for wheat groats $\tau_0 = 0.8857 + 0.1538B + (-100.46 + 13.83)(-0.8494 + 0.5910^{-2}T - 10^{-5}T^2)B$ for $R = 0.98$.

NOTATION

τ_0, initial unit resistance to shear; B, storage time; W, moisture content; σ_{con}, stress state; d_a, arithmetic mean diameter of the particles; T, temperature; R, correlation coefficient.

LITERATURE CITED

1. L. I. Karnaushenko, V. T. Tsynalevskii, and N. K. Kornev, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 22, 377-380 (1979).
2. L. I. Karnaushenko and T. P. Novichkova, "Experimental study of bulk materials," Inzh.-Fiz. Zh., 47, No. 3, 484-485 (1984).
3. GOST 21560.4-76, 21560.5-76. Mineral Fertilizers. Methods of Determining Consolidation. Method of Determining Friability. Moscow (1965), pp. 15-17.
4. N. L. Malonosov and I. M. Kuvshinnikov, Agrochemistry, No. 6, 126-136 (1977).
5. I. M. Kuvshinnikov, "Physicochemical principles and production of noncaking phosphorus fertilizers," Doctoral Dissertation, Engineering Sciences, Moscow (1982).
6. L. I. Karnaushenko, T. P. Novichkova, and A. I. Yakovenko, Izv. Vyssh. Uchebn. Zaved., Pishch. Tekhnol., 72, No. 6, 72-74 (1984).
7. V. I. Kucheryavyi and V. N. Anikin, Khim. Sel'sk. Khoz., 7, No. 8, 24-27 (1969).
8. L. I. Karnaushenko, D. M. Donskoi, and S. F. Yatsenko, Izv. Vyssh. Uchebn. Zaved., Pishch. Tekhnol., 79, No. 1, 79-81 (1985).

DETERMINING THE THERMOPHYSICAL PARAMETERS OF DRUG PREPARATIONS

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Measurements are reported on the heat treatment of synthetic pharmaceutical preparations (levomycetin and its semifinished precursors). An algorithm has been devised for solving the inverse problem for the thermal diffusivity, which is dependent on temperature; the numerical solutions are compared with experiment.

1. The pharmaceutical industry produces a wide range of preparations. The techniques for making many of them involve many heat- and mass-transfer processes. Drying is particularly common. From the technological viewpoint, this determines the quality not only of the intermediate products but also of the finished drug forms. It is necessary to understand the drying mechanism and to choose sound drying techniques, which is impossible without analyzing the thermophysical and mass-transfer characteristics.

Pharmaceutical preparations are examined in detail as regards pharmacological effects, biological activity, composition, toxicity, acceptability, storage periods, etc.; however, very few data appear in the literature on their thermophysical and mass-transfer characteristics [1-3], which is due, on the one hand, to undervaluation of these characteristics as regards production technology and on the other to the lack of reliable theoretical methods and the cost and laboriousness of measurements.

Recently, there have been considerable advances in methods of solving inverse problems and reliable numerical algorithms have been devised. One method is to reduce the determination of thermophysical parameters to minimizing a certain discrepancy functional.

Here we consider determining the thermal parameters and thermal diffusivity for levomycetin and semifinished products preceding it, in particular levoamine.

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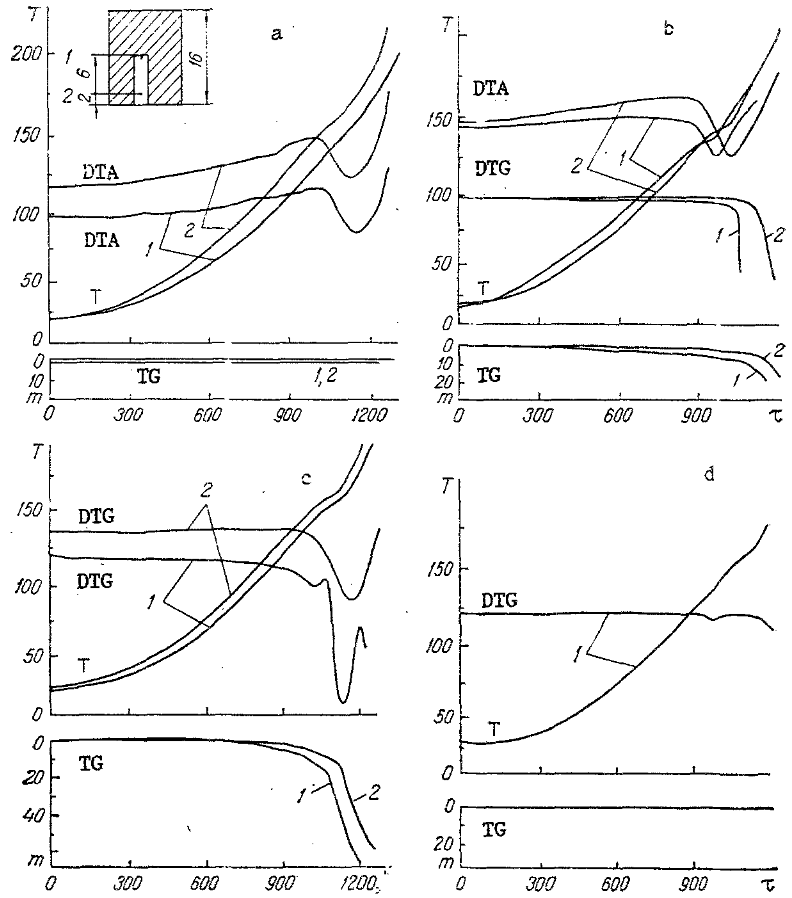

Fig. 1. Thermograms for levoamine (a), oven No. 2, specimen 340 mg, q = 10°C/min, τ = 25 min; threoamine (b), oven No. 1, specimen 470 mg, q = 5°C/min, τ = 50 min; oxymethyl compound (c), oven No. 1, specimen 600 mg, q = 10°C/min, τ = 25 min; dextramine (d), oven No. 1, specimen 500 mg, q = 5°C/min, τ = 50 min; T_{max} = 250°C, TG = 200 mg, DTF = 1/15, DTA = 1/15. The numbers on the curves correspond to the points of temperature measurement 1 and 2 in the scheme; τ in sec, m in mg, and T in °C.

2. Thermal Parameters of Levomycetin. The thermal parameters were examined under dynamic conditions with an MOM derivative recorder [4]; the methods have been described in [5]. The temperature was determined indirectly at two points (Fig. 1a shows the positions of the thermocouple, dimensions in mm). The working conditions were chosen such as to identify a certain stage in the heat treatment of interest and examine it most fully.

We recorded the thermograms for levomycetin and intermediates preceding it (levoamine, threoamine, dextramine, and an oxymethyl compound), particularly curves for the weight loss TG, differential thermogravimetric curves DTG, temperature T, and curves for the variation in heat content DTA (Fig. 1). All the experiments were performed with ceramic vials, with the weights kept strictly constant on repeating the experiments in the region of a gram. The heating temperatures did not exceed 250°C, since the materials are labile. The sensitivities of the balance and in the DTG and DTA were taken as 200 mg, 1/15, and 1/15 in all the experiments. The atmosphere in the oven was air. Dried specimens were used to determine the thermophysical properties of the initial preparations.

The thermograms show that the shapes, nature, and order of the effects are strictly distinctive. The effects above 100°C (for threoamine), 120°C (oxymethyl compound), and 130°C (dextramine) are due to decomposition, with the material subsequently melting and releasing heat, as is evident from the DTA curves.

A knowledge of the physicochemical transformations enables one to predict the behavior under various conditions.

As the compounds are thermally labile, the thermophysical parameters were examined in the region below the decomposition point. The solution to the inverse problem was used with the observed temperature distributions and minimizing the discrepancy functional by the conjugate-gradient method to obtain the thermal diffusivity of levoamine.

3. Model for Extracting Nonlinear Thermophysical Characteristics from Measured Temperature Distributions. Heat transfer in the dry material is described by the one-dimensional heat-conduction equation [6, 7]

$$\frac{\partial T}{\partial t} = \frac{\partial}{\partial x}\left(a(T)\frac{\partial T}{\partial x}\right), \quad l_0 < x < l_1, \quad 0 < t \leqslant t_1, \tag{1}$$

with the initital temperature distribution

$$T(x, 0) = T_0, \quad l_0 \leqslant x \leqslant l_1, \tag{2}$$

and boundary conditions of the first kind

$$T(l_0, t) = y_0(t) \tag{3}$$

$$T(l_1, t) = y_1(t), \quad 0 < t \leqslant t_1, \tag{4}$$

where $y_1(t) = T_0 + qT$, q is the constant heating rate, and the function $y_0(t)$ is set equal to the measured temperature at the point $x = x_1$ $(\ell_0 = x_1)$ (curve 1 in Fig. 1a).

The function $a(T)$ was approximated as

$$a(T) = a_1 + a_2 T, \tag{5}$$

and should be determined in such a way that the solution to (1)-(4) satisfies the additional conditions

$$T(x_i, t) = \varphi_i(t). \tag{6}$$

One derives a_1 and a_2 by minimizing the discrepancy functional

$$I(a_1, a_2) = \sum_i \int_0^{t_1} \beta_i(t)(T(x_i, t) - \varphi_i(t))^2\, dt, \tag{7}$$

relating the measured and calculated temperatures ($\beta_i(t)$ are positive functions defining the additional information).

It was minimized by the conjugate-gradient method [8]; the components of the gradient are written in terms of the sensitivity functions $\psi_i = \partial T/\partial a_j$ in the following form [9, 10]:

$$\frac{\partial I}{\partial a_j} = 2\sum_i \int_0^{t_1} \beta_i(t)(T(x_i, t) - \varphi_i(t))\psi_j(x, t)\, dt. \tag{8}$$

The functions $\psi_j(x, t)$ $(j = 1, 2)$ are determined as solutions to the system

$$\frac{\partial \psi_j}{\partial t} = \frac{\partial}{\partial x}\left(a(T)\frac{\partial \psi_j}{\partial x}\right) + \frac{\partial}{\partial x}\left(\frac{\partial a}{\partial T}\frac{\partial T}{\partial x}\psi_j\right) + \frac{\partial}{\partial x}\left(\frac{\partial a}{\partial a_j}\frac{\partial T}{\partial x}\right), \tag{9}$$

$$l_0 < x < l_1, \quad 0 < t \leqslant t_1,$$

$$\psi_j(x, 0) = 0, \quad l_0 \leqslant x \leqslant l_1; \tag{10}$$

$$\psi_j(l_0, t) = 0, \quad \psi_j(l_1, t) = 0, \quad 0 < t \leqslant t_1. \tag{11}$$

Equations (1)-(11) were approximated by the following difference schemes with a certain error:

$$T^k_{\bar{t},i} = (aT^k_{\bar{x}})_{\hat{x},i}, \quad 0 < i < N, \quad 0 < k \leqslant K, \tag{12}$$

$$T^0_i = T_0, \quad 0 \leqslant i \leqslant N, \tag{13}$$

$$T^k_0 = y^k_0, \quad 0 < k \leqslant K, \tag{14}$$

$$T^k_N = y^k_1, \quad 0 < k \leqslant K, \tag{15}$$

$$\psi^k_{j\bar{t},i} = (a\psi^k_{j\bar{x}})_{\hat{x},i} + \left(\frac{\partial a}{\partial T}T^k_{\bar{x}}\psi^k_j\right)_{\hat{x},i} + \left(\frac{\partial a}{\partial a_j}T^k_{\bar{x}}\right)_{\hat{x},i}, \tag{16}$$

$$0 < i < N,\ 0 < k \leqslant K,$$

$$\psi_{ji}^{0} = 0,\ 0 \leqslant i \leqslant N, \tag{17}$$

$$\psi_{j0}^{k} = 0,\ 0 < k \leqslant K, \tag{18}$$

$$\psi_{jN}^{k} = 0,\ 0 < k \leqslant K, \tag{19}$$

$$I = \sum_{i} \sum_{k=1}^{k} \beta_i^k \left(T_{n_i}^k - \varphi_i^k\right)^2 \tau, \tag{20}$$

$$\frac{\partial I}{\partial a_j} = 2 \sum_{i} \sum_{k=1}^{k} \beta_i^k \left(T_{n_i}^k - \psi_i^k\right) \psi_{jn_i}^k \tau. \tag{21}$$

Equations (12)-(19) were solved by the pivot method, while iteration was applied to (12), in addition to the pivot method, because it is nonlinear.

To determine a_1 and a_2 by this method, we constructed an iteration: if $\overset{(s)}{a_j}$ is known, then $\overset{(s)}{T}$ and $\overset{(s)}{\psi_j}$ can be determined from (1)-(4) and (8)-(11), and then $\overset{(s)}{I}$ and $\partial \overset{(s)}{I}/\partial a_j$ are derived from (5) and (6). The next approximation s + 1 is defined as

$$\overset{(s+1)}{a_j} = \overset{(s)}{a_j} - \overset{(s)}{\alpha}\, \overset{(s)}{p_j},$$

where

$$\overset{(s)}{p_j} = \partial \overset{(s)}{I}/\partial a_j - \overset{(s)}{\beta}\, \overset{(s-1)}{p_j}\ ;$$

$$\overset{(s)}{\beta} = -\frac{\sum\limits_{j} (\partial \overset{(s)}{I}/\partial a_j)^2}{\sum\limits_{j} (\partial \overset{(s-1)}{I}/\partial a_j)^2}\ ;$$

$$\overset{(0)}{p_j} = \partial \overset{(0)}{I}/\partial a_j.$$

The descent parameter $\overset{(s)}{\alpha}$ is chosen such that $I(\overset{(s+1)}{a_1}, \overset{(s+1)}{a_2}) < I(\overset{(s)}{a_1}, \overset{(s)}{a_2})$; the iteration halts for $I < \delta$, where δ is the error in the calculations and measurements.

4. Comparison with Experiment. This method was used in a computer program for deriving the characteristics from the temperatures measured at several points. Figure 1 shows temperature curves recorded for two points, with the thermocouples disposed as shown.

The initial temperature was 20°C, and a constant heating rate of 10°C/min was set at the surface $x = \ell_1$, where boundary condition (4) takes the form $T(\ell_1, t) = 20 + 10t$ (t in min). Curve 1 of Fig. 1a shows $y_0(t)$ as a function of time t in boundary condition (3).

The thermal diffusivity of levoamine varies over the range $0.5 \cdot 10^{-7}$-$0.7 \cdot 10^{-6}$ m^2/sec.

On solving the inverse problem with a constant thermal diffusivity, we obtained $a = 0.515 \cdot 10^{-6}$.

Figure 2 compares the measurements (curve 1) with the calculations (curve 2); at the start (for $\tau < 10$ min), the difference between the theoretical and experimental curves is up to 16%, but it gradually falls to 2%. This initial discrepancy is due firstly to the removal of equilibrium water and secondly to the error in specifying the boundary conditions, as well as to the nonlinear temperature dependence of the thermophysical parameters. To elucidate the role of the latter, we approximated the thermal diffusivity as (5) and used the solution to the inverse problem to determine a_1 and a_2, with $a(T) = 0.5147 \cdot 10^{-6} + 0.1691 \cdot 10^{-8}\, T$; curve 3 shows the temperature variation at x = 0.008. The effects of the nonlinear correction are slight.

Heat-treatment data and inverse-problem solution thus enable one to determine the thermophysical parameters of drug preparations. The numerical calculation on one form of the task requires 10-20 min with an ES-1022 computer.

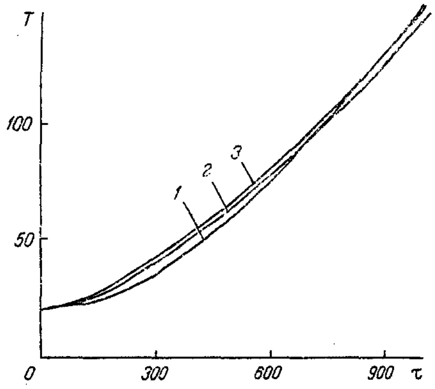

Fig. 2. Comparison of measured and calculated values: 1) measured temperature distribution at x = 0.008; 2) temperature distribution with constant $a = 0.5147 \cdot 10^{-6}$; 3) the same with nonlinear $a(T) = 0.5147 \cdot 10^{-6} + 0.1691 \cdot 10^{-6}T$, T, °C.

LITERATURE CITED

1. S. M. Reprintseva and N. V. Fedorovich, New Methods of Heat Treatment and Drying for Pharmaceutical Preparations [in Russian], Minsk (1969).
2. P. S. Gabets, S. M. Reprintseva, and N. V. Fedorovich, Khim. Framatsevticheskii Zh., No. 10, 23-27 (1975).
3. M. N. Belgorodskii, L. G. Golubev, and K. S. Chukhlebov, Khim. Farm. Zh., No. 12, 18-25 (1971).
4. F. Paulik, J. Paulik, and L. Erdey, Z. Analyt. Chem., No. 4, 160 (1958).
5. W. Wendlandt, Thermal Analysis Methods [Russian translation], Moscow (1978).
6. P. M. Kolesnikov, Methods in Transport Theory for Nonlinear Media [in Russian], Minsk (1981).
7. P. M. Kolesnikov and L. V. Grishanova, Analytical and Numerical Methods in Transport Theory [in Russian], Minsk (1977), pp. 49-79.
8. E. A. Artyukhin, Inzh.-Fiz. Zh., 41, No. 4, 587-592 (1981).
9. P. M. Kolesnikov, R. T. Abramov, and V. P. Veselov, Heat and Mass Transfer 7 [in Russian], Vol. 4, Minsk (1984), pp. 93-97.
10. P. M. Kolesnikov and T. G. Protod'yakonova, Inzh.-Fiz. Zh., 49, No. 6, 909-915 (1985).