OPTIMIZATION OF THE COMPOSITION AND WET GRANULATION TECHNOLOGY OF DROTAVERINE HYDROCHLORIDE TABLETS

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The process of drotaverine hydrochloride decomposition is modeled using data on the drug solution stability and the variation of RGB color coordinates of drotaverine hydrochloride tablets. The introduction of an acid into the drug composition ensures obtaining high-quality tablets of yellow-green color. The pressing of granules with dimensions below 0.6 mm and a relative humidity above 1.8% provides for a uniform coloration of tablets.

As is known, drotaverine hydrochloride is susceptible to decomposition with the formation of perparaldine and 3,4-diethoxybenzoic acid. The reactions of drotaverine hydrochloride oxidation and hydrolysis most readily proceed at elevated temperatures and increased humidity.

This paper presents the results of investigation of the effect of pH-stabilizer and antioxidant additives on the stability and quality of 0.04 g drotaverine hydrochloride tablets.

As is well known, the color of tablets is a highly sensitive indicator of the quality of the parent drug manufactured in this ready-to-use form. Sometimes, a change in color is the first evidence of deteriorated quality, even when the results of chemical analyses are quite satisfactory. However, objective assessment of the drug quality using this characteristic is complicated in the case where the tablets are given mixed colors (orange, yellow-green, etc.). In order to accelerate the stage of optimization of a drug composition with respect to stability and to provide for the economy of expensive instrumentation and reactants, it is sometimes expedient to use a digital analysis of the color of ready-to-use drugs in the course of accelerated aging tests.

In this context, we have studied the possibility of tracing the process of decomposition of an active substance by monitoring the color of tablets containing this drug. Simultaneously, we obtained data on the influence of some technological factors (humidity and granulometric composition of the tabletization mass) on the homogeneity of coloration and on the color coordinates of drotaverine hydrochloride tablets.

The proposed method stipulates a complex approach involving a primary mathematical modeling of the process and the subsequent optimization of the drug composition and production technology within the framework of this model.

MATERIALS AND METHODS

The parent substance of drotaverine hydrochloride was from Chemo Iberica SA (Spain) (Normative Documentation ND 42-7283-97) and from the Irbit Chemico-Pharmaceutical Plant (Temporal Pharmacopoeial Article VFS 42-3937-00). Other reagents: low-molecular-weight poly(vinyl pyrrolidone) (PVP-12600) of pharmaceutical grade (VFS 42-1194-78); lactose (VFS 42-3110-98); potato starch (State Standard GOST 7699-78); and citric acid (GOST 908-79).

The experimental tablets of drotaverine hydrochloride were manufactured as follows. A mixture of 10 g of drotaverine hydrochloride, 14 g of potato starch, 11.25 g of lactose, and 0.5 g of calcium stearate was thoroughly triturated in a mortar, wetted with a solution of 0.75 g PVP in 12 g of water, stirred, passed through a 2 × 20 mm slit sieve, and dried in a shelf dryer at 50 – 55°C. Finally, the material was granulated and tabletized using 7-mm dye matrices. The tablet weight was 0.14 – 0.16 g.

The color characteristics of tablets and granulates were studied with the aid of a digital scanner. The tablets were placed into an HP ScanJet 4470 scanner and processed using the HP PrecisionScan Pro 3.1 program in the following regime: resolution, 1200; sharpness, high; pixel depth, maximum; noise reduction, on; lamp operation time, increased; color depth, 16 bit; dark level, 0; bright level, 255 units. The

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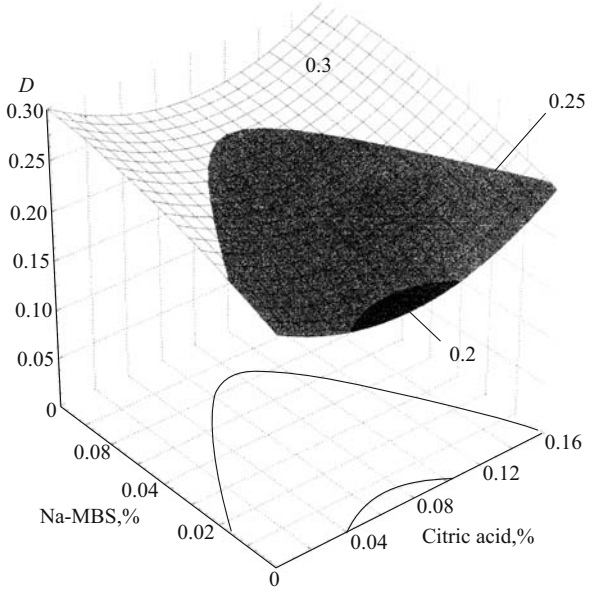

Fig. 1. The surface of the response function for the effect of Na-MBS and citric acid additives on the stability of drotaverine hydrochloride solution.

TABLE 1. Effects of Various Additives on the Stability of Drotaverine Hydrochloride in Solution

Test No.	Additive	Concentration	Optical density of solution
1	Citric acid	0.1	0.273
2		0.2	0.261
3		0.4	0.48
4	Na-MBS	0.1	0.295
5		0.2	0.315
6		0.4	0.325
7	PVP	0.35	0.93
8		0.5	0.92
9		0.75	0.98
10	Magnesium sulfate	0.1	1.18
11		0.2	1.58
12		0.45	1.38
13	Calcium chloride	0.15	1.07
14		0.2	1.13
15		0.45	1.34
16	Control 1	–	0.198
17	Control 2	–	1.15

color rendering was checked by scanning reference samples of white paper (R 255, G 255, B 255).

The tablet color was determined by analyzing the obtained graphic file in the RGB coordinates according to a pipette procedure in the PhotoPaint 7 program using an inscribed square with a side length of about half of the tablet diameter. The experimental results were statistically processed according to recommendations [8] using the Statistica Ver. 6 program package.

The quality of tablets was evaluated in terms of the Temporal Pharmacopoeial Article VFS 42-3107-98 "Drotaverine Hydrochloride 0.04 g Tablets."

RESULTS AND DISCUSSION

The influence of citric acid, sodium metabisulfate (Na-MBS), hardeners (magnesium sulfate, calcium chloride), and PVP was studied in a series of model experiments, whereby the substances were added in various concentrations to a 2% drotaverine hydrochloride solution in 10% aqueous ethanol. The sample solutions were poured into 30-ml vials (BV-30), hermetically closed with PPV-12 caps, and thermostatted at 50°C. The control experiments were performed using parent drug solutions without additives, which were kept either in a refrigerator at 0°C (control 1) or in the thermostat (control 2). A criterion of the oxidative decomposition of drotaverine hydrochloride was the increase in the optical density D of its solution at 440 nm, measured in a 10-mm-thick cell on a KFK-2 spectrophotometer with No. 4 optical filter.

As can be seen from the data presented in Table 1, Na-MBS, citric acid, and PVP reduce the rate of oxidative decomposition of drotaverine hydrochloride, while both hardeners slightly accelerated the decomposition process.

The joint influence of Na-MBS and citric acid on the stability of drotaverine hydrochloride solutions was studied in a series of tests performed according to an orthogonal central composition plan. To 100 ml of a 2% drotaverine hydrochloride solution were added Na-MBS and citric acid additives, the flasks with sample solutions were kept in a thermostat at 50°C for two days, and then the samples were characterized with respect to the optical density at 440 nm. The optimum additive criterion was the minimum optical density of the solution, which corresponded to the minimum degree of drotaverine hydrochloride decomposition. The results of these experiments are presented in Table 2.

The optical density of sample solutions can be described by the regression equation

$$D = 0.2293 - 1.0138x + 1.3968y +$$

$$+ 7.0227x^2 - 1.2004xy - 6.4525y^2,$$

where x and y are the concentrations of Na-MBS and citric acid, respectively. As can be seen from this relation, the maximum effect on the stability of drug solutions is produced by citric acid; there is also a certain synergism in the stabilizing action of Na-MBS and citric acid. Using the results of these tests plotted in Fig. 1, it is possible to determine the intervals of component concentrations (citric acid, 0.04 – 0.10%; Na-MBS, 0.0 – 0.006%) corresponding to a relative stability of the drug solution. Since the maximum effect on the solution stability was produced by the introduction of citric acid, it was concluded that the limiting stage of drotaverine hydro-

TABLE 2. Tablet Composition Optimization Using a Two-Day Orthogonal Central Composition Plan 2^3

Test No.	Concentration,%		Optical density of solution
	citric acid	Na-MBS	
1	0.025	0.025	0.247
2	0.025	0.125	0.289
3	0.125	0.025	0.246
4	0.125	0.125	0.275
5	0.005	0.065	0.279
6	0.150	0.065	0.280
7	0.065	0.005	0.194
8	0.065	0.150	0.236
9	0.065	0.065	0.249
Control 1	0	0	0.192
Control 2	0	0	0.83

chloride decomposition was the conversion of salt into base. Thus, in order to increase the stability of parent compound in the course of wet granulation and drying, it is recommended to introduce a source of acid into the tablet composition.

It should be noted that the results of modeling of the stability of solutions of the drug components do not always correspond to processes in the volume and on the surface of tablets. For this reason, we have also studied the effect of acid additives on the stability of the tablet color. In these experiments, we have varied the content of citric acid in the wetting solution. The wet masses were granulated through an 0.8-mm-mesh sieve and dried to a residual humidity of 2.2%. The visual examination showed that both granulates and pressed tablets free of the acid possess a deeper color and contain relatively dark inclusions.

The results of color evaluation (Table 3) showed a statistically reliable ($p \le 0.05 – 0.001$) decrease in the color coordinate in the tests without acid (B = 156.83) as compared to that for compositions containing 0.7 – 2.1% of citric acid (B = 165). Similar results were obtained in the experiments with tartaric acid as a binder (Table 4). The additives of hydrochloric acid also produced stabilization of the tablet color, but the effect was not as pronounced. This result is probably explained by the evaporation of hydrogen chloride in the course of drying.

TABLE 3. Effect of Citric Acid on the Tablet Color

Citric acid concentration, %	R	G	B
0	255.00 ± 0.00	252.50 ± 0.22	156.83 ± 0.16
0.7	255.00 ± 0.00	255.00 ± 0.00	165.83 ± 0.60
1.4	255.00 ± 0.00	255.00 ± 0.00	165.50 ± 0.56
2.1	255.00 ± 0.00	255.00 ± 0.00	164.83 ± 0.30

Notes. Resolution, 72 × 72 dpi; file format, 24-digit RGB; background color, RGB 255, 255, 255.

TABLE 4. Effect of Citric Acid on the Color Coordinates of Granulates and Tablets

Test No.	R	G	B
1	255.00 ± 0.00	254.83 ± 0.40	157.50 ± 0.61
2	255.00 ± 0.00	255.00 ± 0.00	158.16 ± 0.74
3	255.00 ± 0.00	254.00 ± 0.00	161.33 ± 0.61
4	255.00 ± 0.00	255.00 ± 0.00	163.16 ± 0.30
5	255.00 ± 0.00	255.00 ± 0.00	173.50 ± 0.71
6	255.00 ± 0.00	255.00 ± 0.00	176.33 ± 1.58

Some published data indicate that the stability of tablets may depend significantly on the humidity of the tabletization mass [2 – 5]. In order to determine the optimum humidity, we took the samples of granulates in the course of drying and prepared model tablets using 7-mm dye matrices. In the experiments with a granulate humidity of 22 and 17%, high-quality tablets could not be obtained because the mass sticks to the dye surface. Satisfactory results were obtained using granulates with a relative humidity of 5 and 1.8%. However, the samples of 1.8% humidity exhibited a statistically significant ($p \le 0.05 – 0.001$) change in the tablet color toward white. Apparently, the process of drying is accompanied by the removal of crystallization water, which leads to the formation of a less intensely colored product. It is the admixture of such granules that accounts for the appearance of bright spots on the surface of tablets. Thus, the optimum interval of humidity for the granulate is 1.9 – 5.0%.

In the case of pressing colored granulates, it is rather difficult to obtain homogeneously colored tablets free of spots. This is related to the fact that granules of different size exhibit deviations from the average color. The greater the average granule size, the more clearly pronounced spots are observed on the surface of tablets. In order to eliminate this drawback, it was suggested to reduce the average grain size by separating the coarse fraction of granules. In order to determine the optimum fractional composition of the granulate, the initial wet mass with a humidity of 2% was fractionated by sieving into three fractions with a granule size of > 1 mm

TABLE 5. Characteristics of Tablets Pressed from Various Fractions of Granules

Parameter	Experiment		
	1	2	3
"B" color coordinate of tablets	178.33 ± 4.87	182.33 ± 2.16	182.33 ± 0.51
Bright spot size, mm	0.8	0.2	0.2
Dark spot size, mm	0.6	0.4	0.2

(3), 1.0 – 0.6 mm (2), and < 0.6 mm (1), and then each fraction was pressed into tablets using 7-mm dye matrices.

Data on the quality of these tablets presented in Table 5 show that no statistically reliable differences were observed between the color characteristics of tablets pressed from different fractions of the granulate. However, as was noted above, tablets obtained using coarse granules exhibit large bright and dark inclusions. It should be noted that the friability of granulated drotaverine hydrochloride was virtually independent of the average granule size, which contradicts numerous published data [6]. We believe that this anomalous behavior is explained by certain special properties of drotaverine hydrochloride crystals.

The influence of lubricating agents on the coloration of tablets was studied in a series of experiments with compositions containing 1% of calcium stearate (test 2), stearic acid (test 3), and magnesium stearate (test 4). The results were compared to the control experiment (test 1) using a colorless mixture containing no citric acid. As can be seen from the data in Table 6, the introduction of stearic acid increases the stability of drotaverine hydrochloride in the course of processing. On the contrary, magnesium stearate somewhat accelerated the drug decomposition, which is probably explained by the more pronounced alkaline properties of this compound.

The stability of drug quality is inseparably related to its efficacy and safety. Many problems of instability encountered in the course of the development, production, storage, and realization of drugs are either caused by the incompatibility of drug components or related to insufficient knowledge about the mechanisms of reactions between these components.

The degradation of parent substances may proceed over a rather long period of time. Significant changes in the chemical properties may have a latent form or fall within the limits of parameters stipulated by the corresponding pharmacopoeial articles. In practice, there are many cases when the color of ready-to-use medicinal forms exhibit a change, while the other characteristics obey all requirements of the normative documentation.

Although reactions observed in solutions do not always take place in pressed mixtures, many researchers prefer to obtain preliminary estimates of the stability of solid preparations in experiments with solutions prior to carrying out tests with solid ready-to-use medicinal forms.

TABLE 6. Effect of Lubricants on the Color Coordinates of Tablets

Test No.	R	G	B
1	254.50 ± 0.22	254.83 ± 0.40	162.16 ± 0.98
2	254.83 ± 0.16	254.66 ± 0.33	177.50 ± 0.92
3	255.00 ± 0.00	255.00 ± 0.16	179.83 ± 0.60
4	254.50 ± 0.22	254.00 ± 0.00	165.83 ± 0.30

In this study, we have used a rapid method for modeling the process of drotaverine hydrochloride decomposition traced by monitoring the solution color. It was established that the limiting stage of drotaverine hydrochloride decomposition is the conversion of salt into base; accordingly, it was suggested to introduce acids in the drug composition.

In the development of a model medicinal form, we evaluated the drug stability by monitoring the change in the color characteristics of tablets using a rapid method for determining the color coordinates with the aid of computer-aided scanning. It was established that the proposed method can be used for the quantitative comparison of coloration of experimental and control tablets. In particular, this method showed that acid additives produce a stabilizing effect on the table color in the course of storage. It was also found that the coloration of tablets depends on the average size and humidity of granules used for pressing tablets.

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