

CRYSTALLIZATION OF HEXAMETHYLENE TETRAMINE IN THE CASE OF CONTINUOUS INCREASE IN THE VACUUM

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On the basis of the differential equations of transfer of energy and mass, a mathematical description of the crystallization of solutions by decreasing continuously the pressure of the medium has been developed. The kinetic dependences obtained from the experiments have been used in simulating the process of crystallization of hexamethylene tetramine. By comparing the experimental and calculated data, the adequacy of the mathematical model to the actual process has been established.

The process of crystallization is widely used in the pharmaceutical industry and considerably affects the properties of powders and of a solid medicinal form. Thus, in obtaining hexamethylene tetramine used in the production of calcex, the most important indicators of quality are the disperse composition, the crystal size, and the degree of purification [1]. By virtue of the specific features of solubility of individual substances and the distinction in their concentration in the initial solutions, it is always possible to select such conditions for crystallization under which a pure product is obtained, while undesirable impurities remain in the mother solution [2].

To analyze the influence of crystallization conditions on obtaining hexamethylene tetramine with decrease in the pressure, we have applied the principles of mathematical simulation which are based on solution of a system of differential equations of heat and mass transfer [3] with allowance for simplifications resulting from the justified assumptions made.

It has been found [4] that the time of residence of a suspension in the evaporation zone is 0.2-0.3 sec and when the turbulization level is high this time is sufficient for the same temperature between the phases to be established. Since the system liquid–solid phase is characterized by volumetric boiling of a solution and evaporation of a liquid from the solution surface into the environment in the case of evacuation of the apparatus occurs with a high intensity and does not limit the total rate of the process [5], to describe the processes of heat and mass transfer in the liquid and vapor–gas phases the model of ideal mixing of components is adopted [6]; this model presupposes ideal conditions at all the points of the active volume of a crystallizer. Because of the relatively high evaporation rate of the solution, its cooling, supersaturation, formation of crystallization centers, and crystal growth occur simultaneously over the entire volume. For these conditions the evaporation zone can be considered to be an object with lumped parameters; the size of the crystals obtained will be determined by the capacity of the crystallized salt for producing supersaturated solutions [2]. Under such conditions, the processes occurring in the liquid and vapor–gas phases can be described by the equations of heat and mass balance [4].

The intensities of change in the partial pressures of the vapor and the gas and in the temperature of the vapor–gas mixture [3] written for the one-component liquid (single fluid) will be of the form

$$\frac{dp}{d\tau} = \frac{FR^*T}{V_{fr}\mu} j - p \left(\frac{V_{s,v}}{V_{fr}} - \frac{1}{T} \frac{dT}{d\tau} \right), \quad (1)$$

$$\frac{dp_g}{d\tau} = p_g \left(\frac{1}{T} \frac{dT}{d\tau} - \frac{V_{s,g}}{V_{fr}} \right), \quad (2)$$

$$\frac{dT}{d\tau} = \left\{ \left[\frac{\alpha (T_{\text{liq}} - T)}{c_g \mu_g p + c \mu p} + \frac{j T_{\text{liq}}}{\mu_g p_g + \mu p} \right] R^* F - V_{\text{s.vg}} \right\} \frac{T}{V_{\text{fr}}} \quad (3)$$

A mathematical description of the crystallization process occurring in the liquid phase is based on the differential equations of transfer of mass and internal energy [7] with sources (sinks) which with allowance for the assumptions made and after transformations take the form of the equations of balance of heat and mass for the liquid phase:

$$\rho c dT_{\text{liq}} = q d\bar{x}_{\text{cr}} + r d\bar{x}_{\text{liq}}, \quad (4)$$

$$d\bar{x} = d\bar{x}_{\text{sol}} + d\bar{x}_{\text{cr}}. \quad (5)$$

In Eq. (4), the mean density of the suspension ρ depends on the volume content of the disperse particles ϕ [8]:

$$\rho = \rho_{\text{cr}} \phi + \rho_{\text{liq}} (1 - \phi). \quad (6)$$

To close the system of equations (1)–(6), we used the equilibrium Antoine dependences and solubilities of the substances. According to the Antoine equation [3], which determines an equilibrium between the liquid and the vapor on a saturation line, the temperature of the solution depends on the residual pressure in the crystallizer body [9]:

$$dT_{\text{liq}} = \frac{B}{p (A - \ln p)^2} dp. \quad (7)$$

Based on the experimental data, a solubility curve for hexamethylene tetramine is given in the form of a polynomial:

$$\bar{x}(T) = 0.49 T_{\text{liq}} + 0.00079 T_{\text{liq}}^2 + 1.057 \cdot 10^{-5} T_{\text{liq}}^3. \quad (8)$$

To implement the process of crystallization of the solution following the Gibbs law [8], it is necessary to provide a certain degree of its supersaturation. In this case, the equilibrium existence of the formed crystallization centers is described by the Thompson equation [2]:

$$\ln \frac{\bar{x}}{\bar{x}_0} = \frac{2\sigma \mu_{\text{sol}}}{\rho_{\text{cr}} \bar{r}_{\text{cr}} R^* T_{\text{liq}}}. \quad (9)$$

In Eq. (9), the coefficient of surface tension at the solution–crystal boundary is determined by the relation [9]

$$\sigma = 0.31 \left(\frac{N_A \rho_{\text{cr}}}{\mu_{\text{d.s}}} \right)^{2/3} k T_{\text{liq}} \ln \left[\frac{\rho_{\text{cr}} \mu_{\text{liq}}}{\rho_{\text{liq}} \mu_{\text{d.s}} x_0} \right], \quad (10)$$

while the molecular mass of the solution μ_{sol} is determined by the relation [10]

$$\mu_{\text{sol}} = \mu_{\text{liq}} x_{\text{liq}} + \mu_{\text{d.s}} (1 - x_{\text{liq}}). \quad (11)$$

Under the conditions of mass crystallization, the nucleation of crystallization centers and the growth of the already existing crystals occur simultaneously at various points of the solution. At this level, the heterogeneous processes occurring in systems with a liquid dispersion medium seem to be two-stage. In the first stage, the diffusion of molecules to the interface on the source side of the continuum is accomplished. The second stage is characterized by a chemical reaction on the surface of the dispersed phase. In [11], it is noted that the main assumption of the theory of mass crystallization, which establishes the constancy in concentrations of the solute and the crystal product over the entire volume of the apparatus, can be true only in the case of a rather intense mixing of the solution. Under vacuum

crystallization, it occurs as the result of volumetric boiling that decreases the resistance, caused by a diffusion boundary layer, and favors a more uniform inflow of the dissolved mass to faces. Taking into account the aforesaid, we assume that the crystal mass in the course of the process is distributed between the nuclei and the crystals in proportion to their surface [9]:

$$\frac{dG_{cr}}{d\tau} = \beta F (\bar{x} - \bar{x}_0). \quad (12)$$

The intensity of nucleation is proportional to the probability of appearance of nuclei [12]. To determine it, an empirical power approximation is used in [8], while the growth rate of the crystals in general form can be determined from the equation

$$\eta(l) = k_1 \Pi^a R^{n_1}, \quad (13)$$

where $\Pi = (\bar{c} - \bar{c}_0)$.

We represent the distribution of the crystal mass between the crystals of various fractions by the equation

$$dG_{cr} = \rho_{cr} \Phi \left(dN_0 r_{0cr} + \sum_{i=1}^n N_i dr_{cri}^3 \right). \quad (14)$$

Dependence (14) is the case where the size of the crystals in each fraction is taken to be averaged.

To solve the system of equations, it is necessary to determine the coefficients in Eq. (13) and to assign boundary conditions that correctly describe the process.

We investigated the process of crystallization on an experimental setup that included a hermetic vacuum chamber with a built-in balance (the chamber was connected with a vacuum pump through a pressure relay) and devices for monitoring and recording the parameters of the process (temperature and residual pressure).

The duration of the crystallization varied within 60–90 min. The process whose duration was 60 min was considered as a high-speed regime, while the process with a duration of 90 min was considered as a moderate regime.

The disperse composition of the crystal mass was determined by a microscopic method [14]. To ensure the satisfactory reliability of the disperse composition, the sample contained 1000 particles. The crystal size was measured with a microscope on the eyepiece-micrometer scale. The fraction boundaries were established at an interval of 0.2 mm, and as the fraction size we took its arithmetic mean value $\bar{d}_i = 2\bar{r}_{cri}$. The change from the size \bar{r}_{cri} to its volumetric equivalent was carried out according to the equation [6]

$$R_i = \bar{r}_{cri} \left(\frac{3\Phi}{4\pi} \right)^{1/3}. \quad (15)$$

The numerical value for the shape factor of the crystal, which was used in the calculations according to Eq. (13), was determined from the condition

$$\Phi \rho_{cr} \sum_{i=1}^n N_i \bar{r}_{cri}^3 = G_{cri}. \quad (16)$$

By substitution of the numerical values into Eq. (15), we determined the value of the shape-factor: $\Phi = 0.08326$ for 90 min and $\Phi = 0.08035$ for 60 min.

The discrepancies in the values obtained can be explained by the phenomenon of polymorphism; this phenomenon implies the change in the shape-factor of the crystal of the same substance as a function of the regime parameters of the process [2].

The distribution density of hexamethylene tetramine crystals for different regimes is given in Fig. 1.

Experimental determination of the growth rate was based on the equation [14]

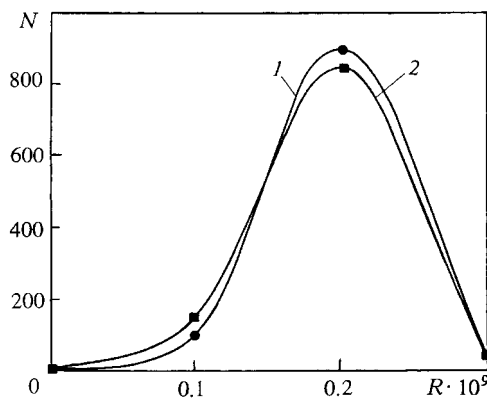


Fig. 1. Size-distribution density of crystals: 1) high-speed regime; 2) moderate regime.

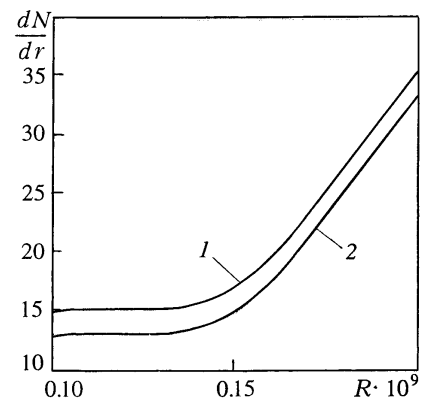


Fig. 2. Ratio dN/dr versus crystal size: 1 and 2) see Fig. 1. dN/dr , $\text{pc}/\mu\text{m}$.

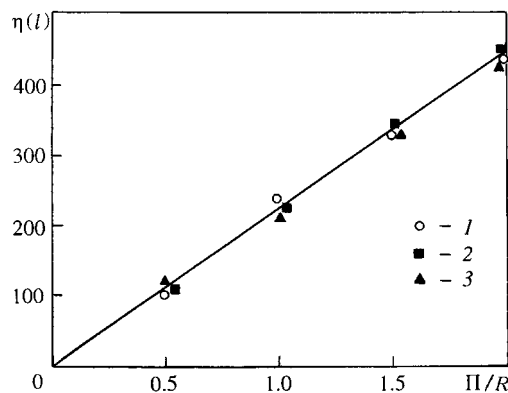


Fig. 3. Dependence of the linear rate of growth of hexamethylene tetramine crystals: 1) $\Pi=0.5$; 2) 1.5; 3) 2.0 kg/m^3 . $\eta(l)$, $\mu\text{m}/\text{sec}$; Π/R , $\text{kg}/(\text{m}^3 \cdot \mu\text{m})$.

$$\eta(l) = -\frac{1}{\langle \tau \rangle} \frac{N}{\frac{dN}{dR}} \quad (17)$$

The quantity dN/dR for different R was determined by graphical differentiation of the function $N=f(R)$. Substitution of the numerical values into Eq. (17) gave the values of $\eta(l)$. Figures 2 and 3 illustrate the results of this work.

To find the values of n_1 and a in Eq. (13), the experimental data were processed in conformity with the recommendations given in [14]. As a result of the calculational operations performed, we obtained exponents that comprised $n_1=0.424$ for 90 min, $n_1=0.384$ for 60 min, and $a=1$ for the boundaries of the time interval.

The coefficient k_1 was determined from the graphical dependence $\eta(l)=f(\Pi/R)$ (Fig. 3). In processing the experimental data it was found that $k_1=0.577$. With allowance for the resulting data, the rate of growth of the hexamethylene tetramine crystals in the investigated range of parameters can be represented in the form of equations:

$$\eta(l) = 0.577 \cdot 10^{-9} \Pi R^{0.424} \quad \text{— for 90 min,} \quad (18)$$

$$\eta(l) = 0.577 \cdot 10^{-9} \Pi R^{0.384} \quad \text{— for 60 min.} \quad (19)$$

The intensity of nucleation of crystallization centers J , formed per unit volume in unit time, was determined from the relation [14]

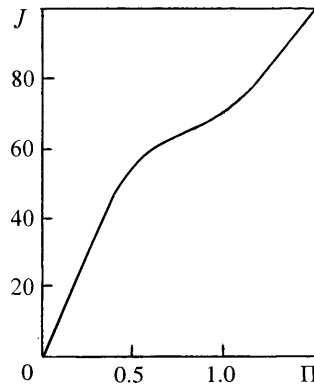


Fig. 4. Dependence of the nucleation rate of hexamethylene tetramine on the supersaturation of the solution.

$$J = f(R) \eta(l). \quad (20)$$

Processing of the data on the disperse composition using the Mathematica application package gave the dependence $J = f(\Pi)$ (Fig. 4), which is described accurate to 20% by the equation of the form

$$J = 0.02596 + 156.53\Pi - 117.99\Pi^2 + 37.75\Pi^3. \quad (21)$$

The system of equations (1)–(21) was solved by a numerical method [13] with the following initial conditions:

$$\begin{aligned} T_{\text{liq}}(0) = T_{\text{vg}} = T_{\text{in}}, \quad p(0) = \exp\left(A - \frac{B}{T_{\text{liq.in}}}\right), \quad p_{\text{g}}(0) = p_{\text{atm}}, \quad \bar{x}_{\text{cr}}(0) = 0, \quad \bar{x}_{\text{liq}} = \bar{x}_{\text{liq.in}}, \\ \bar{x}(0) = \bar{x}_0(T_{\text{in}}), \quad j(0) = 0. \end{aligned} \quad (22)$$

The discrepancy between the calculated and experimental data does not exceed a 20% error interval.

Thus, the presented procedure of investigation, the basis for which is provided by the differential equations of heat and mass transfer and the empirical dependences obtained experimentally, makes it possible to simulate the process of crystallization of hexamethylene tetramine with the aim of determining the parameters that affect the quality of medicinal preparations.

NOTATION

p and p_{g} , partial pressure of the vapor and the gas, respectively, Pa; τ , time, sec; F , heat- and mass-exchange surface, m^2 ; R^* , universal gas constant, $J/(\text{kmole}\cdot\text{K})$; T and T_{liq} , temperature of the vapor and the solvent, respectively, K; j , mass flux, $\text{kg}/(\text{m}^2\cdot\text{sec})$; $V_{\text{s.v.}}$, $V_{\text{s.g.}}$, and $V_{\text{s.v.g.}}$, volumetric capacities of the systems for removing the vapor, the gas, and the vapor–gas mixture, respectively, m^3/sec ; V_{fr} , free volume of the apparatus, m^3 ; μ , molecular weight of the component, kg/kmole ; c , mass heat capacity, $J/(\text{kg}\cdot\text{K})$; β , coefficient of mass transfer, m/sec ; ρ , density, kg/m^3 ; \bar{x} , mass fraction of the component in the liquid, kg/kg ; α , coefficient of heat transfer, $\text{W}/(\text{m}^2\cdot\text{K})$; r , latent heat of vaporization, J/kg ; A and B , empirical coefficients in the Antoine equation; q , specific heat of crystallization, J/kg ; \bar{r}_{cr} , mean radius of the crystal nucleus, m ; Φ , shape factor; G_{cr} , mass of crystals, kg ; ϕ , volume content of the disperse particles; Π , absolute supersaturation, kg/m^3 ; x , mole fraction of the component, $\text{kmole}/\text{kmole}$; \bar{c} , volume concentration, kg/m^3 ; k_1 , a , and n_1 , empirical coefficients; N_{A} , Avogadro number, mole^{-1} ; σ , coefficient of surface tension, N/m ; k , Boltzmann constant, J/K ; R , equivalent radius of the crystal, m ; N , number of crystals, pc ; N_0 , number of nuclei of the crystal, pc ; $\eta(l)\cdot 10^6$, growth rate of the crystals, m/sec ; J , nucleation rate, pc/sec ; d , mean diameter of the crystal, m ; l , characteristic dimension, m ; n , number of fractions. Subscripts: fr, free; s.v, system of the vapor; s.g, sys-

tem of the gas; s.vg, system of the vapor–gas mixture; g, gas; cr, crystal; d.s, dissolved substance; 0, equilibrium; liq, liquid; sol, solution; atm, atmospheric; in, initial; vg, vapor–gaseous; *i*, number of the crystal fraction.

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