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THERMOPHORETIC FORCE IN TARGETED DRUG DELIVERY SYSTEMS: THEORETICAL ANALYSIS OF THERMOPHORETIC FORCES ACTING ON PENICILLIN MOLECULES IN BLOOD

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ABSTRACT

Precise control of drug transport and localization is a major objective in the development of targeted drug delivery systems for improving therapeutic efficacy while minimizing systemic side effects. Among the various transport mechanisms, thermophoretic forces generated under non-equilibrium thermodynamic conditions have attracted increasing attention as a potential means of directing drug molecules toward specific biological targets. This study presents a theoretical analysis of thermodynamic forces relevant to targeted drug delivery, with particular emphasis on thermophoretic effects. The underlying principles of non-equilibrium thermodynamics are reviewed and discussed in relation to recent advances in polymeric, lipid-based, magnetic, and multifunctional nanoparticle delivery systems. Building upon this theoretical framework, the study investigates the thermophoretic force acting on penicillin molecules in the bloodstream as a representative case for evaluating the feasibility of thermophoretically assisted drug transport. The analysis demonstrates the potential applicability of thermophoretic forces in the design of next-generation targeted drug delivery systems. The findings provide a theoretical foundation for integrating thermodynamic transport phenomena with nanotechnology to improve the precision, efficiency, and selectivity of future therapeutic strategies.

Keywords: *thermophoretic force; thermophoresis; targeted drug delivery; non-equilibrium thermodynamics; nanotechnology; penicillin.*

Introduction

Targeted therapy in oncology and infectious diseases has marked a significant milestone in modern medicine. However, many chemotherapeutic and antibiotic agents still suffer from non-selective biodistribution, leading to systemic toxicity and reduced therapeutic efficacy. Nanotechnology offers a promising solution through the design of drug delivery particles capable of being directed specifically toward diseased tissues. In addition to conventional biological targeting via ligands such as antibodies and aptamers, recent studies have explored thermodynamic forces as an innovative mechanism to enhance molecular orientation and selectivity. This paper presents the author's latest findings on the use of thermodynamic forces to develop targeted drug delivery systems, focusing specifically on determining the thermodynamic forces acting on penicillin molecules within the bloodstream.

1. Thermodynamic Forces

The thermodynamic force (thermophoresis) was first discovered by Charles Soret (1854-1904), a Swiss physicist and chemist, in 1879 while studying the diffusion of salts in solution under the influence of a temperature gradient [1, 2]. This phenomenon demonstrates that a net force acts on solute particles due to thermal gradients a phenomenon now known as the Soret effect [2].

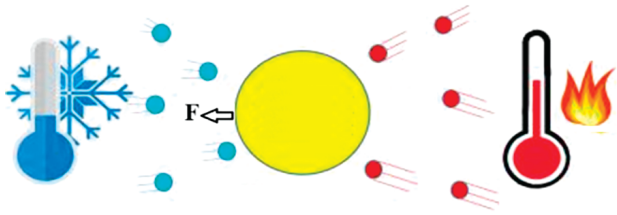

Fig. 1. The thermodynamic force F is generated by the action of gas (or liquid) molecules due to a temperature gradient

The Soret force represents a specific component of the overall thermodynamic force (Fig . 1), responsible for the directed motion of particles from hot regions toward cold ones or, in some cases, in the opposite direction. In quantitative terms, the relationship between the temperature gradient and the resulting concentration gradient at steady state is expressed through the Soret coefficient (ST), which characterizes the magnitude of this thermally induced mass transport [3]:

$$\nabla c = -S_T c(1-c)\nabla T \quad (1)$$

Where: c is the concentration, ∇c is the concentration gradient, T is the temperature, and ∇T is the temperature gradient. The Soret effect serves as the foundation for studying thermal diffusion in gases, liquids, and solutions [4].

Applications of Thermodynamic Forces in Medicine

Thermophoretic forces can be harnessed to enhance drug delivery.

i) Magnetic nanoparticles carry doxorubicin: Superparamagnetic iron oxide nanoparticles (SPION) coated with polymers can be loaded with doxorubicin and directed to tumor sites using an external magnetic field. This serves as a crucial foundation for magnetic navigation drug delivery systems, which combine both targeted accumulation and controlled drug release (Fig. 2) [8].

ii) Nano-theragnostic for breast cancer: Nanoparticles are engineered to simultaneously integrate imaging agents (such as fluorescent dyes, MRI contrast agents, or NIR signal emitters) and anticancer drugs. This dual design enables real-time tumor imaging and localized drug release, forming a "two-in-one" system (diagnosis + therapy). Such applications not only enhance the accuracy of diagnosis but also optimize therapeutic efficacy, particularly in breast cancer, where early detection and controlled treatment are essential [9].

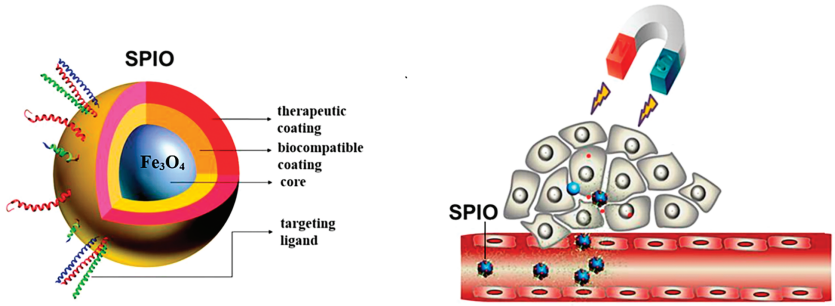

Fig 2. Superparamagnetic iron oxide nanoparticles (SPION) can be loaded with doxorubicin and directed to tumor sites using an external magnetic field

iii) Antibacterial Nanoparticles Against Multidrug-Resistant Bacteria: Silver nanoparticles (AgNPs) capable of generating reactive oxygen species (ROS) and disrupting bacterial cell membranes, as well as polymeric nanoparticles conjugated with antimicrobial peptides that can puncture bacterial membranes, are emerging as promising strategies to combat antibiotic resistance. These nano-systems can enhance bactericidal efficiency, reduce the required antibiotic dosage, and limit the formation of new resistant strains offering an important strategy against the global antibiotic resistance crisis [10].

Strategies for Harnessing Thermodynamic Forces

i) Nanophoresis by temperature gradients: When a temperature gradient arises in a biological environment, drug molecules or carriers can move from the hot region to the cold region, a phenomenon known as nanophoresis. This effect has significant applications in facilitating drug transport through dense tissues (e.g., tumor tissues rich in extracellular matrix) and in overcoming the blood brain barrier, which poses a major obstacle to most conventional drugs [11, 12].

ii) Nanorobotics based on thermally directed motion: Instead of relying on complex mechanical engines, some nanorobot models exploit Brownian motion coupled with temperature gradients to generate directional movement. This approach opens the possibility of designing self-propelled nanorobots capable of autonomously delivering drugs within biological microenvironments without requiring large external energy sources thereby ensuring both efficiency and safety in medical applications [13, 14].

These approaches possess key advantages, including:

- Non-invasive activation using external stimuli (e.g., laser or magnetic fields).
- High selectivity is based on microenvironmental differences.

- Potential for multimodal therapy (combining chemotherapy, phototherapy, and immunotherapy).

However, they also face significant challenges, such as:

- Precisely controlling temperature gradients within the body.
- Overcoming interference from blood flow and immune responses.
- Requiring interdisciplinary collaboration among physics, chemistry, and biology to optimize system design.

Harnessing thermodynamic forces offers a new paradigm for designing targeted drug delivery systems. Across studies involving polymeric, lipidic, magnetic, theranostic, and antibacterial nanoparticles, a unifying trend emerges exploiting the biological microenvironment's heterogeneity to achieve higher specificity. In the future, integrating thermodynamic principles with AI and computational modeling is expected to optimize nanosystem design, shorten experimental timelines, and advance the development of personalized (precision) medicine.

2. Thermophoretic Forces Acting on Penicillin Molecules in Blood

The application of thermodynamic forces in the bloodstream for targeted drug delivery is currently at the theoretical and preclinical research stages (including *in vitro* and *in vivo* animal studies). International research teams have experimented with AuNPs, SPIONs, and thermosensitive liposomes. To achieve a targeted drug delivery effect, it is essential to generate a thermodynamic force acting either on the drug-loaded nanoparticles or directly on the drug molecules themselves. This force arises from temperature gradients within fluids and gases.

Thermodynamic Forces in Gases and Liquids

In non-equilibrium thermodynamics, a thermodynamic force refers to a force generated by a temperature gradient, which induces a particle flux within a liquid or gas medium. The thermodynamic forces acting on various characteristic geometries have been extensively studied [15-20]. Within the framework of kinetic gas theory, analytical expressions have been derived for the thermodynamic forces acting on particles of different shapes such as spheres, cylinders, oblate spheroids, needles, disks, and rectangular boxes [17].

Notably, L. Waldmann and V. B. Dung applied the kinetic theory of gases to determine the thermodynamic force acting on a spherical particle suspended in a gas, assuming elastic collisions between gas molecules and the particle. This relationship is expressed through the Waldmann equation [19]:

$$F_T = -\frac{16K}{15}\frac{R^2 k_g}{\sqrt{\frac{2k_B T}{m}}}\nabla T \quad (1)$$

and V. B. Dung [20]:

$$F_T = \frac{k_B R^2}{4\sqrt{2r^2}}\nabla T \quad (2)$$

However, these equations cannot be directly applied to determine the thermodynamic forces acting on antibiotic molecules such as penicillin in the bloodstream, because blood is not pure liquid. It is a complex suspension consisting of water, red blood cells, white blood cells, and various other biological components. Therefore, it is necessary to establish the thermodynamic force exerted by a mixed fluid on spherical particles.

Thermodynamic Force of a Gas Mixture Acting on Disk-Shaped Particles

According to molecular kinetic theory, gas molecules are in a state of continuous random motion (thermal motion).

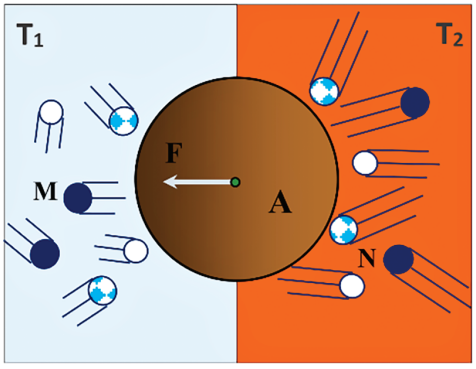

Fig 3. Model of the thermodynamic force (F) acting on a spherical particle A placed in a gas mixture with a temperature gradient (cold region temperature T_1 and hot region temperature T_2)

When this gas molecules collide elastically with objects immersed in a liquid or gas, forces are exerted upon those objects. The sum of all such microscopic forces constitutes the thermodynamic force. This principle can be applied to disk-shaped

particles placed in a gaseous environment, under the condition that the gas concentration is uniform, but the temperature is non-uniform (i.e., a temperature gradient exists) as illustrated in Fig. 3. Based on the kinetic and dynamic equations derived from molecular kinetic theory and non-equilibrium thermodynamics, the equation describing the thermodynamic force acting on spherical particles with radius R (placed in a gas mixture containing N different types of molecules under a temperature gradient ∇T) can be expressed as follows:

$$F = -\left(\frac{k_B}{12\sqrt{2}} R^2 \sum_{i=1}^{N} \frac{f_i}{r_i^2}\right) \nabla T \quad (3)$$

In this context, k_B is the Boltzmann constant, r_i is the radius of gas molecules, and f_i denotes the degrees of freedom of the gas. Equation (3) indicates that the thermodynamic force depends on the temperature gradient, the radius of the particle, the radius of gas molecules, and the type of gas involved.

Thermodynamic Force Acting on Penicillin Molecules in Blood

Penicillin G (benzylpenicillin), with the chemical formula $C_{16}H_{18}N_2O_4S$, is highly soluble in water. During medical treatment, penicillin molecules are transported through the bloodstream to reach target tissues and arrive at the therapeutic site via capillary circulation. Due to systemic blood flow and molecular diffusion, penicillin molecules become evenly distributed throughout the body. However, like most therapeutic agents, penicillin lacks an inherent targeting mechanism that enables it to accumulate selectively at pathological sites. As a result, its antibacterial efficacy decreases, while non-target tissues and organs may be adversely affected.

To enhance therapeutic efficiency, reduce dosage requirements, and minimize side effects, penicillin molecules must be specifically guided and concentrated at the desired treatment site. Because penicillin is readily soluble in water, and blood is a heterogeneous liquid mixture composed primarily of water (~55%) and red blood cells (~40%), with other minor constituents, it is feasible to exploit thermodynamic forces to direct and retain penicillin molecules at the desired location. This can be achieved by locally reducing the temperature at the target region below normal body temperature (37°C). Since thermodynamic forces arise from temperature gradients and act from hotter regions toward cooler ones, a controlled gradient can effectively drive and localize penicillin molecules at the target site.

Within the bloodstream, the thermodynamic force acting on penicillin molecules primarily results from interactions with water molecules and red blood cells, and it can be estimated using Equation (3). Therefore, to optimize therapeutic outcomes, lower penicillin dosage, and limit systemic side effects, it is crucial to design a targeted drug delivery mechanism that harnesses thermodynamic forces within the blood's composition mainly water and erythrocytes to achieve temperature-gradient-driven transport toward the therapeutic region (Fig. 4).

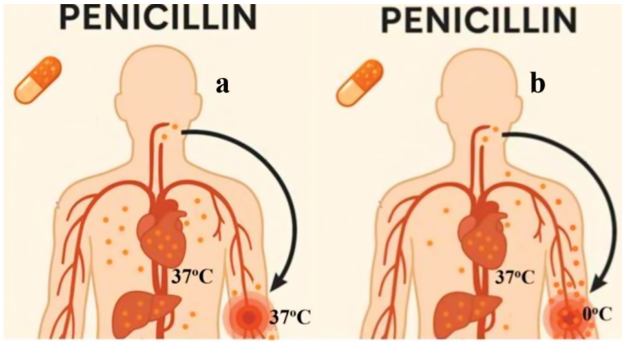

Fig. 4. (a) Conventional treatment shows low efficacy, as penicillin molecules are evenly distributed throughout the body without concentrating at the therapeutic target. (b) Targeted treatment using thermodynamic force generated by a temperature gradient demonstrates higher efficacy and significantly reduced side effects, as penicillin molecules accumulate predominantly at the cooled treatment site

Although Equation (3) was originally formulated to describe the thermodynamic force in gases under the assumption that the affected particles are spherical in shape, the fundamental nature of thermal motion in gases and liquids is essentially similar. Furthermore, the penicillin molecules can be approximated as spherical particles; therefore, Equation (3) can also be applied to estimate the thermodynamic force acting on penicillin molecules in blood.

The parameters used for the calculation are as follows:

- Radius of a penicillin molecule: R = 0.5 nm
- Radius of a water molecule (H_2O): r_n = 0.15 nm
- Radius of a red blood cell: r_{hc} = 0.15 nm
- Degrees of freedom for both H_2O and red blood cells: i = 6
- Boltzmann constant: $k_B = 1.38\times10^{-23}$ J/K

By substituting these values into Equation (3), we obtain:

$$F = -8{,}2 \times 10^{-25} 6 \left(\frac{R^2}{r_n^2} + \frac{R^2}{r_{hc}^2}\right) \nabla T = 6{,}3 \times 10^{-23} \nabla T \quad (4)$$

With the average capillary thickness of $d = 10^{-6}$ m, when the temperature at the target tissue region is reduced to 0°C while the blood temperature remains at T_2 = 37°C, a temperature gradient (∇T) is established that varies with the distance from the treatment site. This variation causes the thermodynamic force (F) acting on penicillin molecules to change correspondingly. The detailed calculation results are presented in Tab 1.

Tab. 1. Data on the temperature of the target tissue (T_1 = 0°C = 273 K), the blood temperature (T_2 = 37°C = 310 K), and the distance (d) from penicillin molecules at various positions to the treatment site, together with the corresponding calculated values of the temperature gradient (∇T) and the resulting thermodynamic force (F).

T_1 (K)	T_2 (K)	d (m)	∇T (Km^{-1})	F (N)
273	310	10^{-6}	37×10^{6}	$2{,}33\times10^{-15}$
273	310	0,5	74	$4{,}66\times10^{-21}$
273	310	1	37	$2{,}33\times10^{-21}$

The calculation results in Tab.1 indicate that:

(i) When the penicillin molecules are far from the target tissue region (at d = 1 m), the temperature gradient is small (∇T = 37 K/m). Consequently, the thermodynamic force acting on each molecule is only $F = 2.33\times10^{-21}$ N, which is very small.

(ii) Conversely, for penicillin molecules located within capillaries immediately adjacent to the target treatment area ($d = 10^{-6}$ m, corresponding to the capillary wall thickness), the temperature gradient becomes extremely large ($\nabla T = 37\times10^{6}$ K/m). In this case, the thermodynamic force reaches $F = 2.33\times10^{-15}$ N, which is about 10^6 times greater than that at a distance of 1 m.

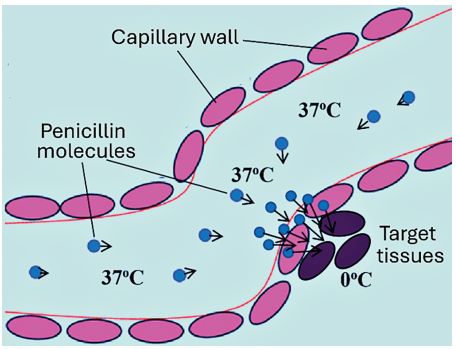

Fig. 5. Under the influence of thermodynamic forces in the bloodstream, penicillin molecules rapidly migrate and firmly attach to the target tissues requiring treatment

Based on the thermodynamic force (F), the acceleration of penicillin molecules can be determined, given their mass $m = 5.6 \times 10^{-25}$ kg. At a distance d = 1 m, and neglecting the viscous friction in blood, the acceleration of a penicillin molecule may reach 4.2×10^3 m/s². This is a very large value, indicating that penicillin molecules have the potential to move rapidly and accumulate in the target tissue region cooled to 0°C (Fig. 5). However, the high viscous resistance of blood significantly reduces the actual migration speed of penicillin molecules.

Thus, it can be concluded that reducing the temperature at the tissue region requiring penicillin treatment creates a temperature gradient, which in turn generates a thermodynamic force acting on the drug molecules. As a result, penicillin molecules are drawn toward and concentrated at the cooled treatment site, enhancing antibacterial efficacy while minimizing side effects on healthy tissues.

Conclusion

The thermodynamic force is the force exerted on particles within a liquid or gaseous medium when a temperature difference exists, that is, when temperature distribution is non-uniform within the medium. This mechanism can be exploited for targeted drug delivery, since blood, being a liquid, can generate thermodynamic forces on drug molecules by lowering the temperature of the target

tissue below the normal body temperature (37°C), thereby creating a temperature gradient. Because the thermodynamic force is always directed toward the cooler region, drug molecules naturally migrate and accumulate in the cooled tissue, leading to improved therapeutic efficiency. The computational results for penicillin demonstrate that:

(i) The thermodynamic force in blood acting on penicillin molecules is primarily determined by interactions with water molecules.

(ii) The thermodynamic force exerted on penicillin molecules located near the cooled treatment region is very strong ($F = 2.33\times10^{-15}$ N), ensuring that the molecules are firmly attached to the target tissue.

(iii) As the distance increases, the thermodynamic force decreases sharply, potentially becoming up to 10^6 times smaller when the distance increases by just 1 meter.

REFERENCES

Köhler, W., Morozov, K. I., Albers, C., & Müller, B. (2023). The Measurement of Soret and Thermodiffusion Coefficients in Binary and Ternary Liquid Mixtures. International Journal of Thermophysics, 44, 142.

Goldhirsch, I. (1983). Theory of thermophoresis. I. General considerations and mode-coupling analysis. Physical Review A, 27(3), 1616-1633.

Bringuier, E. (2011). Thermophoresis of linear polymer chains. Comptes Rendus Mécanique, 339(5), 333-341.

Wiegand, S. (2004). Thermal diffusion in liquid mixtures and polymer solutions. Journal of Physics: Condensed Matter, 16(10), R357-R379.

Bregoli, L., Movia, D., Gavigan-Imedio, J.D. et al. (2016), Nanomedicine applied to translational oncology: A future perspective on cancer treatment. *Nanomedicine* 11(6), 81-103.

Hou, X., Zaks, T., Langer, R., Dong, Y. (2021), Lipid nanoparticles for mRNA delivery. *Nat Rev Mater* 6, 1078-1094

Mura, S., Nicolas, J., Couvreur, P. (2013), Stimuli-responsive nanocarriers for drug delivery. *Nat Mater* 12, 991-1003.

Wu, W., Jiang, C.Z., Roy, V.A.L. (2016), Designed synthesis and surface engineering strategies of magnetic iron oxide nanoparticles for biomedical applications. *Nanoscale* 8,19421-19474.

Chen, F., Hong, H., Goel, S., Graves, S. A., Orbay, H., Ehlerding, E. B., et al. (2015), In vivo tumor vasculature targeting of CuS@MSN based theranostic nanomedicine, *ACS Nano* 9(4), 3926-3934.

Hussain, S., Singh, A., Singh, H., et al. (2022), Nanobiotics against antimicrobial resistance: harnessing the power of nanoscale materials and technologies*, Journal of Nanobiotechnology* 20(1), 375.

Jaque, D., Martínez Maestro, L., del Rosal, B. et al. (2014), Nanoparticles for photothermal therapies. *Nanoscale* 6, 9494-9530.

Piazza, R. (2008), Thermophoresis: moving particles with thermal gradients. *Soft Matter* 4, 1740-1744.

Vigolo, D., Rusconi, R., Stone, H. A., Piazza, R. (2010), Thermophoresis: microfluidics characterization and separation. *Soft Matter* 6(15), 3489-3493.

Xu, T., Xu, L.P., Zhang, X. et al. (2020), Nanorobots: the frontier of drug delivery. *Frontiers in Pharmacology* 11.

C. Y. Li, H. J. Keh (2017), Thermophoresis of a spherical particle in a microtube, Journal of Aerosol Science 113, 71-84.

Y. C. Chang, H. J. Keh (2012), Effects of thermal stress slip on thermophoresis and photophoresis, Journal of Aerosol Science 50, 1-10.

Z. Li and H. Wang (2004), Thermophoretic force and velocity of nanoparticles in the free molecule regime, *Phys. Rev. E.* 70, 021205.

Zhuo, S. et al. (2025), *Thermophoresis of Janus nanoparticles in liquids*. *Physical Review E* 112(1), 015403.

S. Yu, J. Wang, G. Xia, and L. Zong (2018), Thermophoretic force on nonspherical particles in the free-molecule regime, *Phys. Rev. E.* 97, 053106.

V. B. Dung (2024), General thermophoretic force on a small spherical particle in gases, *Indian Journal of Physics* 98, 4505-4513.