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Interaction between the Components of a Five-Component Cold Medicine

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Abstract—The reasons why five-component cold pills, a new complex medicine under development, change their color during shelf life are studied. The oxidation of ascorbic acid (AA) is responsible for the change in color; this process is enhanced in the presence of nitrogen base compounds. The IR spectra of equimolar mixtures of AA with some such compounds signify these changes. The results of this work can be used to eliminate undesired effects.

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The popularity of medicines containing two or more active components is progressively increasing [1]. Such medicines have complex formulations, and they cannot be regarded as mere mechanical mixtures of auxiliary and active substances. Components can enter various physicochemical interactions, which affect the stability of the medicine during production and shelf life, change its appearance, and generate unidentified impurities [2–4].

Farmstandart-Leksredstva (Kursk, Russia) is now working on a new five-component cold medicine. These pills, with decongestant and analgesic effects, contain ascorbic acid (AA), chlorpheniramine maleate (CM), phenylephrine hydrochloride (PE), paracetamol (P), codeine phosphate (CP), and shaping components. When a pilot lot of the pills was stored for two years at room temperature, pill cores changed their color from white to cream and the percentages of some components changed.

The goal of this work was to elucidate the reasons for these changes and to study the reciprocal effects of the components of the medicine.

EXPERIMENTAL

Reagents, solutions, and equipment. Binary model mixtures of the test compounds were prepared by pounding in an agate mortar. In order to speed up and enhance transformations, the mixtures were heated at 110°C for 2 h in a drier. They were dried at 40°C after pounding to remove excess liquid components.

The IR spectra of the reagents and their mixtures (1 : 100) were recorded as KBr disks on an Nicolet Avatar 360 E.S.P. FT-IR spectrometer in the wavenumber range 4000–400 cm^{-1} with the resolution 4 cm^{-1}. UV absorption spectra of aqueous–organic solutions were obtained on a Hewlett-Packard HP 8453 spectrophotometer.

The medicinal and auxiliary substances used in the work were of pharmaceutical quality; they were verified and certified by the quality control department of the manufacturer. For spectroscopic measurements, KBr (for IR spectroscopy, from Fluka, USA) and acetonitrile (0 grade, for gradient chromatography, from Cryochrom, Russia) were used. The other reagents used were of at least analytical grade.

RESULTS AND DISCUSSION

We suggested that AA caused the observed evolution of the pills: AA is capable of reversible or irreversible oxidation and acid–base reactions. Experiments verified our suggestion.

Evolution of the Color of AA and Its Mixtures

The results of the observation of mixtures with AA in technological proportions are displayed in Table 1. Yellowish tints appeared only after heating; the most prominent changes occurred in mixtures of AA with CM, PE, and magnesium stearate. Mixtures with P,

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microcrystalline cellulose, and starch remained practically unchanged. Pure AA changed its color only after moisturizing. The amount of each additive was tens times lower than the amount of AA.

To compare the color intensity for some of the most deeply colored mixtures, we obtained the UV spectra of their solutions. The solvent used was 5 vol % CH_3CN + 0.025 M KH_2PO_4 (pH 7.4); the AA concentration was 0.25 mg/mL. In the absorption spectra for AA + PE, AA + CM, and AA + magnesium stearate mixtures, an increase in light absorption was observed in the form of a plateau at 340–360 nm; the longest plateau was observed for CM. The IR spectra did not reflect the change in color. Apparently, the sensitivity of the method is insufficient for detecting relatively low concentrations of colored compounds.

Reaction of AA with Some Components (Scheme)

Ascorbic acid is known to form H-bonds through its OH group and the nitrogen atoms of nitrogen bases. Complexes of AA with thiamine or nicotinamide were prepared by heating ethanolic solutions of the reagents [5].

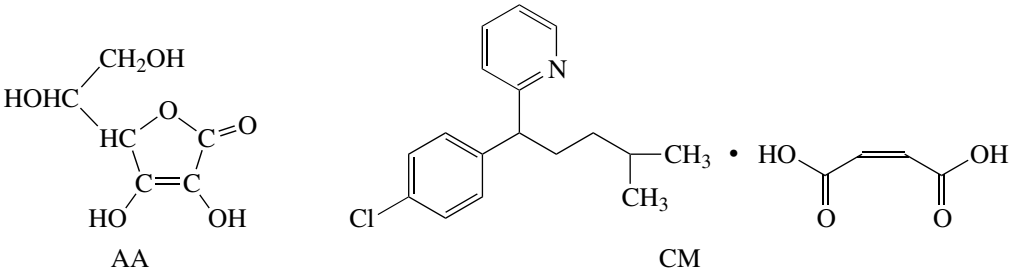
Acids are complexed with substituted pyridines either through H-bonds N···H–O or with the participation of an N^+H···O– ion pair, depending on the strengths of the acid and base. These two bond types differently change the IR absorption bands of the reagents [6]. The degree of ionization of AA can be ascertained from the position of the stretching mode υC=O, which appears at 1754 cm^{-1} in AA and at 1702 cm^{-1} in the ionized 3-OH group of sodium ascorbinate [7, 8]. In attendance, the mode υC=C shifts from 1680 to 1595 cm^{-1} [6].

Our results match the data of the above-cited studies. The main parameters of the IR spectra of AA and its mixtures with CM, diethylamine, and sodium hydroxocarbonate are listed in Tables 2 and 3. Despite the different natures of the second components, the spectral evolution in all cases is the same, associated with the electron-density redistribution in the OH–C=C–OH group in an AA molecule as a result of –O–H···N or O–Na bonding. In addition, in the spectrum of an AA + CM mixture, the characteristic frequency of the protonated tertiary nitrogen of CM changes, indicating the involvement of this atom in the reaction [11]. We also studied mixtures of AA with trimethylamine and diphenylamine. The IR spectra of these mixtures are the sums of the spectra of the reagents. Ascorbic acid does not react in this case, likely because of steric hindrances.

Table 1. Evolution of the color of model mixtures upon heating

Compounds	Color after heating	
	without water	with water
Ascorbic acid (AA)	White	Light yellow
AA + codeine phosphate	Light cream	Cream
AA + phenylephrine hydrochloride	Light cream	Brown
AA + chlorpheniramine maleate	Brown	Dark brown
AA + paracetamol	White	White
AA + magnesium stearate	Light cream	Brown
AA + plasdon K25	Light lilac	Light brown
AA + microcrystalline cellulose	White	White
AA + potato starch	White	White

Our studies allow us to claim that AA in a solid drug can react with some nitrogen-containing components. The strength of the N···H–O bond is affected by the steric hindrance to the reaction and the strength of the base. Other processes can occur concurrently, including those that yield colored products.



Scheme.

Table 2. Some parameters of IR spectra for ascorbic acid, chlorpheniramine maleate, and their mixtures (frequencies in cm^{-1})

Vibration type	Vibration frequency, cm^{-1}			Comments (suggested assignment)
	AA	CM	mixtures	
νC=O	1754	Not found	Virtually unchanged	Not found
νC=C, [1], p. 43	1673	Not found	Decreased intensity	Electron-density redistribution induced by H-bonding
νC–O, [1], p. 128	1140, 1121, 1027	Not found	Decreased intensity	The same
νO–H, [1], p. 116	3526, 3410, 3316, 3218	Not found	A broad band at 3550–3100 cm^{-1}	H-bonding
ν–NH^+, [1], p. 286	Not found	2456	Shifted to 2702 cm^{-1}	Replacement of maleic acid from the CM complex in the reaction and AA

Table 3. Evolution of IR spectra upon mixing ascorbic acid with some bases (frequencies are in cm^{-1})

Mixture	Vibration	Vibration frequency, cm^{-1}		Comments (suggested assignment)
		AA	mixture	
AA + sodium hydrocarbonate	νC=O	1754	Unchanged; appears at 1704	O–Na bonding
	νC=C	1673	Shifted to 1601	Electron-density redistribution induced by H-bonding
	νO–H	3526, 3410, 3316, 3218	A broad band at 3550–3100 cm^{-1}	O–Na bonding
AA + diethylamine	νC=O	1754	Virtually unchanged	Not detected
	νC=C	1673	Shifted to 1597	Electron-density redistribution induced by H-bonding
	νO–H	3526, 3410, 3316, 3218	A broad band at 3550–2600 cm^{-1}	H-bonding

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