Exploring the complexities of drug formulation selection, storage, and shelf-life for exploration spaceflight

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Introduction

Medications have been a part of space travel dating back as far as the Apollo missions. Currently, medical kits aboard the ISS contain medications and supplies to help crew members cope with a variety of possible medical events. NASA reported that 1,867 medical events occurred from 1981 to 1998 on space shuttle flights, STS-1 to STS-89; 498 out of the 508 crewmembers on those flights reported experiencing a medical event other than space motion sickness [1]. In 2000, the Institute of Medicine (IOM) convened a committee of experts, Committee on Creating a Vision for Space Medicine during Travel beyond Earth Orbit, to examine the issues surrounding astronaut health and safety for long duration space missions. The primary theme of the committee's final report is that there is not enough known about the risks to human health during long-duration missions beyond Earth's orbit and ways to effectively mitigate those risks in an environment of deep space [2]. In 2014, the IOM convened the Committee on Ethics Principles and Guidelines for Health Standards for Long Duration and Exploration Spaceflights and released a report emphasizing the importance of prevention, mitigation, and treatment of major risks to human health during exploration spaceflight [3]. NASA's Human Research Program has organized five distinct categories of spaceflight hazards summarized by the acronym "RIDGE" (Space **R**adiation**, I**solation and Confinement, **D**istance from Earth, **G**ravity fields, and Hostile/Closed **E**nvironments) that astronauts may encounter during exploration spaceflight [4, 5]. From those hazards, NASA further derived 30 of the most critical human health and performance risks, including limits to medical care resulting from pharmaceutical degradation [6]. As we prepare for more distant exploration missions to Mars and beyond, risk management planning for astronaut healthcare should include the assembly of a medication formulary that is comprehensive enough to prevent or treat anticipated medical events, remains safe and chemically stable, and retains sufficient potency to last for the duration of the mission. The present editorial will summarize the current state of knowledge regarding innovative formulary optimization strategies, pharmaceutical stability assessment techniques, and storage and packaging solutions that could enhance drug safety and efficacy for future exploration spaceflight missions.

Pharmaceutical Formulary Optimization

A safe and effective medication formulary is essential to maintaining crew health and performance during long-duration spaceflight outside of low-Earth orbit (LEO). Distance from Earth creates four key operational changes that increase medical risks, including communication, consumables resupply, crewmember health, and evacuation [7]. The spaceflight pharmaceutical formulary consists of medications indicated to treat a variety of anticipated medical events and healthcare needs during spaceflight. The specific medications in the formulary may change to optimally align with the mission, crew

compliment, and spacecraft design. Currently, medical support missions at low Earth orbit (LEO) depend on a robust consumables resupply chain, which will be strained for lunar and possibly non-existent for a Mars mission [7-11]. Long-duration exploration missions will differ from missions in LEO due to mission duration, lack of consumables resupply, prolonged exposure to space radiation, and the absence of emergency medical return capability. Increased distance and mission length are expected to increase medical and total mission risk. Loss of medication resupply limits or removes the ability to replace medications that have been exhausted or degraded, potentially exacerbating the medical risk posture. To address these anticipated risks, long-duration missions must consider use of new medical technologies, treatment modalities, and smarter medical systems that offer greater crew autonomy [12].

Personalized medicine refers to an approach to patients that considers their genetic composition but with attention to their preferences, beliefs, attitudes, knowledge, and social context; whereas, precision medicine describes a model for health care delivery designed to optimize efficiency or therapeutic benefit for a particular patient or group of patients and relies heavily on data, analytics, and information[6,10]. NASA and other Space Agencies have started to investigate the benefits of genomics and precision medicine to obtain the scientific evidence needed to understand how humans adapt to and function in the unique environment of space [6]. In 2015, the European Space Agency (ESA) published the results of a pharmacogenomics assessment of the International Space Station (ISS) pharmaceutical formulary. The ESA results revealed a 30% user-specific variance in metabolism, strongly suggesting the need for pharmacogenomic matching for a future exploration spaceflight formulary [13].

The NASA Lifetime Surveillance of Astronaut Health (LSAH) proactively collects data on astronaut medical care and workplace exposures, especially those occurring in the training and spaceflight environments, and conducts operational and health care analyses to look for trends in exposure and health outcomes. NASA's Life Sciences Data Archive also includes data from human subjects derived from both past and current spaceflights, as well as data from analog studies to form a more comprehensive reference database for analysis. The Integrated Medical Model (IMM) is a Probabilistic Risk Assessment (PRA) Monte-Carlo simulation tool developed by NASA to inform ISS and other PRA based mission analyses [7, 11, 13]. The IMM was developed at NASA starting in 2008 and was transitioned to operations in 2017 [14]. The IMM models 100 medical conditions and includes the capability to assess the impact of resource limitation or depletion on successful treatment of medical conditions by incorporating evidence from all ISS missions as well as data from Apollo, Skylab, Mir, and Space Shuttle programs, thereby providing valuable information for mission planners [10]. Correlating LSAH data with supportive IMM incidence data suggests that medications could treat or mitigate many of the medical events experienced by NASA astronauts during previous space missions.

H. Nguyen et al. incorporated the prediction capability of physiologically based pharmacokinetic (PBPK) models into a rational drug degradation risk assessment procedure using a series of model drug degradants (substituted anilines). The PBPK

models are parameterized using a combination of experimental and literature data and computational methods. The impact of model parameter uncertainty is incorporated into a risk assessment procedure based on the novel use of a statistical metric called "PROB" for comparing the probability that a human toxicity-target tissue exposure exceeds the rat exposure level at a critical no-observed-adverse-effect level. When compared with traditional risk assessment calculations, this novel PBPK approach appears to provide a rational basis for drug instability risk assessment by focusing on target tissue exposure and leveraging physiological, biochemical, and biophysical knowledge of compounds and species[15]. Deepika and Kumar summarized recent developments in building quantitative adverse outcome pathways (qAOPs) for several endpoints such as developmental neurotoxicity (DNT), hepatotoxicity, and cardiotoxicity, and how usage of machine learning and artificial intelligence may improve and advance the existing PBPK framework[16].

An increasing number of pharmaceutical and medical device companies are introducing innovations such as nanobots, implants, artificial intelligence (AI), and wearable drug delivery/monitoring devices. AI and Machine Learning (ML) algorithms have slowly but surely begun to revolutionize pharmaceutical industry and drug development in recent years. In 2019, Koromina et al. illustrated how AI, encompassing ML, and other approaches such as deep learning could be implemented in clinical practice towards the improvement of precision medicine and drug discovery. AI and computational algorithms can be harnessed with pharmacogenomics expertise to better guide drug discovery and development pipelines [17].

There are many success stories in the pharmaceutical industry using cell-based disease models to identify new indications or repurposing drugs already approved by the U.S. Food and Drug Administration (FDA) [18,19]. Madrid and Chang proposed that drug repurposing using prior FDA approved drugs with well understood mechanisms of action, qualified chemistry, manufacturing protocols, and safety profiles offered an attractive strategy for delivering a new approach for developing new medical countermeasures (MCM) to protect humans from space radiation in long-term missions. For example, the biologic product Romiplostim (Nplate®) iscurrently approved to treat idiopathic thrombocytopenic purpura. Under a radiation medical countermeasure product development support program funded by National Institute of Allergy and Infectious Diseases, SRI conducted a series of animal studies to support Amgen's FDA supplemental Biological License Application to repurpose Romiplostim as a medical countermeasure for hematopoietic acute radiation syndrome. Madrid and Chang are currently working on an NCI sponsored drug screening program targeting the Artemis endonuclease enzyme for radiotherapy using a miniaturized cellular V(D)J recombination assay with chromosomal substrates [20].

Manian et al. illustrated how multi-modal gene disease and disease drug networks, along with link prediction algorithms, were used to identify the main gene regulators responsible for skeletal muscle atrophy from spaceflight microgravity and the repurposed drug treatments with the highest probability of successfully managing the condition [21, 22]. Harvested muscle tissue from mice exposed to spaceflight, made

available by the NASA GeneLab repository, was exposed to RNA and DNA sequencing to generate transcriptomic datasets. The datasets were then mined to identify key genes and muscle atrophy gene regulators were selected using the Bayesian Markov blanket method. A Gene Disease Knowledge Graph (GDKG) was constructed using a scalable precision medicine knowledge engine. A total of 21 drugs were identified as possible candidates for treating muscle atrophy. This innovative method of combining six GeneLab datasets with other disease and drug databases, followed by use of applied network analysis and artificial intelligence methods, offers promise for furthering drug repurposing efforts [21]. In a follow-up publication, Manian et al. expanded their drug repurposing research by mining seven GeneLab datasets to identify the key genes and drugs associated with skeletal muscle atrophy. The key genes were recognized as those associated with metabolic and neurodegenerative diseases. The repurposed drug candidates targeted by the graph convolution network method were determined to be nutrients, corticosteroids, anti-inflammatory medications, and insulin related treatments. This work offers promise that these network analyses and ML methods can be utilized to generate disease drug networks that are scalable and applicable to multiple datasets, genes, and drugs, which could lead to the identification of repurposed drug candidates for multiple medical conditions [22].

Lu et al. recently developed a de novo design platform, SECSE, that integrates human intelligence for systemic evolutionary chemical space exploration against a specific protein pocket. The platform incorporated design rules of medicinal chemistry, computational evaluation methods, and deep learning models to efficiently speed up the search process of virtual hit compounds. Application of SECSE against phosphoglycerate dehydrogenase (PHGDH) proved its potential in finding diverse, potent, and novel drug-like chemotypes that are attractive starting points for further validation [23].

Seoane-Viano et al. summarized several promising therapeutics for anticipated clinical condition management, emerging technologies focused on pharmaceutical manufacturing (e.g., Chemputing, synthetic biology, and 3D printing), and storage; management in space; and recommendations to facilitate adoption, regulatory oversight, and enforcement [24-29]. Chemputing represents a novel method of synthetizing drug molecules using a modular chemical-robot system known as a Chemputer [26]. Scientists at the University of Glasgow were able to successfully synthesize medications including rufinamide, diphenhydramine hydrochloride, and sildenafil. They also developed the Chempiler, which automated synthesis performed by the Chemputer, thereby generating higher output yields than those achieved manually. The Defense Advanced Research Projects Agency's (DARPA) Pharmacy on Demand (PoD), and the Biologically derived Medicines on Demand (Bio-MOD) programs focus on manufacturing therapeutic products on-demand [25]. The PoD has successfully developed four medications (diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam, fluoxetine hydrochloride) synthetized from raw materials. The Bio-MOD system was designed to generate therapeutic proteins in small doses at the point-of-care within 24 hours [30]. Synthetic biology is an emerging discipline aiming to reengineer microorganisms to manufacture biological, protein-based drug products [31, 32].

NASA's Translational Research Institute for Space Health (TRISH) has funded a project at the Massachusetts Institute of Technology (MIT) to develop a gastric resident device for in-situ production of drugs, called the "mother machine", which uses bacterium to produce and release melatonin, caffeine, and acetaminophen within the stomach after ingestion [24]. In another TRISH-funded project, researchers at the University of California Davis are developing plant-based methods to produce protein-based pharmaceuticals in under 24 hours for use in deep space missions [35]. The researchers chose lettuce as their host plant as it had already been successfully grown on the ISS. Lettuces were infected with Agrobacterium tumefaciens containing a DNA sequence encoding the desired protein, which is subsequently transcribed and translated into the functional protein. They focused on producing three therapeutic proteins (a parathyroid hormone for bone loss, a granulocyte colony-stimulating factor for radiation sickness, an anti-fungal peptide) [36]. The use of probiotics and prebiotics as food additives or supplements were presented as promising countermeasures of microbiome dysregulation to benefit overall gut health during spaceflight [37]. Synthesis of a combination of melanin with selenium, selenomelanin, has demonstrated the ability to absorb X-rays more efficiently than melanin alone [38]. Westover et al. conducted a study of the tardigrade, an invertebrate species sent into space by ESA, which was shown to survive up to 5kGy of ionizing radiation and the vacuum of space. This study revealed a unique damage suppressor protein that protects the organism from exposure to ionizing radiation free radicals. The protective effect of this protein could potentially be used to mitigate oxidative stress damage resulting from chronic exposure to space radiation [39].

Simon et al. explored repurposing therapeutics with bactericidal activity to tackle concerns with multiple drug resistance (MDR). Phenothiazines, as efflux pump inhibitors, may be able to augment the antimicrobial activity of antibacterial agents and increase their intracellular concentration. Although clinical use of most phenothiazines is prohibitive due to clinical and cellular toxicity, their prospective antimicrobial properties offer promise for tackling MDR. Simon et al. conducted stability studies on phenothiazines pre- and post-hypergravity exposure, examining their multifunctionality and ability to transform into antimicrobial agents in response to laser irradiation. PMZ exposure to Ultraviolet-visible (UV-Vis) absorption spectrum in dark and ambient light environments resulted in slowed degradation in the dark environment and changes in the absorption spectra in response to generation of the more polar photodegradation products. Other promising compounds reviewed included the organoselenium compound Ebselen (5-fluoro-2'-deoxyuridine), demonstrating in-vitro and in-vivo antimicrobial activity against Staphylococcus aureus, diazabicyclooctane (DBC) a β-lactamase inhibitor, quinazoline derivatives, imidazolidine-4-ones to boost the effectiveness of antibiotics against S. aureus, and the synergistic increase in antimicrobial activity generated by combining the anti-diarrheal loperamide with tetracyclines [40-41].

Pharmaceutical Stability and Shelf Life

Once the ideal formulary for exploration space is determined, it is essential to establish the chemical and physical stability of each medication compound, as well as its safety by identifying its degradation profiles and products. Therapeutic effectiveness and safety of pharmaceuticals are critical to the success of exploration spaceflight. Although few studies have been conducted to provide evidence on the physicochemical stability of pharmaceuticals during space missions, the data suggests that the spaceflight environment may promote degradation in some pharmaceuticals [9, 10, 42-50]. Changes in active pharmaceutical ingredient (API) concentration or drug dosage form release could lead to inefficacy, treatment failure, or pharmacological toxicity. The United States Pharmacopeia (USP) defines potency, quality, safety, and stability acceptance criteria for finished pharmaceutical products (FPPs) approved by the FDA. Pharmaceutical stability studies are required by the FDA to demonstrate that a pharmaceutical product meets its acceptance criteria or remains within established limits of quality, potency, and purity throughout a specified time of storage[43]. Conducting stability studies help characterize how the API or FPP varies with time under the influence of environmental factors such as temperature, humidity, and radiation[43-44, 51-52]. A drug product's shelf life or expiration dating period is defined as the time that a drug product is expected to remain potent within approved specifications, while stored under the conditions defined by the manufacturer on the container label [51-52]. Many factors contribute to the chemical and physical stability of an FPP, including composition of the API, interactions between the API and excipients or inactive ingredients, environmental conditions during shipment, storage and handling, and the product's shelf life. The chemical stability of an FPP can be influenced by environmental factors such as heat, radiation, moizture, and chemical factors such as pH, oxidation, reduction, hydrolysis, or photodegradation reactions [43, 53 - 54]. An FPP's physical stability can be impacted by attributes such as solid dosage form hardness, brittleness, or particle size, which could compromise API solubility, dissolution, or API release from the FPP [43, 53]. Pharmaceutical excipients are also important components to FPP stability. Excipients serve as diluents, fillers, binders, disintegrants, lubricants, coloring agents, and preservatives in FPPs. Although the ideal excipient is incorporated into the FPP to enhance manufacture, administration, or product stability, some can initiate, propagate, or participate in chemical or physical interactions with the API, leading to compromised drug safety and effectiveness [54 - 55].

Pharmaceutical stability testing conducted under Good Manufacturing Practices (GMP), primarily utilizes the stability-indicating assay and impurities method, a gradient reversed-phase liquid chromatography method such a High-performance Liquid Chromatography (HPLC), or Gas Chromatography (GC), coupled with spectrometry detection capable of separating product APIs, impurities, and degradation products (e.g., Mass Spectrometry (MS), Ultraviolet (UV), Raman, Infra-red (IR), Nuclear Magnetic Resonance (NMR)) [43]. Results obtained from these stability-indicating assays are used by pharmaceutical manufacturers to support the establishment of expiration dates for regulatory filings [56].

Chromatographic techniques require destruction of the drug sample by extraction of the API in organic solvent mixtures and water. Spectroscopy provides fast and nondestructive analyses with high chemical specificity for the determination of drug quality parameters [57]. Spectroscopy is used throughout pharmaceutical production to confirm levels of APIs and impurities. Several spectroscopic techniques such as Raman (using visible light), IR, Near-Infrared (NIR) (using IR or near-IR radiation), combined with chromatographic methods, statistical regression tools, and chemometric tools are now proposed for pharmaceutical quality assessments [58-60]. Raman spectroscopy can not only support non-destructive quality testing of drug substances, it can also support routine safety and quality screenings of FPPs [61]. Although IR spectroscopy had been the spectroscopic method of choice for identification and quantification of pharmaceutical products under standardized conditions, the European Pharmacopoeia (Ph. Eur.) presented the first general chapter for Raman spectroscopy in 2002, with revisions in 2016 and 2021 to include hand-held Raman spectrometers, and their use as process analytical technology (PAT). Likewise in 2016, and in harmonization with the Ph. Eur., the USP replaced former Raman Chapter <1120>, with Chapters <858> and <1858>, made further revisions in 2020—2022, and created a new Chemometrics chapter <1039> [61-62].

K. Shah et al. reviewed recent advancements and applications for Raman spectroscopy in pharmaceutical analysis [57]. K. Berzins et al. conducted a proof-of-principle study demonstrating a new Raman subtechnique from micro-spatially offset using low frequency Raman spectroscopy (micro-SOLFRS) to nondestructively obtain information about pharmaceutical solid dosage forms and surface-driven changes from exposure to environmental conditions (e.g., temperature, relative humidity) [63]. Makki et al. applied Raman and IR spectroscopy for qualitative and quantitative analysis of commercially available therapeutic solutions of anti-cancer drugs (e.g., doxorubicin, epirubicin, daunorubicin), demonstrating that IR and Raman spectroscopy could support quality control of personalized chemotherapeutic solutions prepared for patients [64]. M. Sultan et al. reported the application of Surface Enhanced Raman Scattering (SERS) for the rapid and cost-effective detection of warfarin in pharmaceutical dosage forms and plasma samples. The results were found to be highly precise and unaffected by the presence of excipients in the dosage forms [65]. A novel approach to determining multiple analytes separately and simultaneously has been achieved using SERS substrate. In 2020, C. Liu et al. studied the use of ZnO/Ag substrate for rapid and non-invasive determination of two oral antidiabetic drugs, pioglitazone and phenformin [66]. E.M. da Silva et al. used Raman spectroscopy for the determination of amlodipine besylate and hydrochlorothiazide using a composite of graphite and polycaprolactone polymer in the analysis of tablets and urine samples [67]. Z. Wang et al. compared the effectiveness of Raman spectroscopy with that of terahertz spectroscopy for the determination of enantiomers of ibuprofen. The results revealed higher accuracy (up to 97.04%) for the detection of (R)-(-)-ibuprofen and (S)-(+)-ibuprofen by terahertz spectroscopy compared to that of 52.89% for Raman spectroscopy [68]. J. Zini et al. worked on the determination of metronidazole and vitamin C in anionic nanofibrillated cellulose hydrogels [69]. G. Sarp and Yilmiz used Raman spectroscopy along with other advanced techniques for

characterization of multifunctional hybrid material g-C 3 N 4 @TiO 2 @Fe3O4 obtained by the degradation from trimethoprim and isoniazid [70].

Confocal Raman microscopy (CRM) is an alternative analytical tool to investigate API stability and quality control utilizing two-dimensional sample characterization. Recent applications of Raman mapping on pharmaceutical formulations include the composition of tablets and the connection between composition and dissolution rate [71-76]. S. Fateixa et al. utilized Raman imaging methods to characterize the main components of commercial acetaminophen (APAP) tablets and the hydrolytic degradation product, 4-aminophenol (4-AP). This research demonstrated that the degradation product 4-AP in APAP tablets could be detected as low as 0.05 % w|w using Raman images [71].
A satellite laboratory "toolkit" consisting of a handheld Raman spectrometer, portable direct analysis in real-time mass spectrometer (DART-MS), and portable Fourier transform infrared (FT-IR) spectrometer, was employed to examine 926 pharmaceutical products collected at an international mail facility for the presence of declared and undeclared APIs. In 68 days, the toolkit successfully identified over 650 APIs, using two or three devices. Comparative analysis conducted by a full-service analytical laboratory confirmed that 90.2% of the identified APIs, with no false positives, could be accurately detected by use of a minimum of two toolkit devices [77].

Conducting stability testing is rigorous, expensive, and time-consuming, thereby warranting consideration of alternative methodologies that may offer statistically accurate estimations. In 2003, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed a systematic approach to drug design and testing known as "Quality-by-design" (QbD), which uses predefined objectives, science, and risk-based management approaches to gain product and process understanding. Quantile regression, or mixed model tolerance interval methods with similar approaches, analyze the observed data from sampled batches and model a quantile of the distribution of true batch shelf lives. These and other statistical modeling techniques may prove to be useful tools for predicting drug shelf life [77-79].

Accelerated Predictive Stability (APS) is considered a useful tool for defining and predicting the drug development life cycle, kinetic degradation, packaging selection, API retesting, and products of degradation, as well as understanding formulations [80]. APS has gained popularity, mainly to set expiry for clinical materials, has been accepted by multiple regulatory agencies, and is currently being investigated for stability prediction of biological products and extrapolation of dissolution slowdown of solid dosage forms [56, 80-83]. APS approaches, such as the Accelerated Stability Assessment Program (ASAP) and Accelerated Stability Modeling (ASM), are emerging approaches for performing Risk-Based Predictive Stability (RBPS) assessments. ASAP uses a moisture modified Arrhenius approximation, employing degradation kinetics at a few stressed conditions during 1–2 weeks, and extrapolates to lower temperatures and humidity for longer timeframes [81, 82]. The advantages of this strategy are the shorter experimental timelines and the fewer resources required. The accuracy of this model assumes a first-order reaction, typical of hydrolysis-based degradation [56]. APS studies, carried out over a 3–

4-week period and combining extreme temperatures and relative humidity (RH) conditions (40–90 °C)/10–90% RH, have emerged as novel approaches to predict the long-term stability of pharmaceutical products in a more efficient and less time-consuming manner [83].

C. Merienne et al. estimated the shelf-life of two formulations of amoxicillin using a semi-predictive methodology. The characterization of amoxicillin-MCC mixture was assessed by attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR). The content profiles were determined by a stability indicating chromatographic method and fitted to pre-defined kinetic models performed by APS. A rationalization of formulation was elaborated by considering molecular structures, vibrational spectrometry analysis of amoxicillin dosage forms, the HPLC-UV quantification of amoxicillin degradation products, and the fit of experimental data to degradation models enabling to predict the shelf-life of amoxicillin dosage forms in a lean approach of storage conditions [84].

Furness et al. proposed Modeling Approaches to Reimagine Stability (MARS) to support establishment of tentative drug substance retest periods and/or shelf-life of the FFP. MARS refer to using stability data collected over a much shorter time span of 3–6 weeks at elevated temperature and humidity beyond conventional ICH Q1A (R2) stability protocols. Data mining of Investigational New Drug (IND), New Drug and Abbreviated New Drug Applications (NDA, ANDA) that used “Accelerated Stability Assessment” or other MARS tools (e.g., ASAP, ASM, APS, RBPS) yielded 172 results, from 2007–2021, including 121 IND, 39 NDA, and 12 ANDA. An underlying assumption of MARS is that there are no physical changes such as API melting or polymorph interconversions. The results illustrated that MARS data can provide an important bridge between the supportive stability data and the limited primary stability data to enable establishing a tentative retest/expiration dating period [85].

Pharmaceutical Packaging and Storage Considerations

Non-destructive pharmaceutical analysis and statistical modeling techniques could optimize exploration spaceflight medical care by enabling early detection of suboptimal therapeutics. Likewise, novel packaging, storage strategies, and dosage form innovations are promising countermeasures to enhance drug stability and shelf-life of exploration spaceflight medications [40-44]. P. Mandal et al.[86] reviewed recent pharmaceutical packaging strategies aimed at controlling humidity and oxygen levels. Presented strategies included desiccant film technology developed as active-blister packaging to protect oral solid dosage forms from hydrolytic degradation, incorporation of antioxidants, specialized coatings applied to the API, use of oxygen scavengers, and use of modified atmosphere packaging materials.

Jafarzadeh et al.[87] reviewed the utility of biopolymer films with synthesized nanomaterials. The reviewed research demonstrates the unique characteristics of nanomaterials, particularly their high surface area, making them ideal for higher process efficiency. This review also presents nanocomposite films as the next generation UV-blocking composite material that could be improve pharmaceutical packaging and

storage. Presented packaging enhancements included the development of a gellan gum-TiO2 nanotubes-based bio-nanocomposite film added to a gellan gum/xanthan gum nanocomposite by Rukmanikrishnan et al.[88] This combination provides increased thermal stability, tensile strength, and decreased the water vapor permeability of the nanocomposite films, ideal for food and pharmaceutical packaging [88]. The review also included a study by Patil et al.[89] who developed a highly flexible, transparent, and re-emissive composite film from polyvinyl alcohol (PVA) and tea waste-derived (WTR) Carbon quantum dots (CDs). They found that the higher the concentration of WTR-CDs in PVA films, the higher the ultraviolet (UV) blocking ability of the composite films (100% of UV-C, 100% of UV-B, 20–60% of UV-A region). These observations demonstrate that composite film could be the next generation UV-blocking composite materials for pharmaceutical storage. Razali et al.[90] developed gellan gum-TiO2 nanotubes-based bio-nanocomposite film with high TS, Young modulus, and antibacterial activity against Streptococcus, E. coli, Pseudomonas aeruginosa, and S.aureus. Similarly, zinc oxide NPs were added to the gellan gum/xanthan gum nanocomposite, increased the glass transition temperature, thermal stability, and TS and decreased the WVP of the nanocomposite films, which can be used in food and pharmaceutical packaging [88]. Incorporating kaolin into thermoplastic starch led to an around 130% and 50% increase in the TS and elastic modulus of the film, respectively. In addition, kaolin resulted in a significant decrease in moisture uptake in comparison with the pure starch matrix.
It has been reported that the mechanical and physical properties of conventional composites or pure polymer can be remarkably improved by the nanometer-size dispersion of polymer–clay nanocomposites [91]. There have been similar results reported by Tang et al.[92]

Since compacted lunar soil samples have shown shielding qualities against space radiation, Chakravarti et al.[93] proposed constructing a barrier from lunar soil as protective pharmaceutical storage on the Moon and to consider Martian soil for comparable storage on Mars. Several materials (e.g., polyethylene, boron, water, and tungsten) were also discussed for their abilities to effectively absorb primary radiation, thereby eliminating the generation of secondary radiation. Boron carbide composites were highlighted as lighter than traditional aluminum shields with better tensile qualities than high-density polyethylene.

Seoane-viano et al.[24] reviewed packaging materials that could help prevent radiation-induced degradation of drugs. Low atomic number and hydrogenous materials (e.g., polyethylene) were found to be more effective than high atomic number materials (e.g., aluminum), at reducing space radiation exposure. Two reviewed studies (Iguichi et al.[94] and Naito et al.[95]) proposed that novel hydrogen-rich materials with better radiation shielding capabilities could help protect drugs from space radiation on future space missions.

J. Vieregg et al.[96] studied the hybrid packaging material known as SioPlas™, consisting of an ultrathin multilayer ceramic coating applied to the interior of cyclic olefin polymer (COP) plastic container with a plasma-enhanced chemical vapor deposition. The novel coating process decreases oxygen permeation through the vial wall 33-fold, as

compared to uncoated COP containers. Two biologic drug products, exposed to gamma and electron beam sterilization and stored in SioPlas™ vials, revealed lower levels of oxidation as compared to matching control and irradiated products stored in glass vials.

According to Mehta and Bhayani [43], pharmaceutical shelf-life can be influenced by dosage form, excipients, and packaging material. Suggested strategies to stabilize pharmaceuticals in space included use of radiation attenuating container/closures and packaging materials constructed of polymeric materials with low atomic number (e.g., high density polyethylene), which can be further enhanced by incorporating boron or tungsten fillers.[97] The importance of FFP excipient selection was also highlighted with emphasis on radioprotective excipients (e.g., mannitol, nicotinamide, and pyridoxine) shown to prevent degradation during radiosterilization [100]. The use of novel dosage forms (e.g., micro/nanoformulations) has demonstrated radioprotection against ionizing radiation [98-99].

Ionizing radiation (IR) poses a growing threat to human health; thus ideal radioprotectors with high efficacy and low toxicity still receive widespread attention in radiation medicine. Despite significant progress made in conventional radioprotectants, high toxicity, and low bioavailability still discourage their application. Nano-radioprotectants are characterized by high efficacy, low toxicity, prolonged blood retention, and are equipped with enhanced bioavailability, improved stability, and increased solubility. Guo et al.[101] reviewed recent advances in nanocrystallization of traditional radioprotectants, which involves the polymerization (e.g., emulsification, high-pressure homogenization) of radioprotective agents into nanoparticles, improving solubility, efficacy, and bioavailability [102-103]. Currently nanotechnology-based preclinical studies are underway, as well as clinical trials evaluating nanotechnology-based delivery systems for the treatment of cutaneous melanoma[104].

Protection of moisture sensitive oral dosage forms is esential to product stability and quality. Drug hydrolytic degradation, caused by atmospheric moisture, significantly reduces the therapeutic effect of pharmaceutical solid dosage forms. Moisture barrier film coating is one of the most appropriate and effective approaches to protect the API from hydrolytic degradation during the drug manufacturing process and storage. Yang et al.[105] summarized recent advances in moisture barrier coatings and strategies to effectively decrease water vapor permeability and improve the moisture barrier function of film coating. Those strategies include newly designed coating formulations containing polymers with optimized functionality of moisture barrier and newly developed dry coating processes that eliminate the usage of organic solvent and water. Film-forming polymers include water-soluble, cationic, anionic, or neutral insoluble polymers from different chemical structures. Several new formulations comprising plant-based materials like zein and abietic acid have been designed and developed. Additionally, new and effective additives, such as suberin fatty acids (SFAs), have also been developed to improve the commonly used moisture barrier polymers such as hydroxypropyl methyl cellulose (HPMC).

Rolley et al.[106] spotlighted the development of an instrumented microfluidic pilot considered as a Galenic Lab-on-a-Chip to formulate nanomedicines. Benefits linked to the use of nanocarriers for delivery of drugs are a decreased degradation of active agents and a reduced toxicity. The concept of Quality by Design has attracted a growing interest in the development of new nanocarrier based dosage forms. This study demonstrates how additive manufacturing and microfabrication techniques can be used for the production of lipid nanocapsule nanomedicines.

Tablet coating is a process driven by technology, relying on advancements in coating techniques, equipment, coating materials, and quality assessment techniques. A. Salawi et al.[107] provided a review on film coating of solid dosage forms (e.g., tablets), with a focus on the polymers and processes used for tablet coating. Tablets susceptible to degradation through moisture or oxidation can be coated using a film-coating (FC) technique using biopolymers [108]. APIs, which are sensitive to light, can be protected by coating with opacifying agents. Zein, a natural polymer derived from plant origin, is more beneficial than synthetic polymers. Because it is resistant to water, heat, and abrasion[109], products prepared using zein have improved shelf life. Active Film Coating (AFC) is a process of coating tablets or granules containing APIs using a solution or suspension. AFC can improve product stability, prevent interactions between APIs, and enable fixed dose combinations[110-111]. FC is a critical but common process that enhances drug stability.

Highly hygroscopic pharmaceutical solid FPPs are prone to significant changes in their physicochemical properties due to chemical degradation and/or solid-state transition, resulting in adverse effects on their therapeutic performances and shelf life. L. Ng et al.[112] recommends four physiochemical stabilization strategies consisting of film coating (to form a thin film acting as moisture-barrier around the solid core containing the active ingredients);encapsulation (to envelop the active ingredients with polymers via spray-drying/freeze drying or complex coacervation), co-processing with excipients (to formulate the active ingredients with hydrophobic excipients to divert water away), and crystal engineering (to transform the crystalline form of the active ingredient to less-hygroscopic crystal forms). For hygroscopic pharmaceuticals, film coating and co-crystallization are the most common stabilization strategies. Film coating and encapsulation work by acting as barriers between the hygroscopic active ingredients in the core and the environment, whereas co-processing with excipients works mainly by adding excipients that deflect moisture away from the active ingredients. Most film-forming polymers for moisture-barriers are synthetic polymers, classified as water-soluble (e.g., polyvinyl alcohol, hydroxypropyl methyl cellulose), water-insoluble (e.g., ethyl cellulose), or entero-soluble polymers (e.g., shellac, Eudragit®). Plasticizers and pigments also play important roles in film coatings. Multiple cited examples from the literature demonstrate hygroscopic stabilization, including Zheng et al. who used hydrophilic poly(vinylpyrrolidone)'s (PVP) to coat citric acid-containing effervescent tablets to overcome high hygroscopicity [113].

Innovative galenic strategies are employed to overcome low solubility in pharmaceutical formulation design. A. Zarinwall et al.[114] successfully validated mesoporous silica

aerogels as an amorphization carrier matrix for the poorly water-soluble drug ibuprofen. Spatial confinement of APIs inside the pores of the silica aerogel matrix has the ability to substantially hinder the transformation into the crystalline state and hence tremendously improve the long-term stability of an amorphous drug.

Most sustainable polymer alternatives cannot compete with traditional plastics as gas and moisture barriers, thereby warranting the need for innovative chemistries and processing technology to enhance their barrier properties. B. Trinh et al.[115] compiled a comprehensive summary regarding improvements on gas and moisture barrier properties of sustainable polymer packaging. The summary highlights signature accomplishments on the effect of tuning the microstructure, surface energy, morphology, and self-assembly of polymers to gas and moisture barrier properties of films and coatings. Recent developments in multiphase and multicomponent system design and the impact of nanotechnology on sustainable packaging was emphasized. The three main categories of polymer films and coatings are enhanced barrier, active, and intelligent/smart packaging materials. Barrier packaging provides moisture, gas, protection during production, transportation, and storage. Active packaging provides functional attributes in addition to a barrier. The only biodegradable polymer that provides superior moisture and oxygen barrier properties is poly(glycolic acid) (PGA)[116]. The combination of multiple materials in the form of blends, multilayers, and nanocomposites are proven strategies to meet industrial barrier standards (e.g., beverage, food, cosmetics, pharmaceutical). To further enhance the moisture and oxygen barrier properties, the addition of micro and nanofillers into the barrier layers such as nanoclay, nanocellulose, graphene, and metal oxide may also be employed [117, 118]. With the current interest in nanotechnology, nanocomposite materials have attracted substantial research interest for packaging films and coatings. Different modelling approaches have proven that barrier properties have significantly improved with high aspect ratio nanoparticles in polymer matrices[119]. Natural hydrophobic biopolymers, and proteins (e.g., zein, keratin), are used to improve the water vapor permeability of packaging films due to their hydrophobic structures[120, 121]. Zein, extracted from corn, is known to be insoluble in water and contain a large amount of hydrophobic amino acid domains[122, 123]. Fabra et al.[124] developed a multilayer structure which includes interlayers of zein nanofibers on PHBV films to enhance the water vapor barrier of the resulting films. Similarly, keratin, found in mammal hairs and bird feathers, is hydrophobic and insoluble in water[125, 126]. Thus, keratin has been incorporated with other biopolymers to improve water vapor barrier properties of multicomponent systems[127].

Bioregenerative life support systems may be a way to close this risk gap by leveraging in situ resource utilization (ISRU) to perform pharmaceutical synthesis and purification. M. McNulty et al.[128] used the equivalent system mass (ESM) metric to evaluate pharmaceutical purification processing strategies for longer-duration space exploration missions. Monoclonal antibodies, representing a diverse therapeutic platform capable of treating multiple space-relevant disease states, were selected as the target products for this analysis. Six technologies (three biotic and three abiotic capture methods) were compared and scheduled to minimize ESM for each technology. Scenario analyses

were performed to consider a range of input stream compositions and pharmaceutical demand, followed by a comparison of the base case ESM scenarios of alternative mission configuration, equipment models, and technology reusability. Six Protein A-based capture step procedures were analyzed: three commercially available abiotic technologies (pre-packed chromatography (CHM), spin column (SPN), and magnetic bead (MAG)) and three development-stage biotic technologies (plant virus-based nanoparticle (VIN), elastin-like polypeptide (ELP), and oilbody-oleosin (OLE)). McNulty et al. also compared chemical and biological pharmaceutical production for human life support in space. Chemical pharmaceutical synthesis requires reaction-specific inputs, complex synthesis steps, the use of organic solvents, and generates substantial waste. Recent advances in biotechnology offers promise for biological pharmaceutical production as a means to address low occurrence, high impact health hazards (e.g., sepsis, ear infection, glaucoma)[129].

Conclusion:

The risk of ineffective or toxic medications during long-duration exploration spaceflight is elevated for a Mars planetary mission. The challenge remains to assemble a comprehensive and robust formulary to address anticipated medical needs, that can remain stable, safe, and effective for the duration of an exploration mission, and—when accompanied by pharmaceutical stability assessment techniques—to verify purity and efficacy in a non-destructive, remote environment. Storage and packaging solutions are also warranted to optimize shelf life, purity, and quality. This literature review provides a compilation of research efforts currently underway offering innovative risk mitigation strategies and countermeasures aimed at providing safe and efficacious pharmaceutical care for exploration spaceflight.

Dedication:

This article is dedicated to the memory of NASA scientist Dr. Lakshmi Putcha who blazed a trail of research and innovation and whose contributions continue to inspire Pharmaceutical Scientists to reach for the stars.

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