96.0	91.9	97.5	94.8	98.8	94.7	97.2
Salicylic acid	0.4	0.6	0.5	0.6	0.5	0.6	0.4	0.3	0.3	0.3	0.2	0.3	0.4	0.4	0.2	0.2
Caffeine	92.1	97.5	93.6	94.7	91.7	95.0	92.9	95.2	94.4	91.9	91.5	94.9	91.8	95.0	92.9	93.3

Results expressed as in Table 2. S = single tablet analysis. M = analysis of a homogeneous mixture of 10 tablets. ND = not detectable.

The total variation, i.e. of the chromatographic system, the extraction mode and the tablet content, was examined by repeated single tablet analysis of a batch of type AA and B. The results are reported in Table 4. Figures are corrected to the mean batch weight. The RSD of the tablet contents is calculated using results from Table 2. Weight uniformity results are listed in Table 5. From Tables 4 and 5, it is clear that the uniformity of formulation B was much better than that of formulation AA. Comparison of the new formulation AB with formulation B, after treatment at 37°C and 50°C, showed no significant difference of stability. At 50°C, t_{90} of phenylephrine was about 100 days. No other phenylephrine derivative was observed. At both temperatures the salicylic acid level remained below the 3.0% limit for 250 days, and was slightly lower for type B than for type AB.

The results obtained at 70°C are shown in Fig. 3. The variation of the results is demonstrated by the standard error of estimate, $S_{y,x}$, shown for caffeine, whose stability is supposed to be unaffected in the conditions used. Most of this variation arose because single tablet analysis was performed. After 35 days no phenylephrine is left in either type of tablet. The acetylsalicylic acid decomposition is faster in AB, t_{50} (70°C) being 20 days,

Table 4
Tablet content variation

			Tablet components			
	Tablet type	Parameter	Phenylephrine	Acetylsalicylic acid	Caffeine	Phenacetin
9 single tablet analyses of the same batch; 1 injection each	AA	x	106.7	97.5	110.7	100.0
		RSD	26.2	7.8	9.9	6.5
	B	x	103.3	98.8	95.0	NI
		RSD	4.7	4.2	4.6	
calculated RSD of single tablet content	AA	RSD	25.5	7.8	9.8	6.4
	B	RSD	3.1	4.1	4.6	NI

Results expressed as percentages of the claimed content for active constituents (see text). x = mean. RSD = relative standard deviation. NI = not in the formulation.

Table 5
Tablet weight variation

Type AA			Type B		
Batch age (months)	Mean weight (mg) (n = 11)	RSD (%)	Batch age (months)	Mean weight (mg) (n = 9)	RSD (%)
65	781.8	3.2	65	786.7	1.9
65	817.7	2.9	58	800.6	2.0
50	798.3	4.5	50	805.6	3.1
38	805.3	3.8	49	808.6	1.9
31	834.2	4.4	37	805.0	1.2
25	809.5	5.0	24	806.9	2.5
16	798.3	3.8	16	791.4	2.2
14	804.3	6.2	15	786.6	1.8

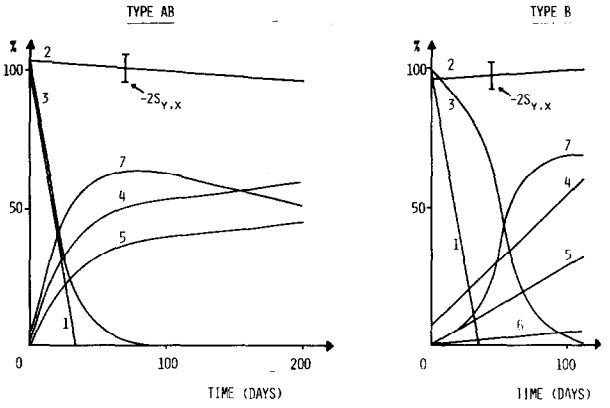

Figure 3
Thermal treatment at 70°C of tablets of type AB (a) and of type B (b). 1, Phenylephrine; 2, caffeine; 3, acetylsalicylic acid; 4, N-(3,β-dihydroxyphenethyl)-N-methylacetamide (I); 5, N-(3-acetoxy-β-hydroxyphenethyl)-N-methylacetamide (IIa); 6, N-(3-hydroxy-β-acetoxyphenethyl)-N-methylacetamide (IIb); 7, salicylic acid.

while for B tablets t_{50} (70°C) was 50 days. Derivatives I and IIa were also formed at a slower rate in B than in AB, but IIb was present in B tablets but not found in AB. The levels of salicylic acid in tablets AB can be explained by sublimation, followed by condensation on the vial walls. The latter phenomenon was observed in practice. The fast decomposition results (Fig. 3) deviate from those calculated from results at 50°C [17], which predict a t_{90} (70°C) of about 10 days. This fast decomposition is not in accordance with previous studies [1, 2], in which powder mixtures containing acetylsalicylic acid and phenylephrine hydrochloride contained at least 50% of the original phenylephrine after 35 days at 70°C unless magnesium stearate was present. The poor agreement between the 50°C and 70°C experiments could be explained by the better contact between phenylephrine and acetylsalicylic acid realized at higher temperatures, where the tablets start to get sticky. This might also explain why faster decomposition was found than in earlier studies [1, 2], where semiliquid was probably not formed. It should be borne in mind that the active constituents are incorporated in different parts of the tablets. At lower temperatures a reaction between phenylephrine and acetylsalicylic acid is impossible, unless migration from the tablet core to the outer layer (or vice versa) occurs. This migration would be facilitated by tablet water, or by another solvent such as acetic acid, formed by the decomposition of acetylsalicylic acid. The influence of lubricants (e.g. magnesium stearate) and tablet humidity on the decomposition of acetylsalicylic acid has been discussed in the literature [18–23].

The lower stability of formulation AA is probably related to the use of phenylephrine base, which is acetylated more readily than its hydrochloride. The presence of magnesium stearate could also be significant. The care taken during the production of formulation AA is also important. The greater variation of weight (Table 5) is an indication of insufficient control of production. Too high a humidity during tablet preparation could explain the lower stability of AA. Under stressed conditions (Fig. 3) some difference was observed between AB and B, almost identical formulations from two different plants, but no naturally aged samples of formulation B were available to confirm these results.

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