Mathematical Modeling of Cryochemical Formation of Medicinal Substances in Nanoforms. The Role of Temperature and Dimensional Parameters.

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Abstract: The work is aimed at creating a mathematical model of cryochemical synthesis of nanoforms of pharmaceutical substances. The therapeutic efficacy of pharmaceutical substances largely depends on the size and morphology of the particles. Reducing the particle size of pharmaceutical substances to nanoscale makes it possible to obtain highly effective drugs, which makes it possible to use smaller doses of drugs and, thus, reduce side effects and toxicity. Cryochemical synthesis is one of the most powerful methods for obtaining nanoforms of medicament. The method, which is completely new, is based on sublimation or evaporation of the initial pharmaceutical substance under high vacuum conditions and the introduction of the resulting vapors into an inert gas stream, followed by low-temperature condensation of the flow of molecules of the substance from the gas phase on the cooled surface. The first step in the mathematical modeling of cryochemical synthesis processes is the calculation of the temperature field in the carrier gas flow interacting with the cooled surface. For this purpose, a stationary equation of thermal conductivity with mass transfer is used for the one-dimensional case. We prove existence and uniqueness theorems of the solution. Analytical solutions of the equation for Dirichlet, Neumann and Robin boundary conditions are found.

Key-Words: Cryochemical Formation, Medicinal Substances, Nanoforms, Inert Gas Flow, Mathematical Modeling, Boundary-Value Problem, Existence and Uniqueness.

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1 Introduction

The dimension and morphology of medicinal substances particles effect the therapeutic efficiency of different antibacterial, antiviral, anti-inflammatory, anesthetic, analgesic, cardiological sedative and soothing etc. medicaments, [1], [2].

These parameters can determine the qualities of medications such as bioefficiency and bioavailability. Lowering drug powders particles size down to nano sizes allows us to obtain the medications with high medical efficiency due to a huge total surface area and permits to use lower medication doses and thus

to decrease the side effects and toxicity, [3]. Such approach is based on the development of new methods for obtaining of nanoforms of medical substances.

One of the powerful methods for production of medications nanoforms is cryochemical modification of drug substances. The method is based on the sublimation or evaporation of drug substance under high vacuum conditions and incorporation of the vapors obtained into the stream of inert gas followed by the low temperature condensation of drug substance molecular beam from gas phase on the cooled support surface. The cryochemical production of drug nanoparticles with the definite size and morphology and narrow size distribution led to the obtaining of medications with desired properties and led to the creation of innovative cryochemical technology for drug nanoforms production. The technological stages of cryochemical modification process are following.

The initial drug substance was heated up to definite temperature in the previously heated warm inert gas flow. The molecular beam of drug substance vapor incorporated into the inert gas flow and transferred to the vacuumed cryochemical rector volume, supplied by cooled support. Reaching the cooled surface of support drug substance molecular beam rapidly cooled and high supersaturation of drug molecular vapor in the gas phase was achieved. This led to the conditions allowed rapid gas-phase nucleation and formation of many nanocrystal germs - the embryo of new nanophase of drug substance. Further growth of nanocrystals obtained was limited by rapid decreasing of drug substance molecules concentration in the gas phase near the cooled support surface. These facts make it possible to obtain drug particles of the size close to the dimension of critical crystal germ –about several dozen of nanometers. The exact size of drug nanoparticles depends on the ratio of the rates of nanocrystals nucleation and nanocrystals growth. The behavior of these processes is determined by several experimental parameters: temperature of the initial drug substance evaporation/sublimation, temperature of gas-phase, the gas-carrier flow, the size and construction geometry of the cryochemical reactor and the temperature of the cooled support.

The goal of this work lies in the creation of mathematical models describing the physico-chemical processes occurring during a cryochemical modification of drug substances and determination of the optimal combination of technological (experimental) parameters of these processes for two antibacterial drug substances, dioxidine and chloroamphenycol, as examples.

The work on mathematical description of cryochemical modification of drug substances can be divided in two main tasks:

- the description of the temperature field of the molecular beam incorporated in the inert gas flow and interacted with the cooled support surface;
- the creation of the kinetic model, a model that takes into account the processes of drug nanophase nucleation and nanocrystals growth in the gas phase in the given temperature field.

Nowadays the needs of modern medicine and pharmacology to develop new drugs is determined by the fact that well-known, long-established drugs do not meet the requirements of the 21st century. However, the creation and testing of new molecular forms of drugs (drug discovery) require not only huge material costs, reaching several billion dollars, but also long, reaching several years, time spent on various clinical and preclinical tests, at the cost of which are human lives.

From this point of view, another approach is more promising to increase the effectiveness of known medicines and improve methods of their targeted delivery (drug delivery). This can be achieved, for example, by reducing the particle size of the active drug up to the nanoscale state, [4], as well as by synthesizing new or obtaining previously known thermodynamically metastable polymorphic modifications in the form of kinetically stable forms, [5].

Various physical and chemical methods are used to produce nanoforms of drugs, [6], which are divided into top-down and bottom-up methods, [7]–[9]. The essence of top-down methods is to reduce the particle size by mechanical action on initially large particles of the source substance. In this direction, "dry" and "wet" mechanical crushing is most often used in special mills, [10], including using low temperatures (cryo-milling), [11]. High-pressure homogenization methods have also been developed, [12], techniques using nanoporous membranes, [13], [14] and others. On the contrary, the bottom-up approach consists in converting the initial Pharmacopoeia drug into a homogeneous state, which is a collective of individual molecules or small molecular associates, and creating conditions for the subsequent Assembly of new phase embryos, their growth and formation of nanoparticles, [15]–[17]. Examples of such techniques are: solvent replacement method, [18], synthesis using supercritical fluids, [19]–[21], techniques including freeze drying (spray drying), [22]–[24], cryochemical synthesis, [25]–[27].

The size is of primary importance, since the size parameters largely determine the bioavailability of the drug, [28]. For example, reducing the particle size of the antigonadotropic drug dibazole in an aqueous suspension from 10 microns to 169 nm led to an increase in absolute bioavailability from $5.1 \pm 1.9\%$ to $82.3 \pm 10.1\%$, [29]. Increasing bioavailability allows

to reduce the therapeutic dose and, consequently, possible side effects. The effect of particle size may consist not only in changing the solubility and rate of dissolution, but also in enabling the penetration of drug particles through the body's biological barriers, [30]–[31].

2 Problem Setting

Essentially, the technology of cryochemical modification of pharmaceutical substances is as follows. The initial substance is heated up to a certain temperature in a stream of preheated carrier gas. The resulting vapors of the initial compound are captured by the carrier gas stream and carried through the nozzle into the external free vacuum space. The scheme of the experiment is shown in Figure 1 with

1 - heated copper screen (mixed molecular flow shaper),

2 - cold carrier gas flow,

3 - copper screen heater,

4 - copper–constantan thermocouple junction for determining and regulating the temperature of the copper screen,

5 - initial substance in the container,

6 - nozzle of the mixed molecular flow shaper,

7 - heated flow a carrier gas carrying vapors of a medicinal substance (mixed molecular stream),

8 - a cooled mixed molecular stream,

9 - a cold surface (when cooled with liquid nitrogen, the surface temperature is about 77 K (-196°C),

10 - the flow front of the carrier gas,

11 - a layer of cryochemically modified substance.

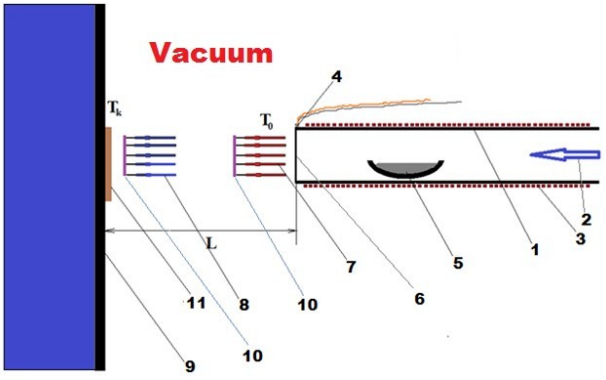

Figure 1: Scheme of the experiment.

When the mixed molecular stream moves from the nozzle of the shaper to the cold surface, it is sharply cooled by the mechanism of thermal conductivity. As a result, the gas phase turns out to be multiple supersaturated relative to the equilibrium pressure of saturated vapors of the compound and conditions are being created in the system for rapid gas-phase nucleation. In turn, the high rate of nucleation quickly impoverishes the gas phase with the vapors of the compound, which limits the further growth of crystallites. Thus, it is possible to obtain crystallites with sizes close to the sizes of critical nuclei, which are several tens of nanometers for organic compounds. The task to describe mathematically the process of cryochemical modification of pharmaceutical substances is divided into two parts:

- calculation of the temperature field in the stream of the carrier gas interacting with the cooled surface;
- construction of a kinetic model that takes into account the processes of nucleation and growth of nanoparticles in the gas phase in a given temperature field.

To solve the first problem, we need to make a number of assumptions:

- the mixed molecular stream does not dissipate when moving from the nozzle of the molecular stream shaper to the cold surface,
- the mixed molecular stream has the same temperature throughout the cross section,
- the temperature of the mixed molecular stream is equal to the temperature the cooled surface when reaching it,
- thermophysical characteristics of the carrier gas do not change when the molecules and nanoparticles of the pharmaceutical substance are included in it.

Under these assumptions, the thermal conductivity equation with mass transfer for the one–dimensional case can be used to calculate the temperature field created by the carrier gas stream:

$$\frac{\partial T}{\partial t} = V\frac{\partial T}{\partial x} - \frac{\mu}{\rho C_V}\cdot\frac{\partial}{\partial x}\left(\lambda\frac{\partial T}{\partial x}\right). \qquad (1)$$

Here ρ, μ, λ are the density $\left(\mathrm{kg/m^3}\right)$, molecular weight (kg/mol), thermal conductivity $(\mathrm{W/(m\cdot K)})$ of the carrier gas, respectively, C_V is the molar heat capacity of the carrier gas at constant volume $(\mathrm{J/(mol\cdot K)})$, V is the linear velocity of the carrier-gas flow front (m/s).

In stationary mode we have $\partial T/\partial t = 0$ and equation (1) reduces to the ordinary differential equation

$$\frac{dT}{dx} - \frac{\mu}{\rho V C_V} \cdot \frac{d}{dx}\left(\lambda \frac{dT}{dx}\right) = 0. \qquad (2)$$

The flow rate of the carrier gas is controlled during the experiment with the help of an external device (an industrial gas pipeline with accuracy, according to its passport data, not worse than 5%). The regulated gas stream of the carrier, passing through a heated copper screen (a mixed molecular flow shaper) of cylindrical shape, heats up to a certain temperature, captures the vapors of the initial substance and takes them out into the vacuum space. Let the nozzle area of the mixed molecular flow shaper be $S(\mathrm{m}^2)$ Then the molar flow rate of the carrier gas is $dN/dt(\mathrm{mol/s})$ and can be written as

$$\dot{N} = \frac{dN}{dt} = \frac{\rho V S}{\mu}.$$

In this case, the ratio of the molar flow rate of the carrier gas dN/dt $(\mathrm{mol/s})$ to the nozzle area of the mixed molecular flow shaper, that is, the density of the carrier gas flow dn/dt $\left(\mathrm{mol}/(\mathrm{m}^2 \cdot \mathrm{s})\right)$ can be represented as

$$\dot{n} = \frac{dn}{dt} = \frac{\dot{N}}{S} = \frac{\rho V}{\mu}.$$

Now equation (2) can be written as

$$\frac{dT}{dx} - \frac{d}{dx}\left(\frac{\lambda}{C_V \dot{n}} \cdot \frac{dT}{dx}\right) = 0. \qquad (3)$$

It can be solved analytically, taking into account the dependence of the thermal conductivity of the carrier gas on the temperature. An interesting fact is that the heat capacity of gases in a wide range of pressures practically does not depend on the pressure. This circumstance received its explanation from the molecular kinetic theory. A large number of gases, such as nitrogen, helium, argon, carbon dioxide, etc., have the square-root dependence of the thermal conductivity on the temperature expressed by the approximate formula

$$\lambda = \frac{ik}{3\pi^{3/2} d^2}\sqrt{\frac{RT}{\mu}}, \qquad (4)$$

where

- i is the sum of translational and rotational degrees of freedom of molecules (5 for diatomic gases, 3 for monatomic ones),
- k is the Boltzmann constant,
- μ is the molar mass,
- T is the absolute temperature,
- d is the effective diameter of molecules,
- R is the universal gas constant.

Representing λ in (4) as $\alpha\sqrt{T}$ with the appropriate coefficient α, we obtain

$$\frac{\lambda}{C_V \dot{n}} = \frac{\alpha\sqrt{T}}{C_V \dot{n}} = b\sqrt{T} \text{ with } b = \frac{\alpha}{C_V \dot{n}}.$$

Now equation (3) can be represented as

$$\frac{d}{dx}\left(T - b\sqrt{T}\frac{dT}{dx}\right) = 0, \quad b > 0. \qquad (5)$$

3 General Decreasing Solutions

We study the dependence of the temperature on the distance from the nozzle under three types of boundary conditions, namely the Dirichlet, Neumann, and Robin ones.

The Dirichlet condition specifies the temperature value at the boundary.

The Neumann condition specifies the boundary value for the derivative of the temperature.

In the Robin condition, we specify a linear combination of the temperature value and the derivative of the temperature at the boundary.

The coefficient of the temperature value in the Robin condition is the Biot number (the ratio of the conductive thermal resistance inside the object to the convective resistance at the surface of the object).

Note that similar problems were considered for a heat process in [32].

Theorem 1. *Each positive solution T to equation* (5) *is either constant or strictly monotonic. Each strictly decreasing solution has the form*

$$T(x) = c^2\,\Theta\left(\frac{x - x^*}{bc}\right)^2, \qquad (6)$$

where x^* and $c > 0$ are arbitrary constants while Θ is a decreasing function $(-\infty; 0) \to (0; 1)$ implicitly defined by

$$x = 2\Theta(x) + \ln\frac{1 - \Theta(x)}{1 + \Theta(x)}. \qquad (7)$$

The left-hand side of (5) *contains an expression in parentheses, which must be constant and, for the solution defined by* (6)*, equals c^2.*

If maximally extended, such T is defined on the interval $(-\infty; x^*)$ and satisfies

$$T(x) \to c^2 \text{ and } T'(x) \to 0 \quad \text{as } x \to -\infty, \qquad (8)$$
$$T(x) \to 0 \text{ and } T'(x) \to -\infty \quad \text{as } x \to x^*. \qquad (9)$$

Proof. First, by the substitution $T = Z^2$ with $Z > 0$ we convert equation (5) into the form

$$\left(Z^2 - 2bZ^2Z'\right)' = 0, \tag{10}$$

which immediately yields

$$Z^2 - 2bZ^2\,Z' = C = \text{const}$$

with further transformations depending on $\operatorname{sgn} C$.

If $C = 0$, then either $Z \equiv 0$ or $1 = 2b\,Z'$, which entails that $Z' > 0$ and Z is strictly increasing.

If $C = -c^2 < 0$, then we obtain $Z^2 + c^2 = 2bZ^2Z'$. This shows again that $Z' > 0$.

Finally, if $C = c^2 > 0$ with $c > 0$, then we obtain

$$Z^2 - c^2 = 2bZ^2Z'. \tag{11}$$

Now, if $Z(x) = c$ at some point x, then, by the uniqueness theorem, Z must coincide with the constant solution $Z \equiv c$. If not, then either $Z > c$ on the whole domain or $Z < c$. We reject the first case (with $Z' > 0$ due to (11)) as well as the previous constant one. In the second case we put

$$Z(x) = c\,z\Big(\frac{x}{bc}\Big), \;\; 0 < z < 1,$$

which converts (11) into

$$z^2 - 1 = 2z^2z'. \tag{12}$$

This can be written as

$$1 = \frac{2z^2z'}{z^2-1} = \left(2 + \frac{2}{z^2-1}\right)z',$$

whence, for $0 < z < 1$,

$$\begin{aligned} x - a &= \int_0^{z(x)} \left(2 + \frac{2}{\zeta^2-1}\right) d\zeta \\ &= 2z(x) + \ln\frac{1-z(x)}{1+z(x)} \end{aligned}$$

with some a. We have a general family of implicitly defined strictly decreasing solutions to (12) satisfying $0 < z < 1$. One of them, with $a = 0$, is just Θ defined by (7). All others can be obtained from Θ by a horizontal shift. Thus, we have (6).

It follows from (7) that

$$\begin{aligned} &\Theta(x) \to 0 \;\text{ as }\; x \to 0, \\ &\Theta(x) \to 1 \;\text{ as }\; x \to -\infty. \end{aligned}$$

Then, using (12), we obtain

$$\begin{aligned} &\Theta'(x) \to -\infty \;\text{ as }\; x \to 0, \\ &\Theta'(x) \to 0 \;\text{ as }\; x \to -\infty. \end{aligned}$$

These limits, together with (6), produce the first three limits in (8) and (9). For the fourth one, we use (11) to obtain

$$T' = 2ZZ' = \frac{Z^2 - c^2}{2bZ} = \frac{T - c^2}{2b\sqrt{T}} \to -\infty \text{ as } T \to 0.$$

□

4 On Existence and Uniqueness of Solutions

Theorem 2. *For any constants $x_0 < x_1$ and $T_1 > T_0 > 0$, equation* (5) *has a unique solution T defined on $[x_0; x_1]$ and satisfying the conditions*

$$T(x_0) = T_0, \quad T(x_1) = T_1. \tag{13}$$

Proof. The boundary conditions show that, according to Theorem 1, the solution T must strictly decrease and therefore have the form given by (6) and (7). So, the boundary conditions become

$$\frac{\sqrt{T_j}}{c} = \Theta\left(\frac{x_j - x^*}{bc}\right), \;\; j \in \{0, 1\},$$

or, by using (7),

$$\frac{x_j - x^*}{bc} = 2\frac{\sqrt{T_j}}{c} + \ln\frac{1 - \dfrac{\sqrt{T_j}}{c}}{1 + \dfrac{\sqrt{T_j}}{c}}, \;\; j \in \{0, 1\}. \tag{14}$$

Thus, we have to prove the existence and uniqueness of a pair (x^*, c) satisfying (14). Putting

$$q := \sqrt{\frac{T_1}{T_0}} \in (0; 1) \;\text{ and }\; k := \frac{\sqrt{T_0}}{c} \in (0; 1), \tag{15}$$

we write the difference of the two equations (14) as

$$\frac{k(x_1 - x_0)}{b\sqrt{T_0}} = 2k(q-1) + \ln\frac{(1-qk)(1+k)}{(1+qk)(1-k)}$$

or

$$\frac{x_1 - x_0}{2b\sqrt{T_0}} = F_q(k) \tag{16}$$

with

$$F_q(k) := f(k) - qf\,(qk)\,, \tag{17}$$

$$f(k) := \frac{1}{2k}\ln\frac{1+k}{1-k} - 1. \tag{18}$$

Lemma 3. *For each $A > 0$ and $q \in (0; 1)$, there exists a unique $k \in (0; 1)$ such that $F_q(k) = A$ with F_q defined by* (17) *and* (18)*. The mapping $(A, q) \mapsto k$ is a C^1 function $(0; +\infty) \times (0; 1) \to (0; 1)$ strictly increasing with respect to both A and q.*

Proof. Note that

$$f(k) = \frac{\ln(1+k)}{2k} - \frac{\ln(1-k)}{2k} - 1,$$

whence $f(k) \to 0$ as $k \to 0$ (by L'Hôpital's rule) and $f(k) \to +\infty$ as $k \to 1$.

Now we study the derivative of f by using its Taylor series uniformly converging on any subsegment of the interval $(0;1)$.

$$\begin{aligned} f'(k) &= \frac{1}{2k(1+k)} - \frac{\ln(1+k)}{2k^2} \\ &\quad + \frac{1}{2k(1-k)} + \frac{\ln(1-k)}{2k^2} \\ &= \frac{1}{k(1-k^2)} - \frac{\ln(1+k)}{2k^2} + \frac{\ln(1-k)}{2k^2} \\ &= \frac{1}{k}\sum_{n=0}^{\infty} k^{2n} + \frac{1}{2k^2}\sum_{n=1}^{\infty} \frac{((-1)^n - 1)k^n}{n} \\ &= \frac{1}{k}\sum_{n=0}^{\infty} k^{2n} - \frac{1}{k^2}\sum_{m=0}^{\infty} \frac{k^{2m+1}}{2m+1} \\ &= \frac{1}{k}\sum_{n=0}^{\infty} \left(1 - \frac{1}{2n+1}\right) k^{2n} = \frac{1}{k}\sum_{n=1}^{\infty} \frac{2n}{2n+1} k^{2n} \\ &= \sum_{n=1}^{\infty} \frac{2n}{2n+1} k^{2n-1} > 0, \end{aligned}$$

whence $f(k) > 0$ as well.

Further, $f''(k) = \sum_{n=1}^{\infty} \frac{2n(2n-1)}{2n+1} k^{2n-2} > 0$, whence f' is strictly increasing and

$$\frac{dF_q}{dk}(k) = f'(k) - q^2 f'(qk) > 0.$$

So, F_q is strictly increasing in k, $F_q(k) \to 0$ as $k \to 0$, and

$$\begin{aligned} F_q(k) &= (1-q)f(k) + q\big(f(k) - f(qk)\big) \\ &> (1-q)f(k) \to +\infty \text{ as } k \to 1. \end{aligned}$$

Therefore, F_q must attain, exactly once, each $A > 0$, which proves the first part of Lemma 3.

The second part follows immediately from the implicit function theorem and the evident inequalities

$$\begin{aligned} \frac{\partial(F_q(k) - A)}{\partial A} &= -1 < 0, \\ \frac{\partial(F_q(k) - A)}{\partial q} &= -f(qk) - qkf'(qk) < 0. \end{aligned}$$

□

We return to proving Theorem 2. Having the unique value of k satisfying (16), we obtain, from (14) and (15), the unique values

$$\begin{aligned} c &= \frac{\sqrt{T_0}}{k} > \sqrt{T_0} \quad \text{and} \\ x^* &= x_1 - 2b\sqrt{T_1} - bc \ln \frac{c - \sqrt{T_1}}{c + \sqrt{T_1}} \end{aligned}$$

to satisfy (14). This completes the proof of Theorem 2. □

Now we are going to prove two theorems concerning other boundary conditions for equation (5).

Theorem 4. *For any real constants $x_0 < x_1$, $T_0 > 0$, and $U_1 < 0$, equation (5) has a unique solution T defined on $[x_0; x_1]$ and satisfying the conditions*

$$T(x_0) = T_0, \quad T'(x_1) = U_1. \tag{19}$$

Theorem 5. *For any real constants $x_0 < x_1$, $T_0 > 0$, and $U_1 < 0$, equation (5) has a unique solution T defined on $[x_0; x_1]$ and satisfying the conditions*

$$T(x_0) = T_0, \quad T'(x_1) = U_1 T(x_1). \tag{20}$$

Proof. We try to prove the existence and uniqueness of a constant $T_1 \in (0; T_0)$ such that the unique solution T existing according to Theorem 2 satisfies the boundary conditions of the related theorem.

According to Theorem 1, $T - b\sqrt{T}T' = c^2$, whence, using notation (15),

$$\begin{aligned} T'(x_1) &= \frac{T(x_1) - c^2}{b\sqrt{T(x_1)}} = \frac{q^2 T_0 - T_0/k^2}{bq\sqrt{T_0}} \\ &= \frac{k^2q^2 - 1}{k^2 q} \cdot \frac{\sqrt{T_0}}{b}, \\ \frac{T'(x_1)}{T(x_1)} &= \frac{k^2q^2 - 1}{k^2 q^3} \cdot \frac{1}{b\sqrt{T_0}}, \end{aligned}$$

where $k \in (0;1)$ is chosen, depending on $q \in (0;1)$, to provide the boundary conditions (13) for the solution T defined by (6).

It follows from Lemma 3 that $k \in (0;1)$ strictly increases with respect to $q \in (0;1)$. So, in both right-hand sides of the last equations, the numerator $k^2q^2 - 1$ is negative and strictly increases in q, while its absolute value decreases. The denominators are positive and also strictly increase. Thus, the fractions are negative with strictly decreasing absolute values.

Now consider their limits at 0 and 1.

Both fractions tend to $-\infty$ as $q \to 0$. As for $q \to 1$, there must exist $k_1 = \lim_{q \to 1} k \in (0;1]$.

If $k_1 < 1$, then it follows from (16)–(18) that

$$0 < \frac{x_1 - x_0}{2b\sqrt{T_0}} = F_1(k_1) = f(k_1) - 1 \cdot f(1 \cdot k_1) = 0.$$

This contradiction shows that $k_1 = 1$. (For this k_1, no contradiction arises because $f(k) \to +\infty$ as $k \to 1$.) Hence

$$T'(x_1) \to 0 \text{ and } \frac{T'(x_1)}{T(x_1)} \to 0 \text{ as } q \to 1.$$

So, both expressions strictly increase from $-\infty$ to 0 as q increases from 0 to 1 (i. e. as T_1 increases from 0 to T_0). Therefore, they both must attain, exactly once, each negative value, and this proves Theorems 4 and 5. □

5 Illustrations

This section presents graphs of solutions to equation (5) with various boundary conditions and various values of the constant b.

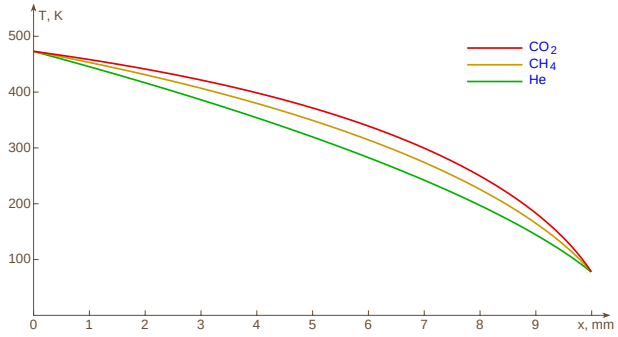

Figure 2: Solutions to a Dirichlet problem for various gases.

Fig. 2 shows the solutions to (5) with the boundary conditions $T(0) = 473\,\mathrm{K}$, $T(0.01) = 77\,\mathrm{K}$ for various values of the constant b corresponding to various gases and the same flow rate $\dot{N} = 10\,\mathrm{dm}^3/\mathrm{h}$ (i. e. $1.156 \cdot 10^{-4}\,\mathrm{mol/s}$). Here b is equal to 0.002991 for He, 0.00063456 for CH_4, and 0.000374 for CO_2 (all in $\mathrm{m}/\sqrt{\mathrm{K}}$).

Fig. 3 also shows dependence of solutions to (5) on the constant b related to various values of the flow rate $\dot{N}$ and the same gas CO_2. Here the value of b changes from 0.000374 (the topmost graph) to 0.0374 (the lowest one) $\mathrm{m}/\sqrt{\mathrm{K}}$, which correspond to the molar flow rates $1.156 \cdot 10^{-4}$ and $1.156 \cdot 10^{-6}\,\mathrm{mol/s}$. Boundary conditions are the same as in Fig. 2.

Fig. 4 shows the solutions to (5) with the boundary conditions $T(0) = 473\,\mathrm{K}$, $T'(0.01) = -10^5\,\mathrm{K/m}$ for various values of $\dot{N}$ and the same gas N_2 with b changing from 0.000393 to $0.0393\,\mathrm{m}/\sqrt{\mathrm{K}}$.

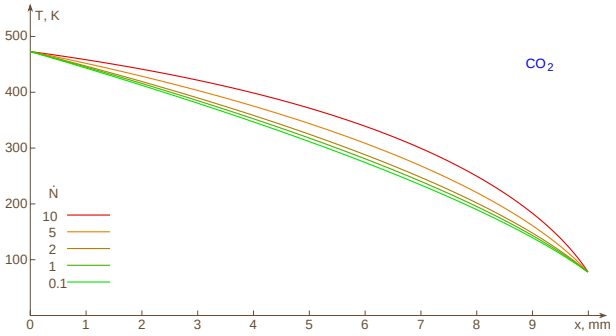

Figure 3: Solutions to a Dirichlet problem for various flow rates $\dot{N}$.

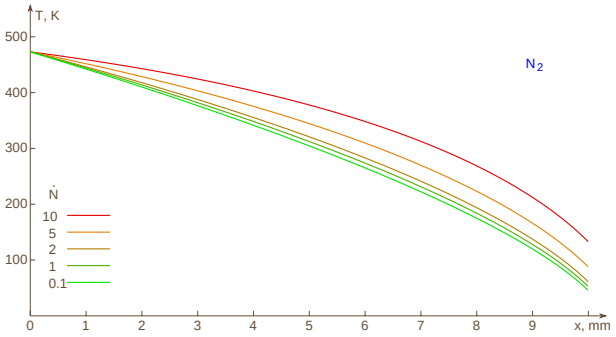

Figure 4: Solutions with a Neumann right-end boundary condition for various $\dot{N}$.

Fig. 5 shows the solutions to equation (5) satisfying the boundary conditions $T(0) = 473\,\mathrm{K}$ and $T'(0.01)/T(0.01) = -10^3\,\mathrm{m}^{-1}$ for the same gas CO and various values of $\dot{N}$. Here the constant b changes from 0.0004169 to $0.04169\,\mathrm{m}/\sqrt{\mathrm{K}}$.

Fig. 6 shows the solutions to equation (5) satisfying the boundary conditions $T(0) = 473\,\mathrm{K}$, $T'(0.01) = (-2, -4, -8) \cdot 10^4\,\mathrm{K/m}$ for the same gas CH_4 and $\dot{N} = 10\,\mathrm{dm}^3/\mathrm{h}$. Thus, here we have $b = 0.00063456\,\mathrm{m}/\sqrt{\mathrm{K}}$.

Fig. 7 shows the solutions to equation (5) satisfying the boundary conditions $T(0) = 473\,\mathrm{K}$ and $T'(0.01)/T(0.01)$ equal to $-10^2, -10^3, -10^4\,\mathrm{m}^{-1}$ for the same gas Ar, the flow rate $\dot{N} = 10\,\mathrm{dm}^3/\mathrm{h}$, and therefore the same $b = 0.0004506\,\mathrm{m}/\sqrt{\mathrm{K}}$.

6 Conslusions

We have analysed dependence of the temperature profile on the distance from the cooled surface and compared the results for various carrier gases such as nitrogen, helium, argon, methane, carbon monoxide and dioxide.

The above calculations show that

1) an increase in the thermal conductivity of the carrier gas, other parameters being constant, leads

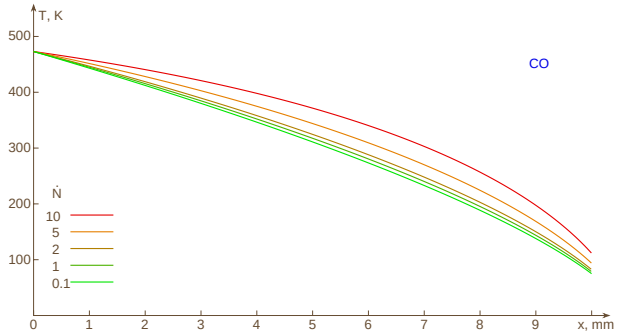

Figure 5: Solutions with a Robin right-end boundary condition for various $\dot{N}$.

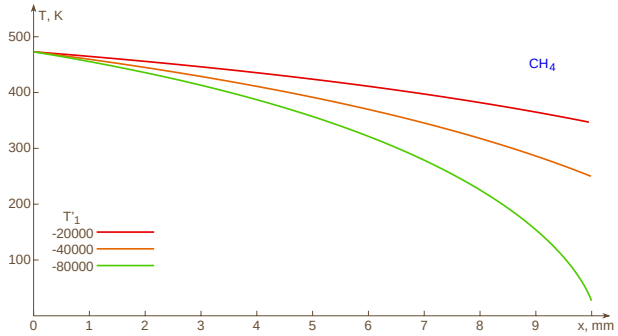

Figure 6: Solutions to Neumann problems with various T_1'.

to more uniform temperature distribution in the stationary temperature field formed in the space between the nozzle of the mixed molecular flow and the cooled surface;

2) an increase in the flow rate of the carrier gas, other parameters being constant, leads to an increase of uneven temperature distribution in the formed stationary temperature field.

Taking into account the identified patterns will contribute, in the future, to the choice of optimal regimes for cryochemical synthesis of nanoforms of pharmaceuticals substances with specified dimensional characteristics.

This is the first step in a complex investigation of the role of various parameters in cryochemical synthesis of various drugs.

The results obtained are confirmed by an experiment on the formation of nanoforms for the antibacterial drug dioxidine with the nitrogen as an inert carrier gas.

Remark 1. The authors' results connected with mathematical modeling in other physical processes can be found in [33]–[36].

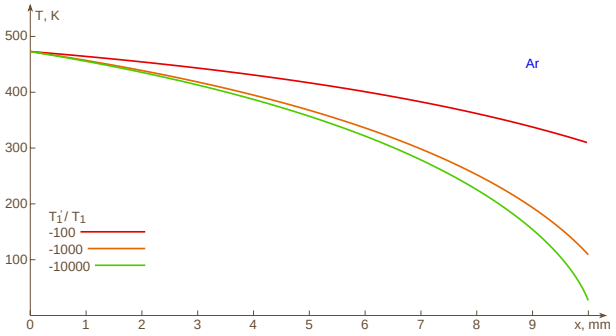

Figure 7: Solutions to Robin problems with various T_1'/T_1.

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The authors equally contributed in the present research, at all stages from the formulation of the problem to the final findings and solution.

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Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.