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A Novel Model for Predicting Pharmaceutical Stability in Space Environments: Theoretical Formulation of Extended Mean Kinetic Temperature (Space-MKT) Incorporating Space Radiation

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Abstract

The expansion of crewed space exploration necessitates robust quality assurance for pharmaceuticals under extreme space environments. Traditional Mean Kinetic Temperature (MKT) models rely solely on thermal degradation, critically overlooking molecular cleavage induced by high-energy space radiation. This study formulates the world's first mathematical model, "Space-MKT," an extended Arrhenius equation integrating both transient temperature fluctuations and radiation dose rates to evaluate combined degradation risks. Kinetic simulations of International Space Station (ISS) and lunar habitat scenarios reveal that standard MKT severely underestimates degradation during Solar Particle Events. Furthermore, combined anomalies—such as a simultaneous thermal control failure (35°C) and radiation spikes—trigger explosive synergistic degradation, reaching a Space-MKT of 59.7°C. The Space-MKT model can be edge-implemented into space-grade data loggers, enabling real-time, autonomous drug usability predictions for astronauts. This metric establishes a foundational standard for Space

22 Good Distribution Practice (GDP) in future deep-space missions.

23 **Introduction**

24 **1. Current Status of Pharmaceutical Stability Evaluation on Earth**

25 The quality, efficacy, and safety of pharmaceuticals must be guaranteed throughout the entire
26 process from manufacturing to the final consumer. Stability testing in drug approval
27 applications is extremely important for evaluating changes over time caused by various
28 environmental factors such as temperature, humidity, and light.¹ Since the establishment of the
29 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for
30 Human Use (ICH) in 1990, the standardization of international stability testing criteria, including
31 the Q1A guideline, has progressed. The foundational framework of this guideline is the concept
32 of Mean Kinetic Temperature (MKT) proposed by Haynes (1971).² MKT is an index that
33 calculates the degradation rate of chemical substances under non-isothermal conditions as a
34 single virtual steady-state temperature, based on the Arrhenius equation.³ In recent years,
35 while there are concerns about global temperature rises due to global warming, research by
36 Miura (2023) has demonstrated that the long-term storage testing conditions ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$)
37 stipulated by the current ICH guidelines remain broadly appropriate.⁴

38 **2. Application and Limitations of Data Loggers in GDP**

39 The application of MKT has expanded beyond stability testing for approval applications to
40 serve as an evaluation tool for temperature deviations within Good Distribution Practice (GDP)
41 in post-marketing distribution.⁵ Recently, by including digital data loggers within shipping
42 containers and packaging and subsequently calculating MKT from detailed temperature

histories, it has become possible to objectively evaluate the risk that transient temperature increases pose to pharmaceutical quality.⁶ However, conventional MKT evaluation has inherent limitations. MKT models solely heat-dependent (temperature-dependent) chemical reaction rates and cannot account for quality degradation caused by environmental stresses other than temperature, such as physical impact, light, oxygen, or phase changes (e.g., crystallization) to which pharmaceuticals are exposed during transport. In particular, the inability to identify the specific causes and durations of transient temperature deviations, as well as the inability to quantify non-thermal factors that decisively affect the three-dimensional structure of formulations, remains a challenge in rigorous quality management.

3. Progress of Crewed Space Exploration and New Challenges

Currently, humanity's advancement into deep space is accelerating, as seen with microgravity utilization on the International Space Station (ISS), lunar base construction under the Artemis program, and crewed Mars exploration. Consequently, the need for the long-term storage and transportation of pharmaceuticals in space for the purpose of maintaining astronaut health and treating diseases is rapidly increasing.⁷ The space environment differs dramatically from that on Earth, and there is a constant risk of extreme temperature cycles (differences of hundreds of degrees) due to malfunctions in Thermal Control Systems (TCS). An even more critical challenge is the unavoidable exposure of pharmaceuticals to "Space Radiation" outside the Earth's magnetosphere. High-energy proton and heavy ion beams originating from Galactic Cosmic Rays (GCR) and Solar Particle Events (SPE) are known to directly or indirectly cleave chemical bonds in pharmaceutical molecules, leading to a loss of potency and the generation of harmful degradation products.^{8,9} Conventional temperature-dependent MKT

models cannot predict degradation caused by such radiation-induced energy supply, posing a fatal risk of either underestimating or overestimating the expiration dates of pharmaceuticals in space environments.¹⁰

4. Objective of this Study

Therefore, this study aims to theoretically extend the conventional heat-dependent Arrhenius equation for space environments and propose a mathematical model for a novel metric, "Space-MKT," which enables the integrated evaluation of the combined effects of temperature fluctuations and space radiation exposure. In this paper, we first formulate an extended reaction rate equation incorporating the radiation dose rate and the material-specific radiation sensitivity. Next, we conduct case simulations using hypothetical environmental data (temperature changes and radiation spikes from solar flares) for the ISS cabin environment and a lunar habitat to comparatively verify the predictive accuracy against the conventional MKT model.

Results

1. Simulation Conditions for Three Space Environment Scenarios

To thoroughly verify the behavior and time-dependent characteristics of the constructed Space-MKT model, we set the evaluation timeframes to three patterns: 24 hours, 48 hours, and 72 hours. Furthermore, anticipating applicability to lunar exploration, we hypothesized a "combined severe environment" where a decline in the Thermal Control System (TCS) capabilities occurs simultaneously with radiation exposure. Simulations were conducted for a total of four scenarios. In all scenarios, it is assumed that the baseline temperature is maintained constantly at 22.0°C by the environmental control system. General values were assumed for the chemical parameters of the pharmaceutical ($E_a = 83.14$ kJ/mol, $E_{a,\text{rad}} = 41.57$ kJ/mol, $B/A = 1.16 \times 10^{-4}$).

- **Scenario 1: On Earth (Control):** Environmental conditions: Constant 22.0°C. Radiation exposure: 0 Gy/h (completely shielded environment).
- **Scenario 2: Inside the ISS Cabin (Steady Space Environment):** Environmental conditions: Constant 22.0°C. Radiation exposure: Steady deep space background radiation sustained at 0.02 mGy/h (2.0×10^{-5} Gy/h).
- **Scenario 3: Solar Particle Event (SPE / During Solar Flare):** Environmental conditions: Constant 22.0°C. Radiation exposure: Same as Scenario 2 during normal times, but assuming a sharp spike in radiation to 50 mGy/h (0.05 Gy/h) for 6 hours from the 20th to the 26th hour due to a solar flare. After the 26th hour, it returns to the steady background radiation level.
- **Scenario 4: Lunar Habitat (TCS Failure + Radiation Burst: Combined Severe**

Environment): Environmental conditions: Simultaneously with a solar flare (50 mGy/h spike from 20-26 hours), a temporary overload occurs in the habitat's life support and thermal control system (TCS), causing the cabin temperature to deviate and rise to 35.0°C for 12 hours from the 20th to the 32nd hour, before returning to 22.0°C. This models a worst-case scenario where temperature fluctuations overlap with a radiation burst.

2. Calculation and Quantitative Comparison of Space-MKT Over Time (24h/48h/72h)

In each scenario, based on the time-series data (T_i , D_i) sampled hourly from the data logger, both the conventional MKT (temperature-dependent only) [Eq. (3)] and the Space-MKT proposed in this study [Eq. (6)] were calculated. To capture the influence that the length of the validation time (evaluation period) has on the metric, the final calculated values at 24 hours, 48 hours, and 72 hours are shown in Table 2.

Table 2: Comparison of standard MKT and Space-MKT across different cosmic environments under varying evaluation periods (Base Temp: 22.0°C)

Scenario	Physical Environmental Conditions	Evaluation Period	Measured Mean Temp	Traditional MKT [Eq.3]	Proposed Model: Space-MKT [Eq.6]	Thermal Eqv. Increase (ΔT)
1. Earth	No radiation (0 Gy/h)	24 hours	22.0 °C	22.0 °C	22.0 °C	0.00 °C
		48 hours	22.0 °C	22.0 °C	22.0 °C	0.00 °C
		72 hours	22.0 °C	22.0 °C	22.0 °C	0.00 °C
2. ISS Cabin	Steady radiation (0.02 mGy/h)	24 hours	22.0 °C	22.0 °C	22.45 °C	+0.45 °C
		48 hours	22.0 °C	22.0 °C	22.45 °C	+0.45 °C
		72 hours	22.0 °C	22.0 °C	22.45 °C	+0.45 °C
3. Solar Flare	6h radiation spike (50 mGy/h 20-26h)	24 hours	22.0 °C	22.0 °C	52.12 °C	+30.12 °C
		48 hours	22.0 °C	22.0 °C	49.26 °C	+27.26 °C
		72 hours	22.0 °C	22.0 °C	45.40 °C	+23.40 °C

4. Moon Habitat	Combined severe env. (Spike + 35°C dev. 12h)	24 hours	24.17 °C	25.75°C	59.73°C	+35.56 °C
		48 hours	25.25 °C	27.18°C	56.78°C	+31.53 °C
		72 hours	24.17 °C	25.75°C	52.58°C	+28.41 °C

3. Kinetic Analysis of Simulation Results

- 1) Stability in Steady Environments (Scenarios 1 & 2):** On Earth (Scenario 1), both metrics align perfectly at 22.00°C across all periods. Inside the ISS cabin exposed to steady deep space background radiation (Scenario 2), the traditional MKT reads 22.00°C, whereas Space-MKT maintained 22.45°C ($\Delta T = +0.45^\circ\text{C}$) regardless of the period length. This indicates that the risk of molecular cleavage from steady radiation translates correctly as a "constant, slight temperature elevation" in terrestrial thermal terms—a steady stress that does not dilute over time.
- 2) Time Decay Characteristics of Transient Radiation Bursts (Scenario 3):** In Scenario 3, where a severe solar flare is experienced between 20-26 hours, a phenomenon where the Space-MKT value fluctuates drastically depending on the evaluation period was confirmed.

 - 24-hour evaluation:** Immediately after the spike (at 24 hours), the ratio of radiation exposure time to the total management time is high, causing Space-MKT to jump to 52.12°C.
 - 48-hour evaluation:** Subsequently, when another 24 hours pass under returned conditions of 22.0°C and steady radiation, the Space-MKT at 48 hours drops to 49.26°C.
 - 72-hour evaluation:** At 72 hours, it is further smoothed down to 45.40°C. This stems from the inherent property of MKT (and Space-MKT) to back-calculate the "average cumulative degradation rate over a certain period" as a virtual temperature. It demonstrates that even for transient severe radiation damage, if a long period of sound

management (cruise period) follows, it mathematically dilutes as an "average hourly degradation risk" over the entire period. However, even at the most smoothed 72-hour mark (45.40°C), it vastly exceeds the ICH accelerated testing condition on Earth (40°C), quantitatively proving how fatal the initial 6-hour spike was in causing cumulative degradation.

- **3) Synergistic Effects in Combined Severe Environments (Scenario 4):** In the lunar habitat (Scenario 4), where a temperature deviation overlaps with a radiation spike, the danger of Space-MKT reaches an extreme. The Space-MKT at 24 hours reaches 59.73°C, 56.78°C at 48 hours, and 52.58°C at 72 hours, displaying severe figures that exceed Scenario 3 across all timelines. As defined in [Eq. (4)], the radiation-induced degradation rate constant k_{rad} is secondarily influenced by the ambient temperature (a thermal amplification effect accompanied by an apparent activation energy $E_{a,\text{rad}}$). This model accurately captures that a direct hit by a high-energy radiation burst under a thermal deviation environment of 35.0°C caused a synergistic interaction between the elevation of molecular kinetic energy and the generation of radiation radicals, leading to an "explosive acceleration" of the drug degradation reaction. Because conventional MKT entirely overlooks ultra-fast degradation by radiation, it harbors a risk of creating a highly critical "overestimation of quality (the illusion of immortality)" during deep space missions.

4. Dynamic Specifications of the Graph for Publication (Figure 1)

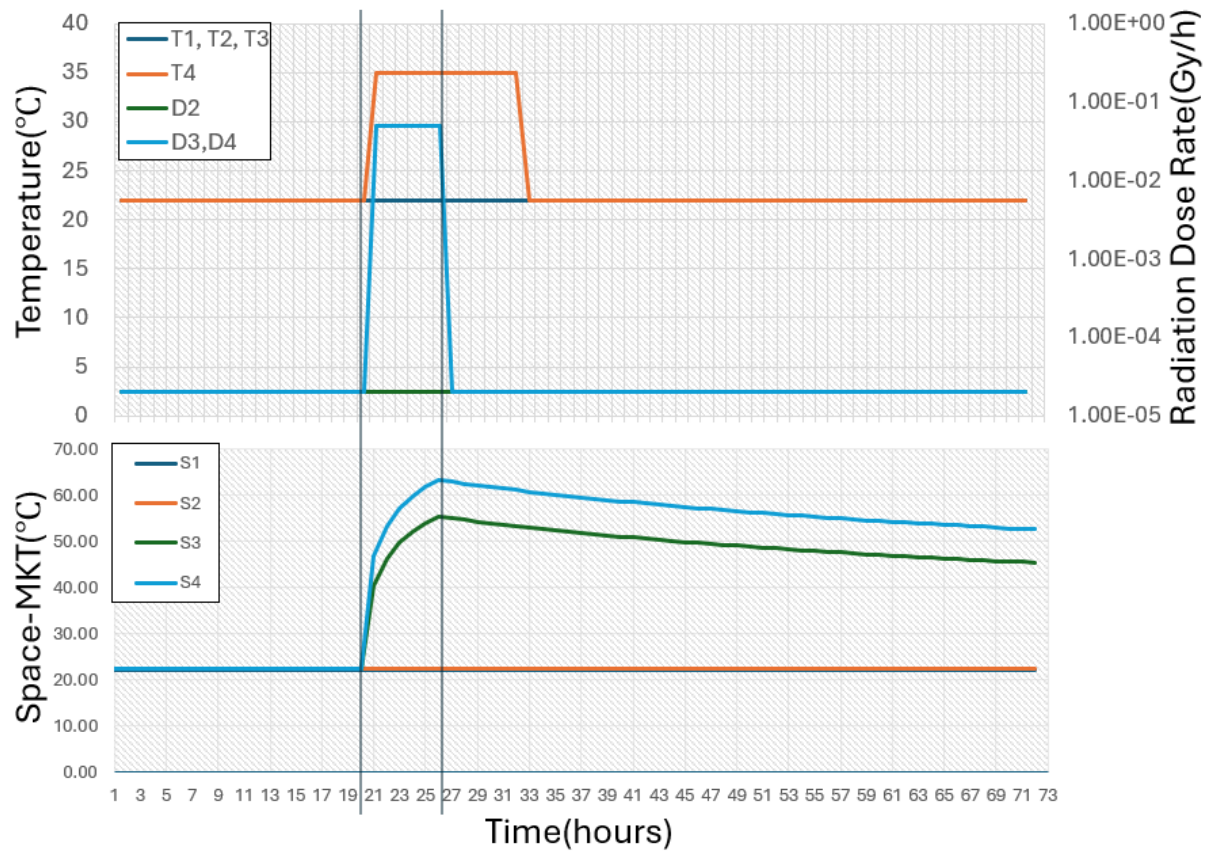


Figure 1. Dynamic changes in environmental conditions and Space-MKT over time. The top graph shows the simulation of temperature and radiation dose rate under four space scenarios (Control, ISS, Solar Flare, and Lunar Habitat). The bottom graph illustrates the corresponding calculated Space-MKT values, highlighting the dramatic synergistic degradation during the combined severe environment.

Discussion

1. Clinical Crises and Impacts on Space Medicine Caused by Radiation-Induced Degradation

In the simulations of this study, despite the temperature environment being held constant at 22.0°C, the degradation during Solar Particle Events (SPE) and in combined lunar environments poses severe paradoxes and crises to the medical safety systems in crewed space missions. On Earth, leaving pharmaceuticals in a severe environment exceeding 40°C for dozens of hours violates the tolerance limits of ICH accelerated testing conditions (40°C ± 2°C), signifying a dramatic shortening of shelf life or the risk of immediate inactivation for many formulations. The "drastic increase of reaction rates by several to over ten times" demonstrated by the kinetic evaluations in Sections 3.2 and 3.3 will trigger immediate and irreversible clinical crises, specifically in the following vital drug groups:

- **Peptide and Protein Drugs (Insulin, Antibody Therapeutics, Growth Hormones, etc.):** Direct molecular cleavage by space radiation (high-energy heavy ions and protons) and reactive oxygen species like hydroxyl radicals ($\cdot\text{OH}$) generated by the radiolysis of surrounding water molecules readily destroy the tertiary and quaternary structures of these macromolecules. Consequently, hormone formulations like insulin experience cleavage of disulfide bonds ($-\text{S}-\text{S}-$) and abnormal intermolecular aggregation, leading to a complete loss of receptor-binding capacity—namely, the ability to control blood glucose.
- **Antibiotics and Chemotherapeutic Agents (Amoxicillin, Ceftriaxone, Erythromycin, etc.):** Specific functional groups present in these molecules (e.g., β -lactam rings or

macrolide rings) are highly vulnerable not only to heat but also to ionizing radiation. Under combined stress where Space-MKT reaches around 50°C, ring-opening reactions and hydrolysis accelerate explosively, leading to a significant loss of potency (antibacterial activity). When astronauts in closed environments, prone to compromised immunity, develop severe infections (such as sepsis or pneumonia), this becomes a direct cause of treatment failure.

- **Risk of Toxic Degradation Product Generation Accompanying Non-specific**

Degradation: Unlike thermal degradation (transition to thermodynamically stable pathways), non-specific molecular breakdown by high-energy radiation carries a secondary risk of generating unknown metabolites or cytotoxic degradation products not anticipated in routine formulation testing on Earth. This not only results in a loss of therapeutic effect but also poses a novel health hazard of drug-induced toxicity to astronauts.

2. Academic Interpretation of Two Major Characteristics Based on Kinetic Analysis

The simulations addressing time dependency (24h/48h/72h) and the analysis of combined environments newly conducted in this study highlighted two kinetically vital characteristics for drug management in space environments.

- **1) The Time-Smoothing (Dilution) Trap of Transient Radiation Bursts:** In Scenario 3, the phenomenon where the value gradually decreases from the 24-hour Space-MKT (52.12°C) to the 72-hour mark (45.40°C) accurately reflects the mathematical property of "integral averaging" inherent in the Space-MKT model. The essence of MKT is to back-

calculate the cumulative degradation amount over a given period into a steady temperature. Therefore, even after experiencing a severe radiation spike, if a sufficiently long "sound thermal and radiation management period (cruise period)" follows, the average degradation risk per hour is diluted over the entire period, making the apparent value appear milder. However, a major quality management trap lies here. Even at the most smoothed 72-hour point (45.40°C), it still far exceeds the highest terrestrial storage standards. This means the irreversible "initial damage" at the molecular level caused by just the initial 6 hours of solar flares was not repaired by the subsequent good environment; it was merely mathematically diluted. Therefore, in space distribution management, the necessity of concurrently monitoring not only the simple long-term average Space-MKT but also a short-term moving average Space-MKT (e.g., a 24-hour window) was theoretically supported for the first time by this time-dependency analysis.

- **2) Quantitative Proof of Synergistic Effects Between Heat and Radiation (Thermal Amplification Effect):** The severe values in Scenario 4 (lunar habitat) that overwhelmed Scenario 3 across all timelines (59.73°C at 24h) strongly validate the interaction term of the extended Arrhenius equation [Eq. (4)] proposed in this study.

$$k_{\text{Space}} = A \exp\left(-\frac{E_a}{RT}\right) + B \cdot D \exp\left(-\frac{E_{a,\text{rad}}}{RT}\right)$$

As this formula shows, the radiation-induced degradation rate constant k_{rad} is a function of absolute temperature T accompanied by an apparent activation energy $E_{a,\text{rad}}$. When a radiation burst overlaps with a thermal control failure environment of 35.0°C (308.15 K), the elevation of molecular kinetic energy and the increase in the diffusion/reaction rate of radicals generated by radiation act multiplicatively, triggering an "explosive acceleration (synergistic effect)" of the degradation reaction. The traditional MKT model

[Eq. (3)] entirely overlooks the reality of molecular breakdown due to radiation. Because this "overestimation of quality" directly links to the risk of administering inactivated drugs to astronauts in deep space exploration, the integrated evaluation of heat and radiation is indispensable.

3. Implementation in "Space Data Loggers" and Practical Realization of Next-Generation Space GDP

The Space-MKT model proposed in this study demonstrates its true value not just in retrospective desktop analysis, but by being implemented into logger hardware as a real-time quality assurance (QA) system during ongoing missions. We propose the architecture of a "Space Smart Data Logger" that extends traditional temperature data loggers by integrating a temperature sensor (T_i) and a compact, low-power semiconductor radiation detector (such as silicon pixel detectors or integrated scintillator-SiPMs) onto a single board.

[Processing Flow of the Space Smart Data Logger]

- [Temperature Sensor (T_i)] + [Radiation Sensor (D_i)] → [High-Reliability Microprocessor] → [Real-time Space-MKT Calculation] → [Prediction of Remaining Drug Potency (k_{Space})] → [LCD Display / Alerts]

By edge-implementing the [Eq. (6)] algorithm as firmware in the logger's internal high-reliability processor, it dynamically calculates and updates Space-MKT at a high frequency of every hour, or every minute upon detecting anomalies like solar flares. Consequently, the logger evolves from a mere environmental "recorder" into a "predictor of remaining drug potency and expiration date". When it detects a solar flare or thermal control failure and Space-MKT

breaches a preset management threshold (e.g., a cumulative value corresponding to a 30°C equivalent on Earth), it instantly issues a warning alert. In deep space (such as Mars missions) where two-way communication delays with Earth take dozens of minutes, there is no margin to wait for instructions (telemetry analysis results) from ground control. Astronauts will be able to make autonomous decisions on the spot—"Is this drug still usable, or should it be discarded and replaced with an alternative?"—based on the scientific and quantitative Space-MKT values shown by the logger at hand, forming the practical framework for next-generation "Space GDP (Good Distribution and Storage Practices for Pharmaceuticals in Space)".

4. Universal Applicability of This Model and Milestones for Practical Application

- **1) Universal Applicability to Extravehicular and Vacuum Environments:** This model is not based on macroscopic physical phenomena of the environment (such as convection) but on the mathematical extension of the microscopic kinetics of the drug-constituting molecules themselves. Therefore, it is universally applicable not only in the managed environments inside spacecraft (ISS or lunar habitats) assumed in this study, but also for portable medical kits during future Extravehicular Activities (EVA) or storage/transport cases exposed directly on the airless lunar/asteroid surfaces (vacuum environments with direct UV and space radiation exposure), as long as the sensors capture the reaching dose rate and local temperature.
- **2) Future Milestones for Practical Application:** On the other hand, to implement this model in society (and space) as a practical Space GDP standard, the following three milestones must be cleared.

- **Database creation for sensitivity coefficients (B/A) and apparent activation energies ($E_{a,rad}$):** General assumptions were used in this simulation, but in reality, these parameters vary depending on the drug's chemical structure, dosage form (liquid, solid, lyophilized, etc.), and the shielding capability of the packaging material. It is necessary to conduct irradiation tests using proton and carbon beams on major essential drugs utilizing terrestrial heavy ion accelerator facilities (such as QST's Takasaki Advanced Radiation Research Institute) to build a comprehensive library.
- **Integration of the Microgravity Factor:** Under microgravity, another major element comprising the space environment, convection within solutions completely disappears. This changes the "molecular diffusion rate" of radicals and unreacted components, potentially exerting a tertiary influence on the degradation reaction rate. In the future, a mathematical evolution into a "Ternary Combined Arrhenius Extended Equation" that incorporates gravitational acceleration (G) is required.
- **Adaptation and Extension to Multi-step/Multi-pathway Reactions:** While this model assumes a simple single-step degradation reaction, further software extensions, such as merging Space-MKT with kinetic parameter predictions using Neural Networks (AI), are anticipated for actual drugs with complex formulation changes or multi-step degradation pathways.

Conclusion

In this study, anticipating humanity's full-scale expansion into deep space, we theoretically proposed the novel "Space-MKT" model, the world's first space-adapted evolution of the Mean Kinetic Temperature (MKT) concept widely used in terrestrial pharmaceutical distribution (GDP). This model is positioned as an extension of terrestrial ICH guidelines. The primary findings and achievements obtained from this study are as follows:

- **Formulation of a Combined Temperature-Radiation Kinetic Model:** We successfully expanded the traditional heat-dependent Arrhenius equation to formulate a combined reaction rate equation [Eq. (4)] that incorporates the dose rate (D) of space radiation—an unavoidable environmental stress in space—and material-specific radiation sensitivity. Furthermore, we mathematically derived the Space-MKT calculation formula [Eq. (6)] to aggregate this as a virtual thermal-equivalent temperature, accounting for the synergistic effect (thermal amplification) of heat and radiation.
- **Proof of the Limitations of Conventional Models under Time Dependency and Combined Severe Environments:** Through simulations covering multiple timelines (24h/48h/72h) and a combined severe environment (temperature deviation + radiation burst) intended for a lunar habitat, the following kinetic traits were revealed:
 - Although a transient radiation burst mathematically "smoothes (dilutes)" during a subsequent sound management period, the irreversible initial damage at the molecular level remains severe, proving the necessity for short-term/moving-average Space-MKT monitoring.
 - In a severe lunar combined environment where a thermal control system failure (35.0°C) and a solar flare (50 mGy/h) overlap, degradation accelerates explosively due to the

synergistic effect of heat and radical reactions, showing that Space-MKT reaches 59.73°C, far exceeding the most severe environments on Earth.

- We quantitatively demonstrated that the traditional MKT model inherently overlooks ultra-fast degradation by radiation, posing a fatal risk of creating a critical "overestimation of quality (illusion of immortality)" during deep space missions.
- **Proposal for Practical Applications in Space Pharmaceuticals:** The proposed mathematical model is exceedingly easy to implement into general spreadsheet software like Microsoft Excel (Table 1). By edge-implementing this algorithm into next-generation "Space Smart Data Loggers" integrated with temperature and radiation sensors, it becomes possible to build a robust decision support system where astronauts can autonomously judge the quality and usability of pharmaceuticals in real-time during deep space missions burdened with communication delays.

Overall, the achievements of this study are universally applicable not only inside spacecraft but also in vacuum environments like Extravehicular Activities (EVA). It transcends the framework of ICH guidelines and GDP standards predicated on the traditional Earth environment, representing a crucial step toward solidifying the academic and practical foundations of "Space GDP" and Space Pharmaceuticals, which will support safe medical provision systems in future lunar bases and crewed Mars exploration.

Theory and Methods

1. Mathematical Foundations of the Traditional Arrhenius Equation and MKT

The chemical degradation rate constant on Earth, k_{thermal} , depends on the absolute temperature T (K) and is expressed by the Arrhenius equation [Eq. (1)].

$$k_{\text{thermal}} = A \exp\left(-\frac{E_a}{RT}\right)$$

---[Eq.(1)]

Here, A is the pre-exponential factor, E_a is the activation energy of the degradation reaction (J/mol), and R is the gas constant (8.314 J K⁻¹mol⁻¹). Under fluctuating temperature environments, the mean degradation rate constant k_{MK} is derived based on the definition by Haynes (1971) using the absolute temperature T_i at each measurement point i , as shown in [Eq. (2)].

$$k_{\text{MK}} = A \cdot \frac{1}{n} \sum_{i=1}^n \exp\left(-\frac{E_a}{RT_i}\right) = A \exp\left(-\frac{E_a}{RT_{\text{MK}}}\right)$$

---[Eq.(2)]

By solving this for the standard kinetic temperature, T_{MK} , which is a virtual single temperature, the conventional MKT calculation formula [Eq. (3)] is obtained.

$$T_{\text{MK}} = \frac{-E_a/R}{\ln\left(\frac{1}{n} \sum_{i=1}^n \exp\left(-\frac{E_a}{RT_i}\right)\right)}$$

---[Eq.(3)]

2. Formulation of the Extended Arrhenius Equation Incorporating Space Radiation

In space, in addition to thermal energy, high-energy space radiation either directly cleaves molecular bonds or accelerates drug degradation through the generation of reactive oxygen species.^{11, 12} Therefore, the total degradation rate constant in a space environment, k_{Space} , can be formulated as a linear combination of thermal degradation (k_{thermal}) and radiation-induced degradation (k_{rad}).

$$k_{\text{Space}} = k_{\text{thermal}} + k_{\text{rad}}$$

Here, we assume that the radiation-induced degradation rate constant k_{rad} is proportional to the absorbed dose rate D (Gy/h) per unit time. However, since chemical reactions induced by radiation (such as radical reactions) are secondarily influenced by the ambient temperature (molecular kinetic velocity), we introduce the apparent activation energy under radiation, $E_{a,\text{rad}}$. Consequently, we propose the reaction rate equation [Eq. (4)] under combined environmental conditions.

$$k_{\text{Space}} = A \exp\left(-\frac{E_a}{RT}\right) + B \cdot D \exp\left(-\frac{E_{a,\text{rad}}}{RT}\right)$$

---[Eq.(4)]

Here, B is the radiation sensitivity coefficient (constant) of the pharmaceutical, and $E_{a,\text{rad}}$ is the apparent activation energy under radiation, which generally takes a lower value than the

379 activation energy of heat alone ($E_{a,rad} < E_a$).

380 **3. Derivation of Space-MKT**

381 To evaluate the total amount of drug degradation upon exposure to a fluctuating temperature
382 history (T_i) and dose rate history (D_i), we calculate the mean degradation rate constant
383 k_{Space} over a certain period (number of data points n) using [Eq. (4)].

384

$$385 \quad k_{Space} = \frac{1}{n} \sum_{i=1}^n \left[A \exp\left(-\frac{E_a}{RT_i}\right) + B \cdot D_i \exp\left(-\frac{E_{a,rad}}{RT_i}\right) \right]$$

386 ---[Eq.(5)]

387 Here, we define a virtual temperature under space radiation exposure: "If there were
388 absolutely no radiation ($D = 0$) and degradation proceeded at this exact same rate solely due
389 to heat, what temperature on Earth would this correspond to?". We name this temperature the
390 "Space-MKT" ($T_{Space-MKT}$). $T_{Space-MKT}$ is strictly an index that converts the "rate of decrease in
391 total potency (active ingredient amount)" into thermal equivalents. That is,

392 $k_{Space} = A \exp\left(-\frac{E_a}{RT_{Space-MKT}}\right)$. By solving [Eq. (5)] for $T_{Space-MKT}$ according to this definition, we
393 derive the foundational Space-MKT calculation formula [Eq. (6)] of this study.

394

$$395 \quad T_{Space-MKT} = \frac{-E_a/R}{\ln\left(\frac{1}{n} \sum_{i=1}^n \left[\exp\left(-\frac{E_a}{RT_i}\right) + \frac{B}{A} \cdot D_i \exp\left(-\frac{E_{a,rad}}{RT_i}\right) \right] \right)}$$

396 ---[Eq.(6)]

397 The ratio B/A in this equation represents the "ratio of radiation sensitivity to the pre-
398 exponential factor ($Gy^{-1} \cdot h$)" and is a value specific to the dosage form and chemical structure

of the pharmaceutical. In the limit where the space radiation dose rate $D_i \rightarrow 0$, this formula perfectly aligns with the traditional [Eq. (3)].

4. Implementation of Space-MKT Calculation Logic in Excel

To apply the proposed [Eq. (6)] to practical quality management, we constructed a calculation algorithm for Microsoft Excel that extends Table 1 from Miura (2023). It is structured to automatically calculate Space-MKT from three time-series data points obtained from space-grade data loggers: "Date/Time," "Temperature (°C)," and "Dose Rate (Gy/h)". This algorithm offers the advantage that formulation engineers and quality management departments worldwide can immediately integrate it into existing QA systems without requiring specialized software. The cell configuration and calculation formulas for implementation are shown in Table 1 below.

Table 1: Space-MKT calculations in Microsoft Excel

Row/Col	A (Measurement)	B (Temp °C)	C (Temp K)	D (Dose Rate)	E (Space Factor)
1	Measurement date and time	Temperature (°C)	Temperature (K)	Dose Rate D_i (Gy/h)	Space Degradation Factor

2	2026/1/1 1:00	22.0	=B2+273.15	0.0005	=EXP(- Ea/(R*C2)) + (B/A)*D2*EX P(- Earad/(R*C 2))
3	2026/1/1 2:00	22.5	=B3+273.15	0.0005	=EXP(- Ea/(R*C3)) + (B/A)*D3*E XP(- Earad/(R*C 3))
~	~	~	~	~	~
73	2026/1/3 24:00	15.0	=B73+273.1 5	0.0500	=EXP(- Ea/(R*C73)) + (B/A)*D73*E XP(- Earad/(R*C

					73))
74	Mean				=AVERAGE(E2:E73)
75	Space-MKT (K)				=- Ea/(R*LN(E7 4))
76	Space-MKT (°C)				=E75-273.15

412 *Note: By inputting the gas constant R (8.314), thermal activation energy Ea, activation energy*
413 *under radiation Earad, and sensitivity ratio B/A as defined names on the sheet or as constants*
414 *in specific cells, the above formulas will function directly.*

415

416 **Data Availability** All data generated or analysed during this study are included in this
417 published article.

418 **Code Availability** The calculation algorithms and formulas used for the Space-MKT
419 simulations in this study are fully described within the Methods section (Table 1) of this article.
420 No proprietary software was used.

421 **Author Contributions** E. M. conceived the theoretical model, designed and conducted the
422 simulations, analyzed the data, and wrote the manuscript.

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424 **Competing Interests** The authors declare no competing interests.

425

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