Pharmaceuticals Exposed to the Space Environment: Problems and Prospects

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Pharmaceuticals Exposed to the Space Environment: Problems and Prospects

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Abstract

The NASA Human Research Program (HRP) Health Countermeasures Element maintains ongoing efforts to inform detailed risks, gaps, and further questions associated with the use of pharmaceuticals in space. Most recently, the Pharmacology Risk Report, released in 2010, illustrates the problems associated with maintaining pharmaceutical efficacy. Since the report, one key publication includes evaluation of pharmaceutical products stored on the International Space Station (ISS). This study shows that selected pharmaceuticals on ISS have a shorter shelf-life in space than corresponding terrestrial controls. The HRP Human Research Roadmap for planetary exploration identifies the risk of ineffective or toxic medications due to long-term storage during missions to Mars. The roadmap also identifies the need to understand and predict how pharmaceuticals will behave when exposed to radiation for long durations. Terrestrial studies of returned samples offer a start for predictive modeling. This paper shows that pharmaceuticals returned to Earth for post-flight analyses are amenable to a Weibull distribution analysis in order to support probabilistic risk assessment modeling. The paper also considers the prospect of passive payloads of key pharmaceuticals on sample return missions outside of Earth's magnetic field to gather additional statistics. Ongoing work in radiation chemistry suggests possible mitigation strategies where future work could be done at cryogenic temperatures to explore methods for preserving the strength of pharmaceuticals in the space radiation environment, perhaps one day leading to an architecture where pharmaceuticals are cached on the Martian surface and preserved cryogenically.

Introduction

Human space missions require pharmaceuticals to address crew health issues. Pharmaceuticals stored on the International Space Station (ISS) exhibit a shorter shelf-life in space than corresponding terrestrial controls; and radiation is thought to be as a possible cause (Ref. 1). The Pharmacology Risk Report by the Human Research Program (HRP) Human Health Countermeasures Element discusses the concern over pharmaceutical durability in terms of risks and gaps (Ref. 2). Given the report findings, the risk involves a "risk of therapeutic failure due to ineffectiveness of medication" caused by exposure to deep space radiation. The knowledge gap encompassing the risk states: "What is the effect of long-term spaceflight on drug stability and what measures can be employed to extend the duration of drug efficacy?" The HRP Requirements Document identifies the Human Spaceflight Risk of "Medications Long-Term Storage" for deep space journey/habitation as a high consequence that requires mitigation (Ref. 3). The HRP Human Research Roadmap for planetary exploration includes a "Risk of Ineffective or Toxic Medications Due to Long-Term Storage (Ref. 4)."

This paper discusses the problems and prospects for pharmaceuticals exposed to the deep space environment. The first part of the paper discusses the active ingredient strength observed in the pharmaceutical inventory contained in the terrestrially administered Shelf Life Extension Program (SLEP) conducted by the Food and Drug Administration (Ref. 5). The US Pharmacopia specifies that the active ingredient must retain at least 90 percent of its labeled potency or strength, defined as the active ingredient

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[*]Retired.

concentration. Chromatography, spectroscopy, and various other analytical techniques were used to assay the active ingredients in the SLEP study. The study considered other failure modes including appearance, pH, impurities, and in some cases mechanical failure of the delivery system. The SLEP study prompts a discussion suggesting that some pharmaceuticals may be sufficiently robust for long-term space flight while others may suffer from the loss of active ingredients, the generation of toxic substances, or an alteration in excipient characteristics. The next part of the paper summarizes research done on pharmaceuticals flown on ISS and returned to Earth for post-flight analyses. Not surprisingly, given the premium of return mass and volume, there exists only a few cases where specimens with space exposures have been returned to Earth to gather post-flight data. Wotring reports a retrospective study of pharmaceuticals use by astronauts, where in most cases efficacy was thought to be "somewhat to very effective (Ref. 6)." Du, et al., describe the physical and chemical changes of 35 different pharmaceuticals flown in kits on ISS over an 880 day test period (Ref. 1). Four analogous kits remained on the ground as controls. The Wotring and Du studies prompt a discussion suggesting that some pharmaceuticals may be robust during long-term spaceflight while others may not. These evidence-based studies are derived from space flight exposures in the low Earth orbit environment. Extrapolating their findings to long-term space flights outside of Earth's magnetic field is considered both a problem and a prospect. In addition, a discussion of the Du data provided in the context of Weibull statistics illustrates their usefulness in probabilistic risk assessment modeling. The third part of this paper discusses recent work in radiation chemistry.

Terrestrial and Orbital Studies of Pharmaceutical Durability

One objective of the system integration process is to estimate mission risk by estimating the risks of constituent parts, and summing the risks to obtain an overall mission risk. One of the risks of greatest concern is that of astronaut health—specifically ill health brought on by insomnia, pain, headaches, gastro-intestinal discomfort, and infection. Pharmaceuticals are available on ISS to treat such conditions. A similar inventory of pharmaceuticals is expected to be included for missions to Mars. Several studies address the durability of pharmaceuticals. Reviewing these studies provides a means to understand the problems and prospects of pharmaceutical durability in long duration deep space missions.

The Terrestrial SLEP Study

The Food and Drug Administration conducted a terrestrial study to evaluate pharmaceuticals that were stored beyond their original expiration date based on a comprehensive testing program (Ref. 5). The study summarized the long-term stability of 122 drug products stored in their original containers and evaluated beyond their labeled expiration date. Interpretation of the data was accomplished by arranging the pharmaceuticals into five groups based on their dosage form. In general the findings showed that solid oral products exhibited the greatest longevity, whereas liquids exhibited the least longevity—suffering from numerous failure mechanisms. Creams and ointments exhibited mixed longevity results.

Tests were performed on the pharmaceuticals based on their attributes. Potency was evaluated for all products by conducting active ingredient assays. Regression analyses of real-time assay data determined if shelf life extensions were granted or if no shelf life extensions were granted. A termination failure occurred when a pharmaceutical already granted an extension could not be granted any further extensions. An assay value dropping below 90 percent of the stated active ingredient was sufficient to trigger a termination failure. The solid oral products, reconstituted dry powders, creams and ointments, injectable solutions, and autoinjectors were also subjected to other tests. Other attributes triggering a termination failure included the attributes summarized in Table 1. Notice that a unique category was developed for liquids dispensed by injector—mechanical failure of the injecting mechanism.

In short, 88 percent of the pharmaceutical lots in the SLEP study were extended beyond their original expiration date. The SLEP study supports the rather general conclusion that many pharmaceuticals can be extended beyond their expiration date. It further reveals the conclusion that pharmaceutical stability is dependent on manufacturer and can even vary from one manufacturing lot to another.

TABLE 1.—SLEP TESTING, BASED ON PHARMACEUTICAL ATTRIBUTES.

	Assay	Impurities	Water Content	Dissolution	Physical Appearance	pH	Preservatives	Degradants	Mechanical Failure
Solid Oral Products	x	x	x	x	x				
Reconstituted Dry Powders	x		x		x	x			
Creams & Ointments	x				x	x			
Injectable Solutions	x	x			x	x	x		
Autoinjectors	x				x	x	x	x	x

It is difficult to extrapolate the results of the SLEP study to a deep space mission. The environmental conditions of temperature and humidity during a deep space mission could be controlled and therefore could be comparable to storage conditions on Earth. However, a deep space mission occurs primarily outside of Earth's magnetic field, an environmental condition not encountered in storage conditions on Earth. High CO_2 concentrations in the spacecraft pose a unique environmental condition where enhanced diffusion of CO_2 through packaging walls may be detrimental to select pharmaceuticals.

Although the SLEP study does not specifically identify those pharmaceuticals that will survive the duration of a Mars mission while traversing the deep space environment, one could use the SLEP study as guide, where long-term storage on a deep space mission might be possible for those pharmaceuticals in the SLEP study that exhibit multiple shelf-life extensions. Mars missions requiring many years become problematic and may need to rely on new pharmaceutical formulations or resupply. Ideally, future work ought to include collecting durability data on specific pharmaceuticals intended for use during a Mars mission in a simulated or relevant environment.

Samples and Data Returned From Orbiting Spacecraft

Wotring conducted a retrospective study on medication use during spaceflights greater than 30 days, evaluating trends in usage (Ref. 6). Results were compared to shorter space shuttle mission records. The most frequently used item was sleep aids—zolpidem, zaleplon, or melatonin—used to address sleep difficulties brought about by the absence of circadian rhythm cues and occasional slam shifts to support mission activities. Back pain, muscle pain, and occasional headaches were most often treated with ibuprofen or acetaminophen. Promethazine was the preferred medication to address space adaptation syndrome. Efficacy was thought to be "somewhat to very effective" for all of these treatments. Two reports for rash treatments, thought to utilize an ointment—though not specifically identified as such— were deemed "ineffective."

Du, et al., have conducted an investigation into 33 pharmaceutical products, 22 solids, 7 semisolid, and 4 liquid formulations, packaged in payload medication kits that were flown to, and returned from, ISS via the space shuttle (Ref. 1). Ground controls stored in an environmental chamber were available for comparison. Four payloads were returned after an on-orbit duration ranging from 13 to 880 days. Cumulative radiation dose during the 880 days was observed to be linear over time. Du, et al. found that "the number of formulations that did not meet content requirement of Active Pharmaceutical Ingredient (API) was higher in flight kits compared to the corresponding control kits from all four payloads" and the "difference in the number of unstable formulations between flight and control increased with the length of storage time in space."

The pharmaceutical testing from Payload 1 revealed that no ground control samples exhibited physical changes and none failed the chemical potency test. Of the Payload 1 inflight pharmaceuticals, two semisolids were found to have physical changes, both discolorations, and another one failed the chemical potency test. In Payload 2, no ground control pharmaceuticals showed any physical changes and two pharmaceuticals failed the chemical potency test. Of the Payload 2 inflight pharmaceuticals, seven had signs of physical changes—six discolorations and one with some other physical change—and eleven failed the chemical potency requirement. Ground control pharmaceuticals from Payload 3 showed no physical changes, but the number of pharmaceuticals failing the chemical potency test increased to eight. Inflight pharmaceuticals from Payload 3 showed six with physical changes and 17 that failed the chemical potency test. In Payload 4, two control pharmaceuticals exhibited discoloration and liquefaction and 16 control pharmaceuticals failed the chemical potency requirement. In Payload 4, six inflight pharmaceuticals showed signs of physical changes and 24 failed the chemical potency requirement. The ground control and inflight trends suggested ongoing physical changes with time. Decreasing chemical potency is observed in both ground control and inflight specimens, and the decrease in potency is more prevalent for the inflight specimens.

One of the most degraded in both ground control and inflight specimens was clavulanate, suggesting it is "inherently unstable." Degradation of amoxicillin was also observed, though the flight specimens dropped below 90 percent active pharmaceutical ingredient in the vicinity of 500 days consistent with the expiration date. Promethazine also exhibited degradation during space flight faster than in the ground control, with the injection version "reaching less than acceptable potency before the expiration date." Atorvastatin and cefadroxil degraded more than two times faster in flight than on the ground. Trimethoprim and sulfamethoxazole exhibited similar behavior for flight and ground control. Du tempers these 880 day observations by indicating (with the exception of clavulanate) that "while degradation was faster in space than on the ground for most of the APIs, loss of API content was <20 percent of label claim except for levothyroxine and trimethoprim which were 28 and 21 percent, respectively." In the context of a Mars mission, it should be noted that the pharmaceuticals from the Du study were stored on ISS, an environment within the Earth's magnetic field. On a deep space mission, outside of the Earth's magnetic field, degradation is likely to be more rapid varying with the stage of the solar cycle. Du also found "consistent with the general consensus on the ground that stability issues are less frequent with solid than liquid or semiliquid formulations."

Given the comparatively short duration of 880 days embedded within the eleven year solar cycle, one could approximate the radiation dose on ISS during the Du study as constant with time. The degradation in space-based pharmaceuticals above that observed in ground controls, at the molecular level, could then be considered as the random breaking of bonds in the active pharmaceutical ingredient by, for example, high energy protons. In the context of a Weibull distribution describing the so-called bathtub curve, the random degradation would represent the bottom of the bathtub curve where failure rate is neither decreasing (wearing in) nor increasing (wearing out), but staying the same, i.e., a shape factor of m = 1 (Ref. 7). Of course, a more rigorous interpretation over the duration of the solar cycle could include the variation in high energy proton arrival and the corresponding variation in the breaking of molecular bonds.

Picking clavulanate from the Du study, one can re-plot the flight degradation data in the context of a Weibull distribution to identify the time scale, Θ, and failure rate, λ. The summary is shown below in Figure 1.

Clavulanate was selected here because it represents a worst case scenario based on the pharmaceuticals examined by Du. The failure rate is estimated to be 0.0026 per day. Another pharmaceutical from the Du study, ciprofloxacin is presented in Figure 2 utilizing a similar analysis. As can be seen, the time scale is necessarily longer and the failure rate is necessarily smaller because of the greater stability exhibited by the ciprofloxacin. It should be noted that the data are being extrapolated significantly in time, though the line passing through the four points at the far left appears to be a good fit to the eye. The failure rate for Ciprofloxacin is more than an order of magnitude less, at 0.00018 per day.
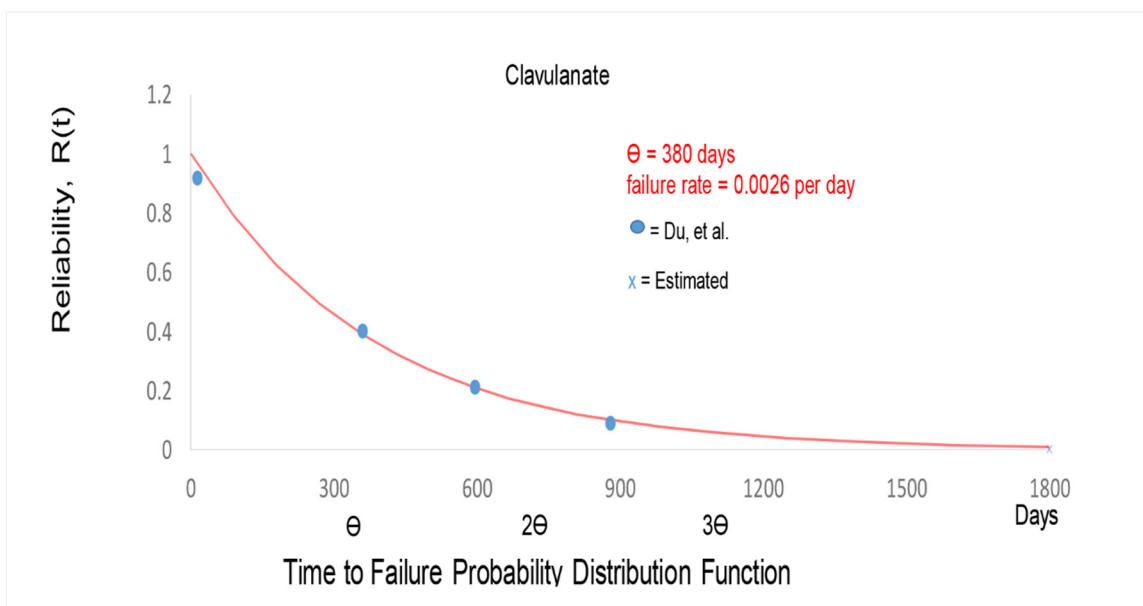
Figure 1.—Probability distribution function and time to failure for clavulanate, based on the work of Du, et al. (Ref. 1).
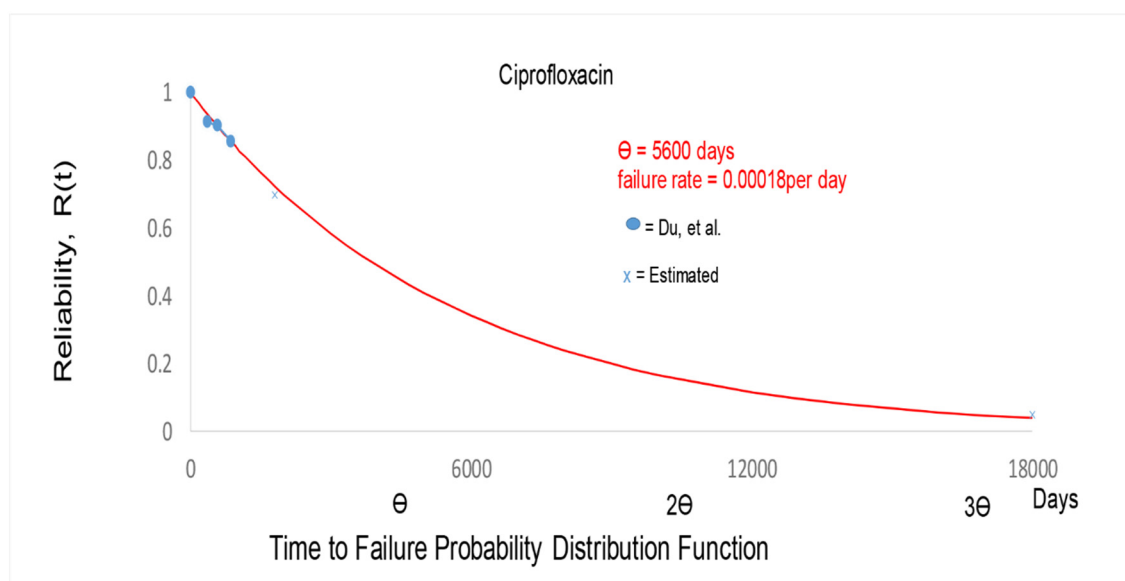

Figure 2.—Probability distribution function and time to failure for ciprofloxacin, based on the work of Du, et al. (Ref. 1).

Follow-on experiments to the Du study need to be contemplated. One prospect to consider is to use an experimental design conducive to interpretation via Weibull statistics for the purpose of utilizing the failure rate results in predictive tools such as probabilistic risk assessment. Multiple long duration exposures in a deep space environment and multiple examples of each type of specimen would improve the failure rate statistics. Passive payloads of selected pharmaceutical specimens as part of sample return missions going beyond Earth's magnetic field, such as returns from Mars or asteroids, could yield deep space exposures for pharmaceuticals of interest, and offer the prospect of identifying failure rate statistics based on multiple mission and multiple specimen post-flight analyses.

Radiation

One rudimentary path to consider is shielding pharmaceuticals from the radiation environment via robust storage. Rather than storing pharmaceuticals in a medical kit, it may be possible to shield the pharmaceuticals from high energy protons by protecting the supply of pharmaceuticals via ample use of aluminum shielding, where the storage unit for the pharmaceuticals is a purposely thick vault with suitable temperature and humidity controls inside. This path is problematic when trying to minimize overall mass, volume, and power.

Another path being considered—with respect to human missions to Mars —is the use of multi-purpose shield solutions. Simonsen reports for a human mission to Mars that "The Most Challenging Medical Standard To Meet For A Mars Mission Is That Associated With The Risk Of Radiation-induced Cancer (Ref. 8)." Radiation risk mitigation strategies currently under consideration include investing in innovative multi-purpose shield solutions—such as water filled composite shield sections and reconfigurable personal shielding—as well as biological countermeasures—using pharmaceuticals for repairing damaged DNA. Packaging of logistics around the habitat reduces radiation exposure and radiobiology countermeasures enable a living system to effect repairs. By analogy, pharmaceuticals stored in the habitat along with the astronauts would benefit from reduced radiation exposure. However, pharmaceuticals are inanimate by definition and cannot be repaired. The subject of pharmaceutical durability in a reduced space radiation environment during a Mars mission, en route and on the surface, remains of interest.

Biological Samples at Cryogenic Temperatures, a Possible Mitigation Strategy

This section introduces a possible way to mitigate radiation damage in pharmaceuticals carried on long duration missions. Considerable work has been done in the study of radiation chemistry since the 1960s, and much of the work in ionizing radiation damage has emphasizes the cleavage of hydrogen bonds and the formation of free radicals. Energetic protons and the high-Z nuclei characteristic of space radiation impart damage via a Linear Energy Transfer mechanism. In general, the energy of ionizing radiation encountered in deep space is thought to be approximately 5 times more severe than in low Earth orbit (Ref. 9).

One prospect is considered here for the purposes of discussion and future work. The literature suggests that biological specimens cooled to around 100 K can tolerate a significantly higher dose of radiation as delivered by an intense x-ray source during the process of x-ray crystallography of biological specimens. Cooling the specimen further results in a further reduction in radiation damage. Utilizing cubic insulin crystals as a model compound, Meents, et al., have shown that at 50 K, radiation damage to disulfide bridge structures is reduced by a factor of 4 compared to analogous observations at 100 K (Ref. 10). Extrapolating, one possible mitigation strategy to consider for future work is to purposely store pharmaceuticals at cryogenic temperatures for the purpose of increasing radiation durability. One could envision a cache of pharmaceuticals purposely delivered and stored cryogenically on the Martian surface prior to astronaut departure from Earth, and upon arrival, the pharmaceuticals could be reconstituted or warmed to room temperature for use, as needed.

The initial steps of such a future research effort could start by utilizing a model pharmaceutical compound rather than insulin. A beam line could facilitate exposures of the model compound to energetic protons, with an engineering emphasis placed on cooling the specimens while being illuminated. Post-exposure analyses would reveal the extent that the active ingredient was maintained as a function of temperature.

Conclusions

The Pharmacology Risk Report by the Human Research Program discussed the problem of pharmaceutical durability in terms of risks and gaps. There exists a risk of therapeutic failure due to ineffectiveness of medication caused by exposure to deep space radiation and there exists a gap in understanding what the effect long-term spaceflight will have on drug stability. A study conducted by the Food and Drug Administration to evaluate pharmaceuticals stored beyond their original expiration date identified shelf life extensions for 88 percent of the pharmaceutical lots studied, based on assay and other observations. In general, solids received more extensions than gels or liquids. The Du study conducted on samples returned from ISS after in-space exposures of 13 to 880 days revealed that the number of formulations not meeting active pharmaceutical ingredient content requirements was higher for inflight samples compared to ground controls. Data from two products were re-plotted based on a Weibull distribution to identify their failure rates, opening the prospect of incorporating such data into probabilistic risk assessment models. Passive payloads of key pharmaceuticals as part of sample return missions conducted outside the Earth's magnetic field offer the prospect of gathering long duration active pharmaceutical ingredient data in a relevant environment that could be used for failure rate calculations and modeling activities. Recent studies on innovative multi-purpose shield solutions, such as water filled composite shield sections, offer the prospect of reducing radiation exposure in a deep space habitat. One prospect for a mitigation strategy arises from observations made on insulin crystals, where cooling the specimen to 50 K reduces damage to disulfide bridge structures by a factor of 4 compared to analogous observations at 100 K. Initial steps toward future research include exposing selected pharmaceuticals to high energy protons, with an engineering emphasis on cooling the specimens. Perhaps one day, pharmaceuticals may be cached on the Martian surface and preserved cryogenically prior to astronaut departure from Earth.

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