Analysis of the Effect of Spaceflight on Drug Potency to Quantify the Risk of Medication Failure for Exploration Space Missions

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Abstract

Pharmaceuticals selected for exploration space missions must remain stable and effective throughout mission timeframes. Although there have been six spaceflight drug stability studies, there has not been an analysis of these data. We sought to quantify the rate of spaceflight drug degradation and the time-dependent probability of drug failure resulting from loss of active pharmaceutical ingredient (API). Additionally, a review of previous spaceflight drug stability studies was performed to identify strategic research gaps that should be addressed prior to exploration missions. Data were extracted from these six spaceflight studies and analyzed to quantify API loss for 36 drug products with long-duration exposure to the spaceflight environment. Medications stored for up to 2.4 years in low Earth orbit (LEO) exhibit a loss of potency that, for most drugs, is within 5% of terrestrial lot-matched controls. Models estimate that spaceflight is associated with a ~1.5-fold increase in degradation rate and a corresponding increase in the probability of failure. However, this extra risk of drug failure is a fraction of the baseline failure risk observed for matched controls. All existing studies of spaceflight drug stability have focused primarily on repackaged solid oral medications. It is established that non-protective repackaging exposes medications to atmospheric factors that facilitates loss of potency. Our analysis suggests that although spaceflight exposure is associated with a loss of drug potency, the effect is a fraction of the terrestrial baseline. We conclude that a primary factor contributing to API loss may be nonprotective drug repackaging. This analysis highlights a critical need to evaluate the effect of current drug repackaging practices on API degradation, and if necessary develop and *validate* operationally appropriate protective drug repackaging for use on exploration missions.

Introduction

As the National Aeronautics and Space Administration (NASA) and its international partners seek to develop capabilities to conduct exploration space missions away from Earth's orbit, it is anticipated that roundtrip planetary missions to Mars will exceed two years in duration.[1] Unlike regular resupply to the International Space Station (ISS), planetary missions will be too distant for resupply and therefore need to be self-sufficient. Long-duration exploration missions will expose astronauts to new and increased hazards and, therefore, an anticipated higher incidence of medical conditions. At the same time, resource constraints on exploration spacecraft will require that those vehicle systems (including the medical system) function with less mass/volume/power/data transmission.[2] Pharmaceuticals are a critical resource required to manage high-probability or potentially severe medical conditions during deep space missions. Therefore, pharmaceuticals selected for exploration missions must remain stable and effective throughout the entire timeframe of such missions.[3]

Most drug products undergo degradation over time. Degradation can begin during the manufacturing and packaging process, and is one source of impurities in finished drug products. [4] Drug degradation is a chemical reaction that typically progresses at a consistent rate under a consistent set of storage conditions, assuming co-reactants are available in excess[4–7] Many active pharmaceutical ingredients (APIs) are susceptible to degradation when exposed to atmospheric factors (e.g., oxygen or humidity), non-ionizing radiation (e.g., ultraviolet light) and ionizing radiation (e.g., gamma and alpha radiation). Degradation of formulated drug products can be complex and, in addition to environmental factors, may also involve interactions with excipients and impurities, which are pharmacologically inactive but not chemically inert.

NASA has previously supported six investigations into the stability of drugs after prolonged storage in LEO on board the International Space Station (ISS). Except for Du et al.,[8] most of these studies (5/6) have been opportunistic by design (see Table 3 for a summary). Each opportunistic study has analyzed sui generis medications returned from

orbit after varying periods of spaceflight but did not include controls for comparative evaluation of spaceflight drug stability. In contrast, Du *et al*. conducted a longitudinal drug stability study where spaceflight drugs were matched to corresponding terrestrial controls from the same manufacturing lot across four time points.[8] Despite the advantages of this design, the Du *et al.* (2011) study is limited because the analysis provided a qualitative assessment of drug stability for a limited set of individual drugs instead of assessments of overall drug stability or failure risk.

Table 3
Opportunistic Spaceflight Medication Stability Studies.

Study	Cory et al., 2017	Cory et al., 2016	Wotring, 2016	Wu and Chow, 2016	Wotring and Khan, 2014
Space Platform	ISS	ISS Medical kit	ISS Medical kit	ISS Medical kit	ISS (retest of Du samples)
Publication status	NASA Report	NASA Report	Published	NASA Report	NASA Report
No. of drug products/APIs	3/3	5/5	9/9	4/3	3/3
Spaceflight time points	Three time points; different timepoints for each medication	One time point; different duration for each medication	Single time point of 550 days	Two time points for promethazine inj; Three for all others	Two time points but also includes prolonged period of terrestrial storage
Control time points	One per API; no storage time points	One per API; no storage timepoints	No controls	One per API; no storage timepoints	Mixed. Some Correspond to spaceflight time points, some do not
Matched or unmatched design	Unmatched	Unmatched	NA	Unmatched	Each flight sample has lot-matched control
Independent replicates	Independent between lot analyses for the same drug; unclear if within lots replicates are independent (n = 10 replicates)	Independent between lot analyses for the same drugs ; unclear if within lot are independent (n = 9 or 10 replicates)	Independent replicates of a Single lots. (n = 4 or 5 replicates)	Independent replicates; likely tested a single lot for each drug and timepoint (n = 3)	Independent replicates, Analytical analysis performed at FDA per USP monograph and repeated on separate days.
No. of lots tested	Three separate lots/flight medication + an unmatched control for each medication	One lot/flight medication + unmatched controls for each medication.	Not discussed; likely one lot per medication	Different lots for each time point/control; no indication samples were from the same manufacture at each time point	Different lots tested for each drug or time point (one control is pair-matched to one flight sample)
Repackaged	All flight samples repackaged; controls packaging not described.	All flight samples repackaged; controls packaging not described.	All medications were repackaged.	All flight samples repackaged; Controls packaging not described.	All flight samples repackaged.

Study	Cory et al., 2017	Cory et al., 2016	Wotring, 2016	Wu and Chow, 2016	Wotring and Khan, 2014
APIs Tested	**Amoxicillin**[2], Aspirin[1], Pseudoephedrine[1]	**Levofloxacin**, **Ibuprofen**, **Phenytoin**, Valacyclovir, **Sertraline**	Aspirin[1], Acetaminophen, **Ibuprofen**, Loratadine, Loperamide, Melatonin, Modafinil, Pseudoephedrine[1], Zolpidem	**Promethazine**[3], **Azithromycin**, **Ibuprofen**	**Levothyroxine**, **Levofloxacin**, **Azithromycin**
Analytical instrumentation	HPLC with electrospray LC-MS	HPLC with UV or electrospray LC-MS	HT HPLC with PAD detector or UV DAD detector	UPLC-MS/MS	HT HPLC with DAD
Analytical performance (API)	Not discussed	Not discussed	Not discussed	Accuracy, precision, LLOQ, LLOD	Accuracy, precision, specificity, LLOQ, LLOD

[1] APIs shared across other studies that were not amongst drugs tested by Du *et al*. (2011)

[2] Du *et al*. tested amoxicillin in combination with clavulanate whereas Cory *et al*., 2017 tested amoxicillin as a single API drug product.

[3] Both tablet and injectable formulations.

Bolded APIs was one of the drug substances tested by Du et al. (2011), although product manufacturers may be different between studies.

API, active pharmaceutical ingredient; ISS, international space station; HPLC, High-performance liquid chromatography, UPLC, Ultra-performance liquid chromatography; MS/MS, tandem mass-spectroscopy; DAD, Diode Array Detector; PAD, Pulsed Amperometric Detector, LLOQ, lower limit of quantitation; LLOD, Lower limit of detection; LC-MS, liquid chromatography-mass-spectroscopy

Consequently, uncertainty persists in this area of analysis.[9] In this paper, we reanalyze the primary data from six previous spaceflight drug stability studies to quantify and better understand the effect of spaceflight exposure on drug potency. The goal of this work is to identify and address critical research gaps and uncertainties by implementing an experimental pharmaceutical testing strategy based on well-designed stability and stress studies.

Methods

A literature search was performed to identify all English language spaceflight drug stability studies (summarized in the accompanying Supplemental Methods) and ensure a complete dataset and inclusion of data. API content was quantified in all available studies for the majority of drugs studied. Additional measures of drug stability, including impurities and physical characteristics, were only available in some studies and only for a few drugs. For this reason, this paper focuses on API content as the measure of drug stability.

The kinetics of API loss was evaluated based on both zero-order and first-order reaction kinetics. The selection process for the most parsimonious model is captured in Supplemental Methods.

Statistical analysis

All statistical analyses were performed using open-source R statistical software (version 4.0.5) using R Studio (Boston, MA version 1.4.1106) as described in the Supplemental Methods section.

Generalized estimating equation (GEE) models and failure time analysis assume that each drug formulation is a distinct entity that requires independent processing (e.g., API extraction procedures) and analytical procedures (e.g., HPLC columns, buffer conditions, detector response factors). Therefore, each drug product represents an independent test. However, repeated measurements of API potency over the time course are not independent since these represent measurements of a specific drug lot over time and are expected to be correlated. GEE models account for temporal correlation for each individual unit (i.e., drug) and, as a result, are expected to give a better estimate of the population mean response across all tested drugs.

To evaluate the overall effect of spaceflight on drug stability and account for within-in cluster correlation to temporal data, GEE models were used to estimate API content loss rate over time. GEE analysis was performed using the "geepac" package (version 1.3-2) for R software using the geeglm() function with "exchangeable" correlation structure and family = gaussian. APIs served as the clustering id. Analysis was supported by ggeffects (v. 1.1.1), emmeans (v. 1.7.2) MuMIn (1.43.17), ggplot2 (3.3.3) and lattice (v. 0.20–41) packages. Mixed-model regression was also performed, yielding similar results, as presented in Supplementary Methods and Results.

Failure time analysis was performed to estimate the probability of drug failure as a function of time. Failure analysis is the inverse of a survival model that assumes a sequence of stresses, or just time itself, that incrementally increases the probability of failure. The drug content data exhibit left, right, and interval censored events. The sampling interval in the Du et al. (2011) study is approximately 9- to 10-months, which is not trivial given that the shelf-life of many drugs is in the range of 1 to 3 years, which provides strong justification for accounting for censoring in the analysis.[10] In all instances, censored events are considered uninformative since the sampling scheme is based on operational flight schedules distributed at a roughly regular interval without any relationship to drug expiration or stability profiles. Additionally, for determining when drug failure occurs, we use the intersection of the lower 95% confidence interval limit (calculated from summary statistics) with the US Pharmacopeia (USP) specification threshold, which is compliant with US Food and Drug Administration (FDA) guidelines for drug shelf-life testing. Using the available mean and standard deviation for each time point, the lower 95% confidence interval limit on the mean was calculated as:

$$\bar{x} - t * \frac{\sigma}{\sqrt{n}} (df = n - 1)$$

where $\bar{x}$ = the sample mean test values at time point *i*, t = the t-value of 95% CI (t = 4.303), σ = sample standard deviation and n = the number of observations (n = 3). Our analysis uses the current minimum USP threshold for API label strength for all drugs evaluated, not the USP (or author-assumed) thresholds used when studies were published or submitted to NASA.

It is noteworthy that for the GEE, mixed-effect model, and AFT model analyses, the drug clavulanate was excluded from the analysis. Clavulanate exhibited large variance among replicates and is a significant outlier in both the flight samples and terrestrial controls with degradation. This variance is far more extensive than seen in any other drug (Figure S1). Importantly, clavulanate is the *only* drug where the spaceflight sample appears to be *less* degraded than the terrestrial control. Therefore, removing this outlier would be expected to increase the apparent effect of spaceflight (i.e., the likelihood of rejecting the null hypothesis) in the overall model. This observation may represent a conservative health-protective bias since it slightly increases the overall estimate of spaceflight drug degradation.

Results

Six primary English-language research studies were identified that reported spaceflight drug stability data. Of these studies, two have published results. Among these studies, Du et al. (2014) performed the only study with controls, while the five other studies used opportunistic spaceflight samples and manufacturer-matched drugs from different manufacturing lots as comparators (see Table 3). Among these studies, only one is in published format.[11] The four remaining investigations are non-peer reviewed NASA reports[12–14] of which reanalyzed three medications that were the same samples initially tested and reported by Du *et al*. three years earlier.[15]

A discussion of the Du *et al.* study design is relevant to contextualize the analysis that follows. Du *et al*. evaluated eight medication kits, each consisting of thirty-three drug products containing thirty-nine APIs. Of these thirty-nine APIs, thirty-six (36) were assayed for API content (API content for two drug products were not reported). Two APIs were in more than one formulation (ciprofloxacin [3] and promethazine [3]), and three products were combination products containing two separate APIs (a fourth combination drug product containing two APIs, noted above, did not have assay results). Half the medication kits (4) were stored aboard ISS, and the remaining were stored terrestrially in an environmentally-controlled chamber at the Johnson Space Center (JSC). Across all of the medication kits, each drug product was from a single manufacturing lot (i.e., one lot per drug product); hence, all spaceflight drug samples were matched to control samples from the same manufacturing lot across all kits and time points. Terrestrial control samples were stored under temperature and humidity conditions comparable to the flight samples. Among the solid dosage forms, twenty-two of the twenty-four drugs were removed from the original manufacturer's container and repackaged in ridged polypropylene containers. These medication containers are not considered protective since atmospheric factors can permeate plastic containers at defined rates,[16] and there is no record that packaging was sealed or met USP standards for vapor transmission. For all drugs, analytical chemistry testing measured only the amount of API in each formulation at each time point; no evaluation of degradation products was performed, and degradation mass balance was not determined.

Du et al. reported that mean API content in 25 out of 36 medications in the spaceflight group fell below USP standards for labeled API strength (i.e., "failed") after 880 days of storage, compared to 17 out of 36 in the control group at the same time point. Across time points, the number of formulations that failed to meet specifications for API content increased with more prolonged spaceflight exposure. These results are the basis for the conclusion by the study's authors that "…a number of formulations tested had a lower potency or percent content of API after storage in space with a consistently higher number of formulations failing USP potency requirement after each storage period interval in space than on Earth".[8] This conclusion, based on dichotomization of quantitative API content results (i.e., pass/fail outcomes), has been repeatedly cited as evidence that latent factors associated with spaceflight increase the risk of drug failure. However, quantitative analysis of API content can provide more insight into the effect of spaceflight on drug stability. Across all drugs at the 13-day time point, the difference in API content between spaceflight samples is within ± 5% of control content for most drugs (34 of 36) (Fig. 1). At 880 days of spaceflight storage, 39% of flight-exposed drugs (14 of 36) remain within ± 5% of control potency, and no drug has a loss of API exceeding 10% of control amounts. Taken together, this supports a conclusion that the effect of spaceflight exposure on drug stability is relatively small (Table S2).

Intuitively, if spaceflight increases the rate of API degradation (i.e., accelerates chemical reaction rates of APIs), then it should be expected that the *difference* between terrestrial and spaceflight samples should be negligible at the earliest 13-day time point compared to the difference after 880 days of storage period.[17] However, at the 13-day time point a surprising 50% of all drugs in the flight group (18 of 36) have significant ($p < 0.05$) decreases in API content

compared to matched controls (Table S1). The mean difference between the flight and terrestrial samples at Day 13 is 1.18 ± 2.5%, which equates to a rate of API loss of 0.09%/day. By comparison, the mean deviation from controls at the 880-day time point was − 4.76 ± 3.01%, corresponding to a total mean change in potency of only 3.6% (4.76% − 1.18% = 3.6%) for a storage duration of 880 days - fully 60-times longer than the initial 13-day time point. In this regard, the ratio of degradation occurring from Day 14 to Day 880 is approximately 3-times the amount of degradation observed from Day 0 to Day 13, equating to a relative risk associated with spaceflight storage of 0. 045, which is much less than unity. This suggests that that a substantial portion of the observed drug degradation is contributed to by factors present prior to the earliest time point (Day 13), even though the duration of time after Day 13 accounts for 99.5% of the total period of spaceflight exposure. Hence, the loss of API reported for spaceflight drugs is at least partially attributable to factors other than an increased chemical reaction rate associated with prolonged spaceflight exposure.

Focusing on changes in API content occurring between study days 13 and 880 show that spaceflight and terrestrial drug potency are highly correlated (r = 0.894) showing nearly a 1:1 correspondence (Fig. 2). Linear regression of these paired terrestrial and spaceflight potencies yield a slope coefficient of 1.012, which is virtually equivalent to unity and offset only by the y-intercept of -4.64%. On a per-drug basis, the Day 13 and 353 samples are slightly greater than unity, while the Day 596 and 880 samples are slightly less than unity. This indicates that the loss of API over the course of the experiment, aside from the location of the y-intercept, is very similar for control and spaceflight samples overall.

Estimates of chemical degradation rates are crucial to enabling a mechanistic understanding of how API degradation is influenced by environmental conditions and to provide predictive insight for estimating drug strength over time. The FDA and the European Medicines Agency (EMA) assume that drug degradation rates are typically represented by linear kinetics; most commonly first-order.[17, 18] Regression models can test the null hypothesis of equality of slope or intercept relative to a control sample. For stability testing of pharmaceuticals, the lower 95% confidence interval of a regression model is used to describe degradation rate as a function of time, and is used to predict the retest period and shelf life [18–20]. For each drug in this study, rates of degradation are visualized as a series of scatter plots upon which fitted first-order curves (natural log of the response variable) for control and flight samples are superimposed (Fig. 3). From these plots, it can be observed that for many of the APIs, the control and spaceflight degradation curves are close to parallel, with the two curves primarily offset by variability in the location of the y-intercept (i.e., the API strength at time zero). These plots illustrate that, for most of the tested drugs, spaceflight contributes minimally to the degradation, as summarized numerically in Table S3, which also provides extrapolated estimates of API half-life under control and flight conditions, as well as an estimation of API remaining at three years.

Inspection of these rate relationships shows that spaceflight is generally associated with a small increase in the rate of API loss. Rate ratios comparing terrestrial and matching spaceflight samples greater than 1.0 (Table S3) indicate that the spaceflight rates of API loss exceeds that of matching control samples. For thirty (30) out of thirty-six (36) drugs, rate ratios were less than 2-fold, ranging from 0.69 to 1.97. Only 2 of 36 APIs exhibit spaceflight degradation rates exceeding 3-times the terrestrial control rate: ibuprofen tablets (7.02-fold), and lyophilized imipenem for injection (9.43-fold). Clavulanate was the only drug that was *more* stable under spaceflight conditions than terrestrial (rate ratio = 0.69).

Half-life is an intuitive metric for evaluating concentration-dependent loss of API over time. Calculated half-life estimates (Table S3) show that most of the spaceflight APIs (24 of 36) have half-lives exceeding a decade, with the

remaining 12 drugs having half-lives shorter than ten years (controls are 31 and 5, respectively). Extrapolated, the rate of API content loss suggests that, under repackaging and storage conditions analogous to those currently used by NASA operationally, the mean potency remaining in either control or spaceflight drugs at the end of a three-year exploration space mission falls below 90% of the label strength. Although not ideal, most of the tested drugs would have adequate API content remaining to achieve therapeutic efficacy with increased dosages. It is noted that neither current nor previous drug repackaging practices are considered protective for vapor or light transmission as defined by USP[21]

Each paired set of flight and control drugs (i.e., within-drug comparisons) is independent of all other paired sets of medications (i.e., between-drug comparisons) and can therefore be collectively analyzed to estimate an overall effect of spaceflight on drug stability. Visual inspection of the individual fitted regression plots (Fig. 3) collectively suggests slope and intercept variability across APIs contributes to differences in API levels observed between control and spaceflight samples. The evaluation of terrestrial and spaceflight treatments is analogous to whether or not results from independently performed stability tests can be combined under FDA shelf-life stability testing guidance.[17, 22] Linear mixed-effect regression models have been used as one approach for such drug stability evaluationshypotheses.[23, 24] However, a fundamental assumption of the mixed-effect regression models is that slopes and intercepts for each entity (i.e. drug product) are random and normally distributed. Since the drugs tested by Du et al. were arbitrarily selected for testing based, in part, on heuristic operational considerations, the normality of random slopes should not be assumed. GEE models are an alternative approach that do not assume anything about random effects, but do account for cluster correlation for each drug over time. The use of an exchangeable correlation structure allows for a single correlation parameter for all pairwise responses within an API. Thus, the model provides a population-level estimate of longitudinal drug potency accounting for clustered correlation. Here, we assume that different APIs, and potentially different drug formulations containing the same API (e.g., tablet, injectable), have different susceptibilities for degradation over time. Hence the postulated GEE model includes a variable for storage time (in units of months of storage), a factor for the treatment group, and a clustering variable (drug API). In addition, an interaction term is also included in the model to account for the combined effects of storage time with the treatment group (flight vs. control). This interaction is mechanistically justified since storage time cumulatively increases exposure of an unprotected API to environmental factors (e.g., humidity, CO_2, ionizing radiation), or combinations of factors. that individually or synergistically contribute to API degradation. This contribution was evaluated using interaction plots and model selection prior to including this effect as a GEE model parameter (Figure S2). The GEE model results show that time, and the interaction of time and storage conditions, are the most significant coefficients in the model, with the effect of spaceflight itself being a less significant contributor to degradation. The first-order degradation rate for APIs under terrestrial conditions is -0.00317/month ($t_{½}$ = 219 months). These findings compare to a degradation rate of -0.00478/month ($t_{½}$ =145 months) for spaceflight samples, which equated to a ~ 1.51-fold (51%) increased rate, or an *additional* rate of-0.0016/month over the baseline rate. Figure 4 compares the overall first-order degradation of all drugs stored terrestrially to similarly maintained control samples with pertinent GEE model coefficients provided in Table 1, and the marginal supporting effects are provided in Table S4. Converted to an arithmetic scale, this equates to an additional ~ 0.2% loss of API content per month relative to the terrestrial baseline when averaged over the total duration of the experiment. The cluster correlation is estimated to be 0.651 ± 0.0703, indicating substantive temporal concordance within a cluster (i.e., APIs), which strongly supports the GEE approach for modeling cluster correlation.

Table 1
GEE model regression coefficents1

Term	Coefficient	Standard Error	Wald Statistic	p-value
Intercept	4.61E + 00	6.66E-03	481502.6	< 2e-16
Storage	-3.17E-03	3.11E-04	103.9	2.00E-16
Treatment	-1.27E-02	4.98E-03	10.2	0.0014
Interaction	-1.61E-03	1.79E-04	80.8	2.00E + 16
[1]. Model coefficients represent Ln(response)				

Drug "failure" occurs when the API content of a drug product does not meet the minimum percentage of labeled strength, which, in the United States, is established by USP drug specifications. The overall risk of drug failure is a concern of NASA for long-duration spaceflight, especially for deep space exploration missions where resupply may be difficult or impossible. USP specifications of drug API content are minimum API content thresholds that serve as dichotomous binary pass/fail classifiers. USP limits are based primarily on reasonably achievable manufacturing quality and analytical performance; they are not quantitative metrics of pharmacodynamic potency, therapeutic efficacy, or toxicological risk. Therefore, it is recommended that USP quality standards should not be treated as surrogates for therapeutic efficacy. In this paper, the intersection of the lower 95% confidence interval of measured API potency with the lower limit of the USP quality range is used as the threshold to dichotomously classify each drug product as pass or fail.

Failure time analysis focuses on *when* a failure event occurs rather than *if* an event has occurred, as in survival analysis. The risk of drug failure is the probability that a drug will fail to meet USP quality standards at any point, and this probability increases over time. Figure 5 illustrates the cumulative posterior median failure distribution of terrestrial and spaceflight drug samples uncorrected for the mean difference between control and spaceflight API strength discussed earlier. Both spaceflight and terrestrial conditions exhibit a rapid increase in failure probability during the earliest months of storage in this experiment. The risk of failure with spaceflight storage is superimposed upon, but lower in absolute value, than the baseline risk of failure observed for the terrestrial controls.

Overall, the time to failure for drugs exposed to spaceflight, based on assayed API potency, is approximately half (0.55) that of a drug under terrestrial conditions (95% CI = [0.37, 0.82], p = 0.0038) if a proportional hazard is assumed. From the Bayesian model, the median estimated time to failure was 28.6 months (95% CI, 21.0–40.9 months) for terrestrial storage and 15.3 (95% CI, 11.2–20.1 months) for spaceflight. Based on the posterior survival distributions, probabilistic failure estimates for specific storage times are provided in Table 2. Whether the probability of failure for the baseline terrestrial samples is increased due to environmental exposure as a result of repackaging or inherent chemical instability cannot be determined directly from this study since matching controls in unopened manufacturer packaging were not tested. It is important to reiterate that drug failure is related to each tested medication's potency relative to USP specifications, which does not necessarily equate to altered therapeutic efficacy.

Table 2
Probabilities of Drug failure through specific time durations

Median	Storage Duration (Months)			
Probability ± SD	**1**	**12**	**24**	**36**
Terrestrial storage	0.007 ± 0.005	0.188 ± 0.049	0.426 ± 0.072	0.627 ± 0.085
Spaceflight storage	0.0017 ± 0.001	0.388 ± 0.066	0.729 ± 0.065	0.898 ± 0.049

In addition to the study by Du *et al*., five smaller descriptive opportunistic studies of spaceflight drug stability have been performed (Table 3).[12–15] Among these studies, none include initial baseline API measurements prior to long-term spaceflight exposure or terrestrial lot-matched controls. Of these studies, only the study by Wotring (2016) is published, whereas the other four studies are non-peer reviewed NASA reports (extracted data are provided as described in the Data Availability section). The range of APIs tested among these five studies is much more limited than that of Du *et al;* however, there is a much greater focus on characterizing impurities, albeit without lot-matched terrestrial controls. Three of these studies include matched manufacturer controls for each spaceflight exposed medication, however, these controls are from different lots with different expiration dates,[12–14]and one study includes both unmatched and *some* lot-matched controls.[15] Across the six studies (inclusive of Du *et al*.), a total of nine medications (Table 3, bolded) intersect with the list of medications tested by Du *et al*. Of these, ibuprofen is the most commonly tested drug, having been evaluated in four out of six spaceflight studies. Two medications are shared across the five studies in Table 3 that are not included in the Du *et al*. study (‡ superscript), with the remaining drugs having been evaluated in only a single study. The study by Wotring and Khan (2014) is distinct from the other four studies listed in Table 3 in that the three medications tested are the identical medications originally tested by Du *et al*. several years earlier. In this respect, these results are independent measurements on the same Du *et al*. samples but following a considerably longer period of post-flight terrestrial storage. Figure 6 summarizes data from all studies as scatter plots of mean API levels (± SD) for the nine drug products (eight APIs). A trend line incorporating all available data for each medication (blue line) is plotted to illustrate the overall pattern for loss of API content with slopes provided in Table S5. For reference, the trend lines for the matching control and spaceflight medications from Du *et al*. are also provided as described for Fig. 3. A key observation from these composite plots is the large variability in measured API content across studies.

Across all studies, five out of the nine intersecting drugs exhibit higher amounts of API in the follow-up studies than were reported by Du *et al*. at similar or earlier time points. The opportunistic studies of ibuprofen yield API percentages that bracket those reported by Du *et al*., with lower levels of API at all time points reported by Wu *et al*. (2016) and higher levels reported by both Wotring *et al*. (2015) and Cory *et al*. (2016). Both the oral and injectable dosage forms of promethazine were reported by Wu *et al*. (2016) to have lower amounts of API than was reported by Du *et al*. Among the nine composite models, spaceflight degradation rates are reduced in five models (i.e., the rate of degradation is slower) when all data were considered; only phenytoin exhibits an increase in estimated rate of degradation. Rate estimates for amoxicillin, ibuprofen and injectable promethazine (the latter being the only drug maintained its original manufacturer packaging) are relatively unchanged despite large variations in the data.

Discussion

Several studies and review articles have suggested, based on anaecdotal analyses, that long-term exposure to spaceflight may facilitate drug degradation and increase the risk of therapeutic failure [8, 9, 25, 26]. We have performed a quantitative analysis of available data to characterize the overall effect of spaceflight on rate the rate of API loss

and the risk of drug failure. Our analysis suggests that degradation observed in terrestrial control samples is the dominant factor contributing to drug degradation, and that spaceflight storage contributes an additional but much smaller effect.

Existing studies have not directly investigated how factors unique to spaceflight contribute to increased API degradation or which attributes of some drug products may increase susceptibility to degradation. It is pertinent, however, that most of the drugs tested across all the NASA-supported studies have been solid oral dosage forms repackaged into nonprotective packaging for spaceflight testing. The practice of drug repackaging by NASA is essential in order to minimize mass and volume of drug resources. To date, no study has directly compared the spaceflight stability of repackaged medications to the same medications in their sealed manufacturer packaging in order to evaluate the effect of repackaging on drug stability. The study by Du et al., (2011) is the only investigation to date that included multiple drugs that were not repackaged (14/36 drugs). Of these drugs, ten are an assortment of nonsolid formulations, including solutions, ointments, creams, and a suppository. The remaining four APIs that we not repackages were combination products: imipenem with cilastatin (lyophilized powder for injection) and ethinyl estradiol with norethindrone (blister pack oral tablets) (see Table S3). After 880 days of spaceflight, only two of fourteen drugs (~ 14%) remaining in manufacturer packaging deviate from their corresponding controls by more than 5%, compared to nine of twenty-two (41%) repackaged medications. Similarly, for those drugs that failed during the 880-day storage period, the mean failure time for drugs that were not repackaged is 707 days (n = 8), of which most are non-solid formulations (the one exception is ethinyl estradiol). This compares to an average failure time of 633 day for repackaged drugs (n = 12), all of which are either capsules or tablets. Solid formulations typically have longer shelf lives than non-solid formulations of the same drugs. Since it is well established that repackaging can adversely affect the stability of drug products[4, 27–29] the more frequent and earlier failure of solid formulations suggests that repackaging may be an important contributor to drug degradation reported in spaceflight studies. Currently, the effect of drug repackaging on drug stability is not been a concern for LEO missions because ISS can be readily resupplied; however, resupply will be much more limited, if not impossible, for exploration space missions. Therefore, repackaging procedures must be more protective than those used for ISS to assure drug stability throughout the full duration of an exploration mission

The results of the GEE model suggest that control and spaceflight drugs start with a mean potency of approximately 101% of the labeled API strength, and a mean difference between the two storage conditions of 1.35% (Table S4). At the first time point (13-days) some spaceflight drugs exhibit a pronounced decrease in potency with up to 8.5% less API than matched control (Fig. 1, Table S2). If the mean difference in potency observed at the 13-day time point is interpreted as the rate of change (i.e., 1.35% / 13 days = 0.104%/day), and if this rate were maintained throughout the experiment, substantially less than half of the label amount of API would remain at the conclusion of the experiment. Since this did not occur, it appears that the loss of API content prior to Day 13 is much greater than the rate of loss from Days 13 to 880 (Table S2). Therefore, the loss of API prior to Day 13 must be attributable to either exposure of the samples to some extreme environmental factor not directly associated with spaceflight storage (e.g., repackaging or handling, sample processing, off-nominal storage conditions). This difference between control and spaceflight samples persists throughout the experiment and appears to affect most medications similarly, as exemplified by cilastatin (Fig. 3).

On average, the amount of API remaining after spaceflight storage was statistically less than corresponding lot-matched controls across all the medications tested. However, it is essential to distinguish a statistically significant change from a clinically significant one. Statistical significance assumes sample replicates are i*ndependent measures* and, if this assumption is violated (e.g., pseudo-replication), the statistical tests are biased by artificially

low sample variance, which increases the likelihood of falsely rejecting a true null hypothesis, a type 1 error (false-positive result). In such a case, it would be erroneously concluded that treatment samples are “significantly” different from controls when, in fact, they are not. Although API content of most spaceflight medications is significantly less than corresponding controls, especially at the later time points, the magnitude of the difference is relatively small. On average, the difference between terrestrial and spaceflight samples increases with storage time to 2.29% ± 5.55% after 353 days of storage, 3.93% ± 4.09% at Day 596, and 4.76% ± 3.01% at Day 880. Consequently, most spaceflight samples fall within 5% of their respective terrestrial control at 880 days (2.4 years) of storage, and all medications in the spaceflight group were within ± 10% of the matching controls (Fig. 1). Thus, while most spaceflight-exposed drugs have a significant loss of API at the 880-day time point and fail to meet the USP standards for API strength, corresponding controls samples also undergo a loss of API content. For this reason, clinical efficacy of spaceflight medications would likely not differ from the corresponding terrestrial controls.

It was of interest to integrate the results of Du *et al*. with those of other spaceflight stability studies. Across all studies, only nine drug products intersect with the list of drugs tested by Du et al. (bolded text in Table 3). Challenges for comparing results across studies include an absence of baseline results on Day zero, single time point rather than longitudinal study design, and an absence of terrestrial lot-matched reference controls. Although API potency and impurity content for some drugs measured after prolonged spaceflight exposure differ from unmatched terrestrial samples or labeled strength, the absence of a lot-paired sample design means that no determination can made about the effect of spaceflight relative to terrestrial storage over the same period of time. In absolute terms, however, we used these studies as independent benchmarks to contextualize API content for some of the drug products reported by of Du *et al*.

When the individual least-square trends lines for the drugs tested by Du et al. (2014) are updated with potency data of intersecting drugs tested in other studies, spaceflight is not a significant ($p \leq 0.05$) predictor of degradation for any drug. These findings are not surprising given the large variability in potency for the nine APIs (Fig. 6; Table S5). There are several potential explanations for the apparent variability in API potency across different studies. One possibility is that different studies used different brands of equivalent drugs formulated with different excipients. In a few instances, where drug manufacturer information was recorded equivalent drug products tested in different studies (Table S5), different manufacturer products were used (e.g., Cory *et al*. (2017) tested Levofloxacin from Sandoz; Kahn and Wotring (2014) tested the equivalent Janssen product). Drug manufacturer is important because it has been shown that there can be substantial differences in stability between different manufacturers’ brands.[31–33] A second possible explanation for inter-study variability is sample processing. USP specifications are cited by all the spaceflight stability studies as the methods used to analyze API content. However, the USP analytical methods are submitted to the USP by the product innovator, and are optimized for the submitter’s formulation. Equivalent drug products, produced by other manufacturers, are typically formulated with inactive ingredients that are different from the innovator’s product, and therefore the USP analytical procedure (e.g., extraction conditions) may need to be optimized for equivalent products from different manufacturers. Use of unoptimized USP methods can result in reduced extraction efficiency and an apparent loss of drug potency. A third possibility for the variability in potency observed across spaceflight drug stability studies is that drug repackaging practices may be different across studies; hence, environmental exposure at different points in time may vary with differences in repackaging methods.

Of the thirty-six APIs tested by Du *et al*., only potassium clavulanate was significantly *more* stable (i.e., $p < 0.05$, two tailed t-test) during spaceflight compared to matched controls at all time points after 13-days. Clavulanate also exhibited, by far, the most significant degree of degradation among all the drugs evaluated under either storage condition. At the 596-day time point, clavulanate was only 6.6 ± 0.16% and 21.1 ± 1.1% ($p = 0.002$) of label strength

for the control and spaceflight samples, respectively. Clavulanate potency decreased to 3.3 ± 0.31% and 9.1 ± 2.07% (p = 0.04) of label strength at the 880-day time point for control and spaceflight samples, respectively. Hence, clavulanate is an extreme outlier in terms of the magnitude of API lost (Figure S1). Chemically, clavulanate is hygroscopic and highly susceptible to pH-dependent hydrolysis.[34–38] Relative humidity (RH) is a well-established facilitator of drug degradation and mediates the degradation of solid formulations of potassium clavulanate.[39–41] Du *et al.* reported that, on average, terrestrial RH levels were greater than spaceflight levels for matched samples. Since the tablets containing clavulanate were removed from the manufacturer's packaging and repackaged into containers that did not assure protection from atmospheric factors, the higher terrestrial RH may have contributed to greater hydrolysis of terrestrial samples. In addition, the partial pressure of atmospheric CO_2 aboard ISS is in the range of 2.3–5.3 mmHg, which is approximately 10-fold higher than the terrestrially CO_2 level, which is 0.3 mmHg at sea level.[42, 43] Hydrolysis of clavulanate is pH sensitive and inhibited at acidic pH.[34, 35] Hygroscopic pharmaceutical ingredients adsorb atmospheric moisture resulting in slow dissolution of the API by water within the microenvironment of the drug.[44–46] According to Henry's law, an equilibrium exists between atmospheric CO_2 and carbonic acid in the water adsorbed by the solid dosage form.[47] Dissolved CO_2 equilibrates with carbonic acid (H_2CO_3) in water, which acidifies the aqueous solution, which would be expected to slow clavulanate hydrolysis. Thus, the combined effect of lower RH and elevated atmospheric CO_2 during spaceflight may contribute to a rate of hydrolysis that is somewhat slower than that observed in terrestrial samples. Atmospheric CO_2 levels has been previously demonstrated to affect the stability of the drug sevelamer HCl.[48]

USP specifies the standards for protective drug packaging[21, 49–51] that are intended to assure that the container in which a drug product is packaged is suitable to maintain potency through its beyond-use date[27] Key functions of suitable packaging include protecting the drug product from moisture or UV light. Du *et al.* described medication containers as cylindrical "polypropylene" containers. The current operational procedure for upcoming exploration missions will repackage medications in re-closable Ziploc® bags. These closure systems are not consistent with USP guidance for moisture ingress or UV radiation protection [21, 49](personal communication with the manufacturer); rather, they are equivalent to Ziploc® baggies. Such packaging allows the contents to equilibrate with the ambient atmosphere within a couple of days to weeks, even if the packaging remains unopened. Since spaceflight packaging of solid drug formulations is not protective, degradation rates calculated for both terrestrial and spaceflight samples reflect exposure to atmospheric factors (e.g, humidity, CO_2, oxygen) capable of promoting degradation of susceptible drugs. The difference in degradation rates for spaceflight and terrestrial samples is likely attributable, at least in part, to differences in atmospheric factors between the two storage environments. Latent factor(s) associated with increased failure risk in spaceflight samples remain unknown, and elucidation of the relative contribution of these factors to the risk of drug failure should be an area of future investigation for NASA.

One limitation of this analysis that should be noted, is that each of the studies evaluated made observations on a single lot of one particular drug product at each time point. It is well established that different drug brands, formulations, and even different lots of the same drug can have significant variations in degradation rate and shelf life [15, 31, 32, 52]. When only a single manufacturer's product is tested, it is impossible to evaluate the differences in stability across equivalent products from different manufacturers.

Conclusions

Exposure of drugs to long-term LEO spaceflight appears to accelerate the degradation rate of some medication and increases the probability of drug failure based on API content. However, the additional risk of drug failure for

spaceflight samples is a fraction of the baseline risk observed for terrestrial controls. Although the factors contributing to increased degradation have not been established, it is noted that all spaceflight drug stability studies have focused primarily on testing drugs that were removed from the manufacturer's containers and repackaged into containers do not protect medications from the ingress of atmospheric factors. Atmospheric factors (e.g., O_2, CO_2, relative humidity) are well-established mediators of drug degradation. Since baseline degradation of terrestrial control samples accounts for the majority of API loss, repackaging is a simple and well-established explanation for time-dependent drug failure. Hence, simple differences in atmospheric composition between terrestrial and spaceflight storage, inclusive of pre-launch and post-flight logistics, likely cause the observed time-dependent differences in API content. However, although likely, the interaction of repackaging with storage condition has not been investigated during spaceflight. Future NASA studies of drug stability should focus on elucidating the role of current repackaging processes on drug stability and evaluate the benefit of protective packaging for susceptible drug products. For APIs that are likely sensitive to atmospheric factors or ionizing radiation, an effort should be made to identify manufacturer brands or excipients that maximize storage shelf life to assure medication effectiveness for the duration of exploration space missions.

Declarations

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Author Contributions

JFR: Conceived the project, collected the data, performed the data analysis and drafted the manuscript

SEP: Contributed to data analysis, manuscript preparation, content editing and review

KRL: Manuscript preparation including content review and analysis.

MY: Contributed to data analysis, and performed statistical review. Manuscript preparation and content review

BDE: Contributed to data analysis, wrote the manuscript, content editing and review

Competing Interests statement,

The authors declare they have no financial interests, affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Figures

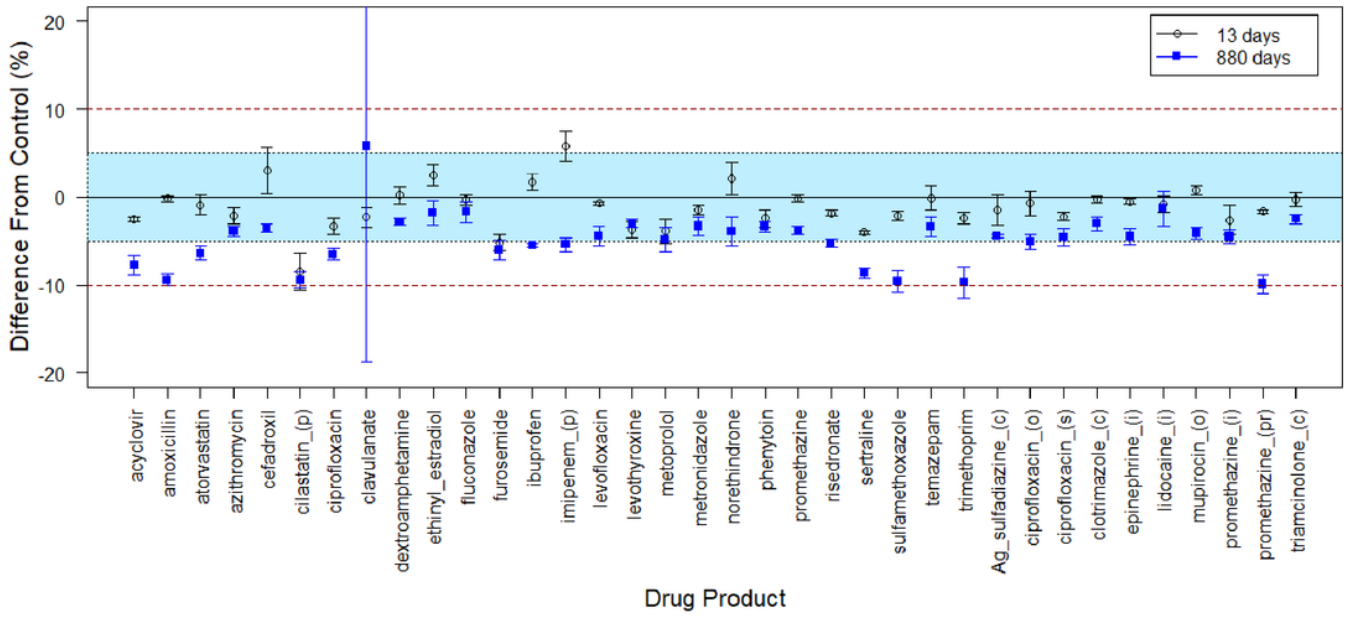

Figure 1

Relative change in API strength at 13 and 880 days of space flight. Plot of the difference between pair-matched control and spaceflight drugs stored for either 13-days (●) or 880-days (¡) samples. Values are calculated as API potency (%) in control-API potency (%) in matching spaceflight samples. Error bars reflect ± one standard deviation to display estimated uncertainty. The blue shaded area represents a difference of ± 5% in API potency; the dashed line represents a ±10% difference in potency. A value of zero indicates no difference in API content between the matched control and spaceflight samples.

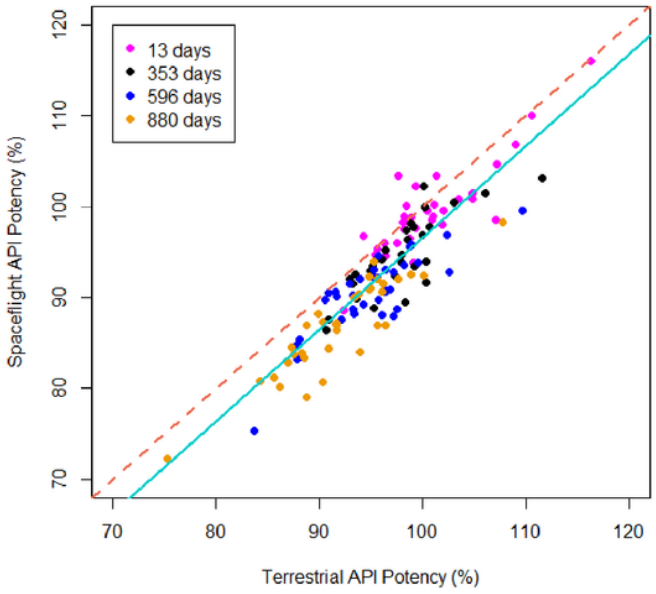

Figure 2

Potency relationship between spaceflight matched controls. Mean potency of spaceflight-exposed drugs are plotted versus matched controlled potency and are highly correlated (Pearson, r = 0.894). The slope of the solid regression line (cyan, slope = 1.012) is close to unity which is indicated by the hashed line (slope = 1 and intercept = 0).

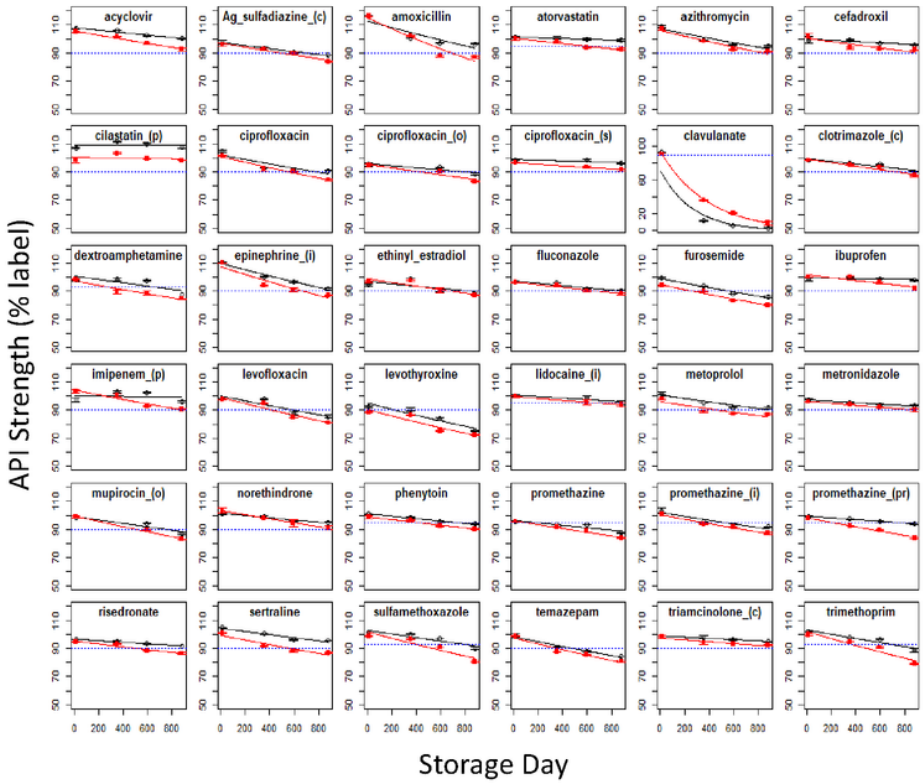

Figure 3

Plots of mean label API strength (± standard deviation) vs. storage time. Points are drug content as a percent of labeled strength corresponding to 13, 353, 396 and 880-day time points for terrestrial controls (black) and spaceflight (red) APIs. Superimposed lines are first-order regression models for each mean drug concentration. The blue hashed line indicates the minimum USP standard as published by Du et al., 2011. Injectable = (_i), cream(_c), ointment = (_o) =, suspension = (_s), suppository = (_pr). Confidence intervals were not calculated and statistical regression analysis was not performed because independence of replicate tests cannot be confirmed based on the methods presented in the publication; NASA investigators were unable to locate the raw study data.

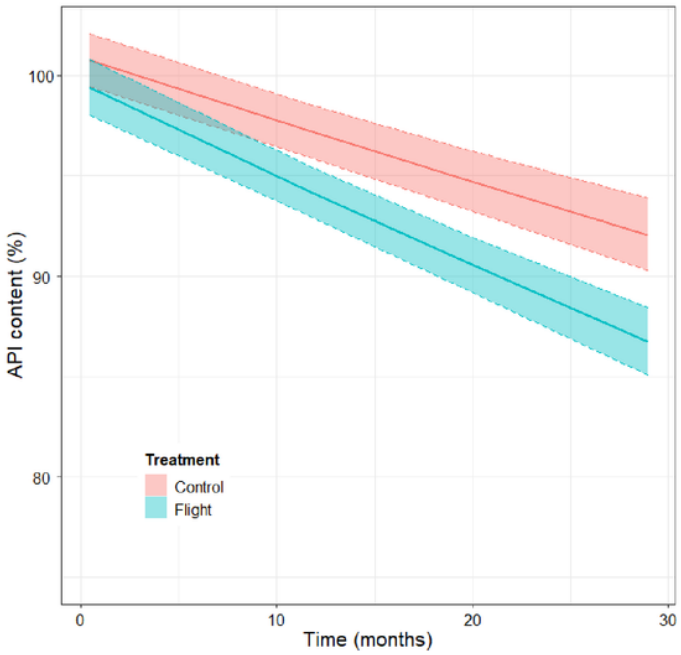

Figure 4

GEE model results for API potency. The shaded bands represent 95% confidence intervals of the regression mean response. Note the scale of the ordinate axis is truanted at 75% API content.

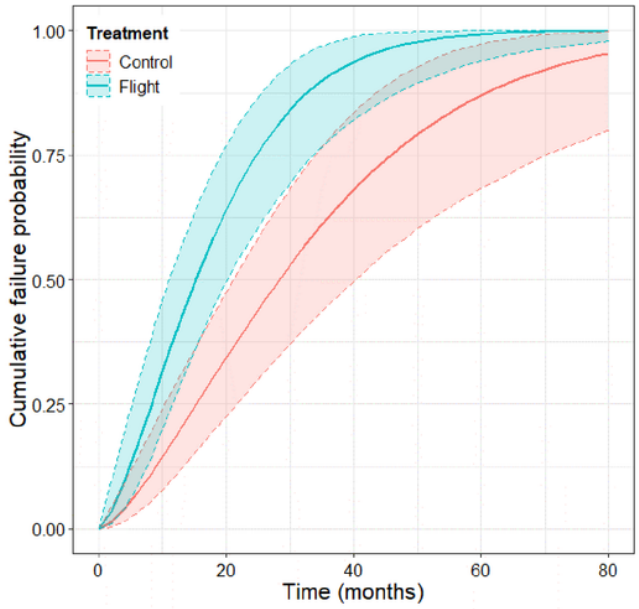

Figure 5

Accelerate failure time model results. The shaded bands represents 95% confidence intervals of the regression mean response.

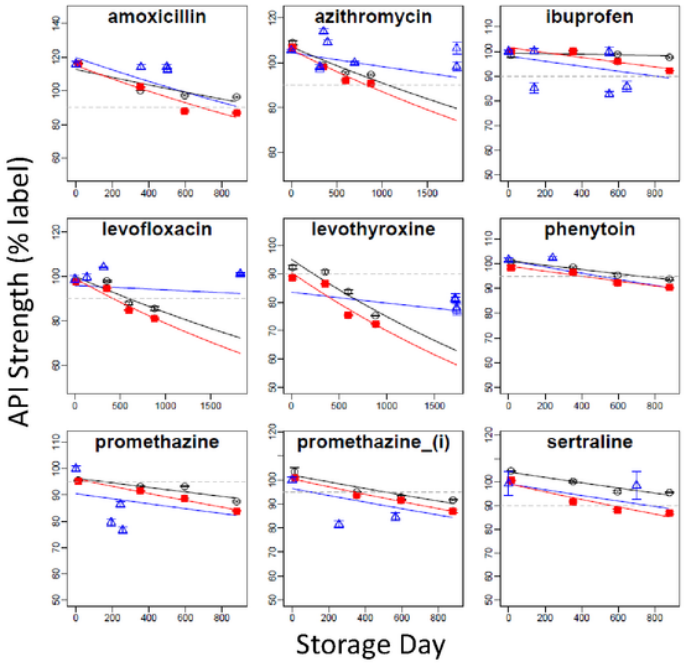

Figure 6

Least squares degradation trends for 8 APIs (9 formulations) based on testing data from all available spaceflight studies. The blue solid line is the overall trend for all available spaceflight data, including results from Du et al. and sui generis results from opportunistic studies. Triangles are mean ± one standard deviation API potency from these opportunistic studies. Black and red data points correspond to mean ± one standard deviation API potency in control (black) and spaceflight (red) samples from Du et al., with superimposed least squares trend lines for Du et al. using figure data only.

Supplementary Files

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