Biopharmaceutical challenges of therapeutics in space: formulation and packaging considerations

“Alternatives to standard oral formulations that include sustained and targeted delivery technologies for preventive healthcare in space will be a welcome addition to the space formulary...”

Keywords: drug delivery ■ radiation ■ shelf life ■ space flight ■ technology development

During the past five decades of human space-flight, potential ailments and astronaut health problems often brought about by physiological changes during missions have been identified and treated. The Gemini flight experiences indicated that, although humans could tolerate exposure to the space environment well, decreases in bone mineral density, plasma volume and erythrocyte mass occurred. An additional concern was the possibility of occurrence of an infectious disease that could adversely affect mission success [1]. As such, the number of medications onboard space missions increased through the Apollo, Skylab and Space Shuttle missions as further potential clinical conditions, such as cardiac arrhythmias [2] and immune deficits [3], became apparent. These advances were paralleled by a comparable increase in complexity of the medical kits developed. The Shuttle Orbiter Medical System and its component kits for the Space Shuttle program came into existence in the late 1970s. Current operational medical kits aboard the International Space Station include many of the Shuttle Orbiter Medical System components, with an array of medications intended for the treatment of minor ambulatory care symptoms, first aid and basic life support [4]. This editorial summarizes the challenges associated with ensuring adequate pharmaceutical stability and efficacy in space and delineates technology development requirements for optimizing pharmaceutical delivery with extended shelf life in adverse and remote environments.

Contributing factors

■ Physical factors

All medications contained in the flight kits are commercially available off-the-shelf formulations used for treatment of illnesses on Earth. However,

transport and storage of supplies, including medications for space missions, must comply with certain engineering and safety requirements to prevent outgassing and damage to equipment, while allowing easy access for crew members.

For this reason, most medications are repackaged into Ziploc® bags and plastic amber vials that are stored in fabric containers with Velcro® closure. Discrete product information labeling is therefore critical, since the manufacturer's label is absent from the kit contents. Operational medical kits for each mission are packed 1–2 months prior to launch; therefore, assuring a sufficient shelf-life period for medications is extremely important.

Furthermore, unique physical and environmental factors of space missions, such as ambient radiation, excessive vibration, multigravity and a CO₂-rich environment combined with humidity and temperature variations may be contributing factors to the stability of pharmaceuticals in space. Attention has only recently been turned to the effect of the unique environment of low-Earth orbit (LEO) on the stability of medications intended for use during space missions and early indications are that pharmaceutical product degradation may limit the value of some medications that are currently packed in on-board pharmaceutical kits [5].

It is noteworthy that in contrast with contributing environmental factors of stability on the ground, results from passive radiation dosimetry demonstrate that the cumulative radiation dose, although at a low level, is much higher in space than on Earth; this radiation enrichment in space is composed of ionizing radiation of protons and heavy ions [6]. The concept of radiation-induced chemical degradation has been suggested in numerous studies in the literature,

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but little systematic research has been done in this area. Although γ radiation is known to be used to sterilize pharmaceuticals in commercial environments, space radiation consists of mixed fluences of high- and low-intensity radiation with a lower dose rate and longer duration of accumulation, in contrast with exposure for pharmaceutical sterilization that lasts for a very short period of time such as a few minutes. Studies of radiation effects on pharmaceuticals on Earth are not aimed to understand or estimate the effect of fragmentation ions on stability; thus, the extent of damage caused by different daughter ions to each class of medications is unknown. With respect to medications, in addition to the concern about radiation effects that can induce significant changes in the levels of the active pharmaceutical ingredient or potency of the medication, it is important to determine the structure and biological activity of degradation products and establish toxicity limits of active degradants in a formulation. This may pose a greater risk of toxicity than efficacy with respect to the therapeutic index of a formulation degraded in space.

■ Physiological factors

Clinical conditions recorded during space shuttle flights include sensory-motor disturbances manifesting mostly as space motion sickness; this was the most common ailment, occurring in close to 40% of shuttle crew members, followed by digestive system disturbances (9%) and infections, which most commonly involved the respiratory or urinary tracts. During the first 33 US space shuttle missions, some medication was taken during flight by 94% of the crew with more than 500 individual doses of 31 different medications taken predominantly by the oral route [7]. Of the doses taken by astronauts during flight, 47% were for space motion sickness, 45% for sleep disturbances and smaller percentages for headache, backache and sinus congestion [8]. While most instances of pharmaceutical use by these astronauts indicated that the medications were well tolerated and presumed effective, approximately 8% of all treatments during flight were reported as 'nonefficacious' [8]. In addition, it is highly likely that changes in human physiology [9] and the composition of the microbial flora of human mucosal surfaces, known to be influenced by extreme environments including microgravity [10,11], will affect therapeutic efficiency by influencing absorption, distribution, metabolism and elimination of medications in space.

■ Microbiological factors

Microbial infections pose a moderate risk during and after LEO missions, but this risk is likely to increase significantly on exploration space missions. Microbes from the commensal flora of the crew will inevitably colonize the spacecraft; microbial contamination from onboard cultivation of plants as a source of food or a component of a bioregenerative life-support system will also contribute to the complexity of the microbial population within the closed environment of the spacecraft [12]. Flight-induced changes in the commensal bacterial flora of the crew, the increased likelihood of lacerations and open fractures requiring prophylactic administration of antibiotics and the negative impact of space travel on immune function will provide opportunities for microbes to establish foci of infection [13]. It is therefore very likely that long-duration space missions will result in a significant increase in usage of anti-infective agents in comparison to LEO missions.

Considerations for research & technology development

■ Radioprotection, infection & immunity

The colonization of the lunar surface, 3-year missions to Mars, and potential missions to Phobos and near-Earth objects such as asteroid 1999 AO10, will expose crew members to risks that differ both quantitatively and qualitatively from those encountered during LEO missions [13] and will impose an unknown safety risk to crew health. Few drug options are available for radiation protection. Amifostine is currently approved for use as supportive treatment in radiation therapy, improving side effects and prognosis of radiotherapy. It scavenges free radicals, may inhibit apoptosis and is considered a broad-spectrum radioprotective [14]. Two developmental drugs are currently in clinical trials as radioprotectants, Ex-Rad®, 4-carboxystyryl-4-chlorobenzylsulfone sodium, developed in part by the US Armed Forces Radiobiology Research Institute [15] and the compound, CBLB502, a flagellin derived from *Salmonella enterica* [16].

Treatment of on-board bacterial infections could be compromised by reversible or irreversible increases in antibiotic resistance and the emergence of multidrug-resistant opportunistic pathogens, a currently unquantifiable risk, suggesting that a wide range of anti-infectives should be made available on board for treatment on exploration missions. Alternative paradigms for the treatment of infections that do not rely

on the killing of the pathogen, with its attendant risk of emergence of drug-resistant variants, but modify them to produce a 'less fit' phenotype with reduced capacity to survive at the site of infection could also be advantageously applied. There are conceptual reasons to suppose that this approach will result in less selective pressure on the bacteria and delay the emergence of resistant genotypes [17]. Drug candidates that reverse resistance mechanisms or reduce bacterial virulence are being actively investigated and these include a number of naturally occurring plant secondary metabolites that could be cultured and purified for treatment of infections [18,19]. Similarly, host-directed therapies, whereby natural mechanisms in the host are exploited to enhance therapeutic benefit, could be used alongside conventional or unconventional anti-infective therapies, to initiate or enhance protective antimicrobial immunity whilst limiting inflammation-induced tissue injury. Such therapies would rely on the multimodal innate and adaptive immune systems and are unlikely to engender resistance themselves. Therapeutically, these strategies would support existing antimicrobial agents to aid resolution of local and systemic inflammatory processes. Again, natural products with immune-enhancing potential could be produced and exploited for treatment of infections in space and such supplements should not engender insuperable drug formulation challenges [20].

■ Shelf life & packaging

At present, medication lots contained in the International Space Station operational formulary that are within 6 months of labeled expiration date are replaced as needed in compliance with the US FDA guidelines. However, this will not be possible for exploration missions planned for the future, which warrants the need for research and development of space-hardy formulations, as well as packaging and dispensing technologies.

Packaging plays an important role in the shelf life of drugs. Drugs marketed in the USA are generally required to maintain 90–115% of the label claim (of dose), while in unopened containers, until the expiration date printed on the container. Solid formulations, such as tablets and capsules, are typically removed from manufacturer's packaging and dispensed to patients in secure closure containers, thus invalidating the expiration date by exposure to environmental factors such as heat, light and

humidity that can accelerate degradation. For space missions, such as to Mars, travel times and repacked medication storage times will likely be longer than manufacturers' expiration dates and radiation exposure in missions beyond the LEO will most likely be higher; therefore, radiation-attenuating properties of packaging and storage materials becomes important. Daughter ions are formed when radiation passes through metals, actually increasing radiodosimetry [21]; thus, radiation shielding of drugs may require use of non-metals and new polymer technologies. On large scales, inert gases have been considered for the protection of spacecraft, but on the small scale, their use in custom manufacturing directly by the pharmaceutical industry may potentially enhance the shelf life of drugs, if not through shielding then by reducing oxidation. Concepts of radiation attenuation by applying portable shielding using lightweight materials, such as high-density varieties of polyethylene (water-, tungsten- and boron-impregnated), may be applicable in the design of medical kits and drug dispensers for long-duration missions [22]. New materials with multiple interfacial layers providing both deflection and attenuation characteristics, such as hydrated organic capillary-porous matrices may also be of interest as shielding materials.

■ Innovative drug-delivery technologies

Alternatives to standard oral formulations that include sustained and targeted delivery technologies for preventive healthcare in space will be a welcome addition to the space formulary and may include controlled-release topical, subcutaneous, intranasal and inhalation dosage forms. Currently, there is less demand for the development of innovative sustained drug-delivery technologies for preventive healthcare on Earth, other than for chronic conditions such as asthma and diabetes. Leveraging operational needs of NASA for space exploration by collaboration with the commercial space industry, the Department of Defense and pharmaceutical vendors can facilitate cost-effective development of novel pharmaceuticals that will enhance chronic clinical care capabilities. An example of such a technology development endeavor can be nanotechnology-based multistage drug-cocktail and vaccine-delivery systems. Nanostructures also have the ability to protect drugs encapsulated within them from physiologic degradation, target their delivery with sustained release and are suitable for per oral routes of administration [23].

The use of nanostructures such as polymeric nanoparticles offers a non-invasive approach for penetrating the blood–brain barrier for management of neurodegenerative disorders, and cerebrovascular and inflammatory diseases [24]. Finally, nanotechnology offers great potential for the development of safe and efficacious drug-delivery systems for preventive health care in space and on Earth.

Conclusion

In conclusion, the technology development challenges for optimizing therapeutics in space must include the development of pharmaceuticals with extended stability, optimal efficacy and bioavailability with minimal toxicity and side effects. Innovative technology development goals may include sustained/chronic delivery preventive health care products and vaccines,

low-cost high-efficiency non-invasive, non-oral dosage forms with radioprotective formulation matrices and dispensing technologies, coupled with self reliant tracking technologies for quality assurance and quality control assessment. These revolutionary advances in pharmaceutical technology will assure human exploration of space and healthy living on Earth.

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