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PHARMACEUTICAL DOSAGE FORM INTEGRITY UNDER SPACEFLIGHT-INDUCED MECHANICAL STRESS: A REVIEW OF THE EFFECTS OF ACOUSTIC VIBRATIONS AND MECHANICAL SHOCK ON FORMULATION STABILITY

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Corresponding Author Email: jasvithamandava.jm@gmail.com**Received:** 15 July 2025 | **Revised & Accepted:** 1 October 2025**Keywords:** Spaceflight pharmaceuticals, Mechanical stress degradation, Vibroacoustic stability, Microgravity formulation integrity, Aerospace drug delivery

ABSTRACT

The structural and functional stability of pharmaceutical dosage forms under spaceflight-induced mechanical stress remains a critically underexamined frontier in extraterrestrial medicine. As human missions extend beyond low Earth orbit, formulations are subjected to high-frequency vibrations, mechanical shocks, and microgravity-altered fluid dynamics stressors capable of inducing tablet lamination, emulsion destabilization, protein denaturation, and container-closure compromise. Current regulatory guidelines (ICH, USP, WHO) inadequately address such mechanical degradation pathways, creating a significant methodological gap. Dosage forms ranging from solid orals to biopharmaceuticals exhibit distinct mechanical susceptibilities, requiring formulation-specific strategies, protective packaging, and mechanical stress modeling. This review consolidates existing insights into mechanistically driven degradation phenomena, evaluates mitigation tactics, and advocates for integration of aerospace-derived mechanical testing within pharmaceutical quality-by-design (QbD) protocols. Formal incorporation of these parameters into space pharmacopoeial standards is essential for safeguarding drug efficacy in autonomous, resource-constrained space settings. Addressing these challenges advances the foundation for space-certified, mission-critical therapeutics within the evolving field of space pharmacology.

1. INTRODUCTION

The advancement of extended space missions has catalyzed the emergence of space pharmacology as a specialized branch within pharmaceutical sciences.[1] As the focus of human spaceflight shifts from short-term orbital operations to long-duration missions including lunar bases and Mars expeditions, the need for stable,

efficacious, and reliable pharmaceutical systems becomes increasingly critical.[2] In such environments, pharmaceutical products are subjected to a set of non-terrestrial stressors that differ significantly from those encountered in Earth-bound conditions.[3] While considerable research has been directed toward the effects of cosmic radiation, microgravity,

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and thermal instability, relatively little attention has been devoted to the impact of mechanical forces, particularly acoustic vibrations and mechanical shocks, on dosage form stability.[4] These mechanical stressors primarily originate during launch, docking, re-entry, and other spacecraft mechanical operations, where drugs are exposed to high-frequency vibrational loads and sudden impacts.[5] These forces can potentially compromise the physical structure, chemical composition, and performance characteristics of pharmaceutical formulations. For instance, frequencies ranging from 20 to 2000 Hz, coupled with intense gravitational acceleration, can degrade drug products before use. Yet, the impact of such conditions on dosage form integrity remains under-investigated in pharmaceutical research, despite its relevance to space medicine and crew health maintenance.[6] This knowledge gap is particularly concerning in the context of limited resupply capabilities during interplanetary missions. The risk of dosage form degradation—whether through tablet capping, phase separation in emulsions, or protein denaturation—has direct implications for dose accuracy, bioavailability, and therapeutic safety.[7] Moreover, current stability testing guidelines, such as those established by ICH, do not incorporate protocols that simulate spaceflight-related mechanical stresses, leaving a significant void in regulatory and quality assurance frameworks.[8] The objective of this review is to provide a systematic evaluation of the effects of acoustic vibrations and mechanical shocks on pharmaceutical dosage forms. The discussion centers on formulation-specific vulnerabilities, underlying mechanisms of degradation, and the role of protective

packaging and design strategies in mitigating damage. Additionally, the review highlights existing methodological limitations and proposes future directions to support the development of space-ready pharmaceutical systems.[9] By integrating insights from formulation science, aerospace technology, and materials engineering, this review contributes to the foundational understanding required for designing mechanically resilient drug products. Such work is crucial to ensuring the efficacy, safety, and longevity of medications intended for use in extraterrestrial healthcare settings.[10]

2. THE MECHANICAL ENVIRONMENT OF SPACEFLIGHT

Pharmaceutical agents intended for extraterrestrial deployment are subjected to an intricate array of mechanical stress modalities that are quantitatively and qualitatively dissimilar from those encountered in terrestrial logistics.[11] Chief among these are acoustic vibrational excitation and impulsive mechanical transients, both of which emerge during discrete mission epochs, including vehicular launch, orbital insertion, mechanical docking procedures, extravehicular manipulations, and planetary descent or re-entry. These perturbations possess the potential to induce microstructural compromise, physicochemical instability, and biopharmaceutical dysfunction in dosage forms, underscoring the exigency for anticipatory formulation engineering and rigorous preflight qualification. [12]

2.1 Vibroacoustic Perturbations During Launch and Orbital Ascent

The launch sequence of orbital missions subjects pharmaceutical payloads to extreme vibroacoustic environments,

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characterized by intense acoustic pressures and mechanical vibrations arising from propulsion systems, aerodynamic turbulence, and structural resonance. Within the confines of payload fairings, sound pressure levels (SPLs) can escalate to 145–155 dB, particularly during ignition and transonic flight phases. These acoustic emissions are translated into broadband, multi-axial mechanical oscillations in the 20–2000 Hz frequency range, generating a complex vibrational field throughout the spacecraft structure. [13]

The resulting root-mean-square (RMS) accelerations, often reaching 10–20 g, vary depending on the vehicle configuration and the stowage location of the pharmaceutical payload. To standardize mechanical qualification, NASA's General Environmental Verification Standard (GEVS, GSFC-STD-7000A) provides codified power spectral density (PSD) envelopes for simulating such vibroacoustic regimes during ground-based testing. [14]

Pharmaceutical dosage forms are susceptible to a variety of deleterious effects under these mechanical loads, notably:

- Capping and lamination of compressed tablets due to cyclic stress fatigue. [15]
- Granular segregation in multiparticulate systems and powder blends, affecting content uniformity.
- Cavitation and phase disequilibrium in suspensions, emulsions, and other biphasic liquids. [16]
- Polymorphic transformations and morphological alterations in drug particles, altering dissolution kinetics. [17]
- Abrasion and coating erosion in controlled-release multiparticulates,

potentially leading to premature drug liberation. [18]

Such stress-induced transformations may not be immediately visible but can result in clinically significant alterations in drug release profiles, bioavailability, and dose consistency—critical factors in the autonomous therapeutic management required for long-duration space missions. [16]

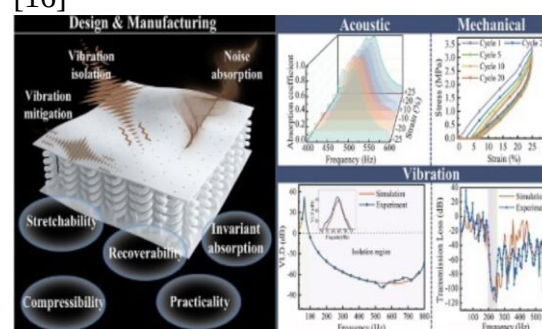


Fig (1): Acoustic and Mechanical vibrations

2.2 Impulsive Mechanical Shock: Stage Separation, Docking, and Planetary Re-entry

In contrast to continuous vibrational loads, mechanical shock events are characterized by short-duration, high-intensity accelerative impulses, typically occurring in the millisecond range. [19] These are commonly encountered during multistage propulsion separations, hard docking or undocking maneuvers, and high-impact deceleration during planetary re-entry or abort scenarios. Shock response spectra (SRS) in such instances may exceed 50–100 g, transmitting abrupt kinetic loads through structural contact points. [19] These impulses can initiate fracture propagation in fragile primary containers such as glass ampoules and vials. [20] In tablets and compacted solids, shock loads may lead to microcracking, surface fissuring, or structural disintegration, especially in

formulations with low plastic deformation thresholds. Flexible packaging systems including polymeric laminates and blister foils are also susceptible to hermetic seal compromise, permitting ingress of atmospheric moisture, gases, or microbial contaminants. Lyophilized matrices may suffer topographical collapse or crustal fragmentation, impairing reconstitution efficiency and altering re-dispersion behavior, thus jeopardizing dose accuracy.[21]

2.3 Cumulative Exposure and Synergistic Mechanical Degradation

Pharmaceuticals destined for extended space missions are rarely exposed to isolated mechanical events; rather, they experience superimposed and recurring stressors across a mission timeline.[22] These include both vibrational and shock vectors, compounded by thermal cycling, radiation, and prolonged microgravity exposure. This cumulative mechanical burden may lead to material fatigue, microscale deformation, and incremental physicochemical instability.[23] Polymeric matrices may incur incipient embrittlement, whereas elastomeric gaskets often demonstrate viscoelastic creep, attenuating their occlusive integrity over prolonged durations. Packaging junctures, especially under oscillatory thermal flux, are prone to thermomechanical attrition, precipitating progressive barrier dysfunction.[24] At the formulation scale, physicochemical transitions such as amorphous-to-crystalline polymorphism, particulate sintering, or colloidal coalescence may clandestinely compromise pharmacological efficacy antecedent to overt instability.[25] Nevertheless, extant stability frameworks (e.g., ICH Q1A(R2), USP <1225>, WHO

Annex 9) lack provisions for simulating the mechanical perturbations endemic to extraterrestrial deployment. This regulatory lacuna accentuates the exigency of incorporating aerospace-contingent mechanoqualitative assays into the evaluative schemas governing space-oriented pharmaceuticals.[26]

3. IMPLICATIONS OF ACOUSTIC VIBRATIONS AND MECHANICAL SHOCK ON SOLID ORAL DOSAGE FORMS

Solid oral dosage forms (SODFs) including monolithic tablets, encapsulated matrices, and multiparticulates are favored in extraterrestrial pharmaceuticals for their physicochemical durability and storage longevity.[27] However, vibroacoustic and inertial stressors encountered during launch and spaceflight induce fractomechanical degradation, such as interlamellar cleavage, capsular dissociation, and coating ablation. Monolithic compacts are especially prone to brittle failure, while multiparticulate capsules suffer stratification and electrostatic migration, impairing dose uniformity.[28] Encapsulation systems, though more compliant, face thermomechanical deformation and shell rupture. Such mechanoinduced perturbations alter dissolution kinetics, bioavailability, and systemic uptake, especially for BCS Class II/IV compounds.[29] Given limited resupply in space, pre-emptive mechanostability assessment, matrix optimization, and shock-attenuative packaging are imperative. Regulatory omission of these factors necessitates integration of aerospace-informed QbD frameworks in space pharmacotechnology. [30]

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4. IMPACT OF ACOUSTIC VIBRATIONS AND MECHANICAL SHOCK ON SOLID, LIQUID AND SEMISOLID DOSAGE FORMS

Liquid and semisolid biopharmaceutical matrices remain indispensable to both terrestrial and exoatmospheric therapeutic regimens, attributable to their multimodal administrability, accelerated pharmacodynamic onset, and posological adaptability. Nonetheless, these systems demonstrate pronounced vulnerability to mechano-induced physicochemical degradation, a consequence of their multiphasic architectures, viscoelastic rheo-dynamics, and dependence on containment–seal apparatus (CSA) integrity.[31] Unlike solid-state formulations with quasi-static supramolecular arrangements, fluidic and semisolid systems are hyper-responsive to vibrational shear, barodynamic perturbations, and thermal oscillations endemic to launch sequences, orbital corrections, and reentry deceleration.[32] This discourse delineates the impact of vibroacoustic energy flux and impulsive mechanical stresses on their structural, functional, and microbiological integrity.[33,34]

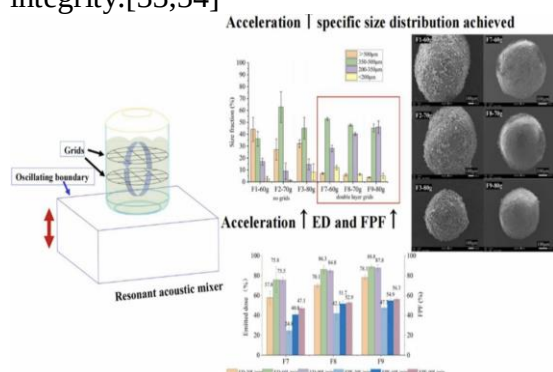


Fig (2): Acceleration studies on dosage form

4.1 Perturbation of Dispersoid Equilibria

Suspensions and emulsions—metastable colloidal biphasic systems—are predisposed to kinetic destabilization. Vibrational forces intensify sedimentogenesis, modulate zeta potential, and initiate Ostwald ripening, leading to compacted sediment, redispersibility impairment, and dosing variability. Emulsions, particularly parenteral or depot types, experience surfactant film disruption, resulting in coalescence, creaming, or phase inversion. Mechanical shock also alters globule size spectra, compromising colloidal sterility.[34]

4.2 Viscoelastic Deviations in Semisolid Matrices

Hydrogels, oleaginous bases, and thermoresponsive constructs possess rheological behavior governed by polymeric scaffolds and amphiphilic agents. Vibrational or impact stress may elicit viscosity reduction, syneresis, and thixotropic collapse.[35] Resultant deficiencies include impaired spreadability, mucosal adhesion, and erratic diffusion kinetics. Emulsified semisolids may undergo stratification and kinetic perturbation of drug release.[36]

4.3 Container–Seal System Integrity and Sterility Compromise

Structural tenacity of CSAs is critical to formulation stability. Repeated mechanical insults may induce microfractures, plunger misalignment, or seal delamination, leading to oxygen ingress, moisture permeation, or volatile loss. Sterility assurance is jeopardized under radiative and thermal duress. Conventional USP <1207> methods remain inadequate and necessitate aerospace-specific adaptation.[37]

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5. MECHANICAL STRESS-INDUCED DENATURATION IN BIOPHARMACEUTICALS

Mechanical perturbations notably shear vectors and vibrational flux are critical destabilizers in the degradation kinetics of proteinaceous biotherapeutics. These stressors disrupt labile non-covalent forces sustaining tertiary structure, precipitating partial denaturation, aggregation, and bioactivity attenuation.[38] Shear stress, prevalent in bioprocessing modalities (e.g., peristaltic pumping, filtration, lyophilization), reveals hydrophobic residues, promoting supramolecular nucleation. Vibrational inputs, encountered during transport or device-mediated administration, exacerbate conformational lability at fluid interfaces.[39]

Vulnerable biologics include:

- Insulin, prone to β -sheet fibrillation under shear
- Monoclonal antibodies, susceptible to domain-specific aggregation [40]
- Cytokines, prone to disulfide-misfolding [41]

In microgravity, diminished convection prolongs interfacial exposure, enhancing aggregation. ISS data confirm reconstitution failure in interferon- α and insulin. Simulated platforms further validate mAb aggregation due to disrupted mass transfer. Countermeasures include interfacial stabilizers (e.g., polysorbate 80), preferential solutes (e.g., trehalose), low-shear processing, and space-adapted delivery platforms, all essential to preserving pharmacological fidelity in extraterrestrial therapeutics.[42]

6. MECHANISTIC INSIGHTS INTO FORMULATION VULNERABILITY

The mechanical resilience of solid oral dosage forms (SODFs) is governed by

how vibrational and acoustic energies are propagated and dissipated within the formulation matrix. These mechanical perturbations, encountered during manufacturing, packaging, and transit, can induce microfractures, lamination, capping, and phase segregation, compromising pharmaceutical performance.[33] Susceptibility to such stressors depends on material properties including elastic modulus, viscoelastic behavior, porosity, and interparticulate cohesion. Rigid matrices promote stress transmission, while systems with enhanced damping attenuate force propagation. Acoustic impedance discontinuities at phase boundaries can cause stress amplification and localized structural compromise.[43]

Formulation strategies significantly influence mechanical robustness. Plastically deformable excipients (e.g., microcrystalline cellulose) enhance compaction and shock resistance, whereas brittle constituents elevate fracture risk. Binder systems modulate tensile strength, and particulate morphology including size, shape, and layering affects crack initiation and propagation, especially in multilayered or modified-release architectures.

Analytical techniques such as vibration simulation, shock testing, oscillatory rheometry, and acoustic emission monitoring enable assessment of mechanical degradation. Finite element modeling (FEM) offers predictive insights into stress distribution and failure zones.

Integrating material science principles with empirical testing and computational modeling facilitates the development of mechanically robust SODFs, ensuring structural fidelity across processing, distribution, and administration stages. [44,45]

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7. PHARMACEUTICAL PACKAGING AS A PROTECTIVE INTERFACE

Pharmaceutical packaging serves as a critical defense against mechanical and environmental stressors encountered during transport, storage, and use. In extended missions particularly in spaceflight it must also withstand vacuum, radiation, and extreme temperatures while preserving sterility, potency, and structural integrity.

7.1 Advanced Materials for Mechanical Stress Mitigation

Pharmaceutical packaging serves as a primary barrier against mechanical insults encountered during transit, storage, and deployment. In spaceflight, it must additionally tolerate vacuum, radiation, and thermal extremes. Modern systems utilize shock-absorptive substrates such as polyethylene or polyurethane foams to safeguard dosage forms during high-impact phases.[46] Viscoelastic polymeric layers attenuate vibrational energy, preventing microcracking and lamination in fragile matrices. Composite laminates integrating aluminum and high-performance polymers offer both mechanical durability and environmental resistance vital for protecting lyophilized biologics and compressed tablets.[44]

7.2 Environmental Compatibility in Spaceflight Conditions

Extraterrestrial packaging must resist outgassing, radiation-induced degradation, and temperature flux. Low-outgassing polymers are essential to prevent condensable volatiles from compromising adjacent systems or drug products. Radiation-stable materials mitigate polymer embrittlement and oxidative decay. Thermally stable laminates ensure dimensional and sealing integrity across extreme temperature

ranges, crucial for long-duration missions without resupply.[47]

7.3 Maintaining Product Quality and Functionality

Packaging must preserve sterility, potency, and structural fidelity. Barrier systems shield against oxygen, moisture, and light, inhibiting degradation of sensitive biologics. For microgravity applications, packaging must also support controlled dispensing, tamper resistance, and compatibility with zero-gravity handling, ensuring safe administration without compromising pharmaceutical stability.[48]

8. REGULATORY AND METHODOLOGICAL GAPS

Despite increasing awareness of mechanical stress as a determinant of pharmaceutical stability, existing regulatory frameworks remain inadequate in addressing vibration and shock-induced degradation. Major pharmacopeias and international guidelines such as ICH, USP, and WHO primarily focus on chemical and microbiological stability under controlled temperature and humidity, with no formalized protocols for evaluating mechanical forces like vibration, compression, or impact.[49] This omission is particularly problematic for transport-sensitive formulations such as solid oral dosage forms, biologics, and lyophilized products, which are vulnerable to physical disruption. Currently, no standardized methodologies exist to simulate real-world mechanical stressors within formal stability studies, hindering systematic risk assessment. The deficiency is further magnified in the context of spaceflight, where pharmaceuticals are exposed to vibration, acoustic shock, thermal cycling, and vacuum conditions stressors not replicated by terrestrial testing protocols.[50] No regulatory body has yet

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issued guidelines to qualify drug products for such environments.

To address this, it is imperative to:

- Develop standardized vibration/shock profiles based on mission data
- Integrate mechanical endpoints in stability assays
- Expand ICH Q1A to include physical degradation pathways
- Foster collaboration between regulatory and spaceflight stakeholders
- Bridging this regulatory gap is essential for ensuring medication reliability both in space and high-stress terrestrial logistics.

9. PROSPECTIVE DIRECTIONS FOR PHARMACEUTICAL RESEARCH

Prolonged extraterrestrial missions necessitate reengineering pharmaceutical design through incorporation of aerospace-calibrated mechanostability paradigms. Emphasis must be placed on the development of vibration-resilient dosage constructs, particularly for lyophilized biologics, macromolecular therapeutics, and high-potency solid matrices.

Key formulation strategies include:

- Utilization of stress-attenuating excipient frameworks and polymeric stabilizers
- Deployment of microarchitectural modifiers to mitigate internal mechanical energy propagation
- Engineering of microencapsulated systems and nanostructured vectors to withstand dynamic load without perturbing release kinetics [51]

To enable predictive stability, mechanodegradation modeling should be embedded into Quality-by-Design (QbD) architectures using:

- Finite Element Analysis (FEA)
- Shock response spectra simulations

- Real-time acoustic emission diagnostics [52]

Collaboration across aerospace agencies, regulatory bodies, and pharmaceutical scientists is vital to codify standardized mechanostress qualification metrics applicable to both space-bound and terrestrial high-strain pharmaceutical deployments.

CONCLUSION

The cumulative evidence underscores the significant impact of spaceflight-induced mechanical stressors on the structural and functional fidelity of pharmaceutical formulations. Exposure to vibration, acoustic shock, and microgravity-altered fluid dynamics creates a complex degradation milieu, accelerating phenomena such as protein denaturation, aggregation, solid matrix fracturing, and potency loss factors insufficiently addressed by conventional stability protocols. These challenges pose serious risks to therapeutic reliability, particularly during long-duration missions with limited resupply options. Pharmaceutical scientists must therefore prioritize the mechanical resilience of dosage forms through a multidisciplinary strategy integrating formulation engineering, aerospace-informed mechanical testing, and protective packaging innovations. Recognizing mechanical stress as a co-equal degradation vector alongside chemical and microbiological factors is imperative. To enable this paradigm shift, standardized simulation methodologies including launch vibration profiles and microgravity exposure protocols must be incorporated into future space pharmacopoeial frameworks. Such advancements will not only ensure drug safety in orbit but also enhance formulation robustness

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across terrestrial high-stress logistics networks.

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