Cosmic-Ray Radiation Effects on Ibuprofen Tablet Formulation Inside and Outside of the International Space Station

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Abstract

In extreme environments people will have different needs for medicine(s). It is important, therefore, to know how medicine efficacy will be impacted by the environment. Ibuprofen is very widely used in tablet formulation in temperate climates on Earth. *Via* the first companion experiment inside the International Space Station (ISS) and outside ISS at the Multipurpose International Space Station Experiment (MISSE) platformwe give evidence that Earth-commercial ibuprofen tablets could fail in space, despite encasing in a commercial pharmacy aluminum-blister. We introduce the concept of 'space medicines', where solid-dosage forms are formulated with excipients, such as iron oxide, to protect the pharmaceutical active from accelerated degradation in spaceflight. We apply Earth radionuclide and photon experiments to simulate dose(s) in ISS and significantly greater, and establish the impact of alpha, beta and gamma rays. We demonstrate that tablet formulation protects from impact of alpha and beta rays; however, gamma rays decompose ibuprofen even when 'masked'. Importantly, we show all rays decompose 'unmasked' pure ibuprofen. We report for the first time a systematic analysis, of nineteen (19) tablet compositions, inside and outside of ISS that permit determination of the effect of compositional changes of the tablet matrix. We confirm that the iron oxide-shielded tablets, according to our four-fold degradation descriptor rating, had 'minimal' reduction of ibuprofen content (<10%) inside ISS, whereas all others had 'moderate' reduction (>10%); with one exception. The tablets exhibited much greater ibuprofen degradation (> 30-50%) outside ISS at the MISSE platform, which permits exposure to harsh conditions including extreme temperature fluctuation, ultraviolet radiation, highly reactive atomic oxygen, and micrometeoroids. Significantly, we find that the flavor has shielding potential, most likely because of radical scavenging. We conclude that efficacy of ibuprofen is adversely affected in space, and that effects will likely be exacerbated on missions to deeper space e.g., to moon and Mars.

1. Introduction

The provision of safe and efficacious medicines is important to ensure the health of astronauts in long-duration travel. Medicines in space have shorter shelf-life than on Earth because of chemical degradation by cosmic rays under microgravity [1]. These effects reduce the active pharmaceutical ingredient (API), the drug, and potentially create toxic substances with threat to human health. Resupply of onboard medicines will not be readily feasible in extended human space missions, e.g., to Mars. Stable medicines will be needed for space that can withstand the harsh environment.

Developments of these medicines will need to protect against a range of space radiations, including high-intensity photons and higher-mass nuclei, neutrons, electrons, gamma rays and heavy particles. In particular, protection will be needed against two (2) space radiations: galactic cosmic radiation (GCR) that comes from outside the solar system and comprises high intensity gamma rays, high energy protons and heavy particles [2]; and solar energy particles (SEP) originating from sun activity that creates high energetic plasma clouds, including solar flares or solar corona [3]. SEP comprises the electromagnetic spectrum from infrared to gamma rays, including particle radiation of protons, neutrons, and heavy nuclei.

The International Space Station (ISS) in low Earth orbit (LEO) is, currently, the only outer-space platform for astronauts and space experimentation [4]. At the altitude of *ca*. 410 km, the Earth's magnetic field and the shell radiation protection of ISS removes parts of cosmic rays; however, significant radiation remains in addition to the secondary radiation formed by the interaction of the primary cosmic radiation [5–9]. Importantly, this implies that any detrimental space effect on efficacy of medicine at ISS (LEO) is likely to be more pronounced with deeper space travel e.g. to the Moon and/or Mars [10].

Drug stability studies aboard the ISS have been reported over some two-decades [1] and a total six (6) major missions. One study included 35 active APIs, whilst in the other five studies some 2 to 9 APIs were investigated. API degradation (loss of efficacy) and a shortened shelf-life during spaceflight were reported compared with Earth [1,11–14]. Cosmic ray degradation of APIs reportedly increases with time, reaching *ca*. 20 times greater magnitude extent after 28 months as compared with Earth [14]. A commercial 'multivitamin' tablet that included riboflavin, vitamin A and vitamin C, decreased in API content 35% following 880 days storage in space [12]. API degradation is accompanied by physical changes of the formulations, including colour change, liquefaction, or morphological separations, that proceed at greater rate than on Earth [14]. Significantly, however, reported findings are not univocal, and apparently conflicting findings are reported for same or similar research aims. For example, an experiment determined the stability of 35 medications in an ISS medical kit following 28 months stowage [14]. Twenty six (26) did not meet United States Pharmacopeia (USP) standards, with six (6) aboard ISS and two (2) control samples having lost significant efficacy. When nine (9) medications were reportedly analyzed following ISS stowage, eight (8) had API content within acceptable USP limits from 5 to 8 months after the expiration date [11]. Additionally reported was that a vitamin B1 formulation exhibited meaningful degradation following 4 month of ISS storage, whilst one formulation failed to meet USP standard following 11 month expiration [13].

Importantly, solid formulations reportedly are generally are more stable than liquid, with semi-solid ranging in between [14]. Liquid formulations degrade *via* indirect ionization [1]. High energy radiation can reportedly split water solvent of liquid formulations to hydrogen and hydroxyl radicals *via* radiolysis [15].

ISS medicine studies look to establish 'best' formulations, e.g. microgravity-induced crystal size and shape of APIs [16] that determine drug bioavailability [17]. Crystal formation is determined by elemental engineering, including diffusion and convection during drug precipitation [18], that are reportedly different in space to Earth [18] and, can, constitute ideal formation conditions [19]. These include crystal polymorphism i.e. generation of different crystal forms for the same API that can have significantly different solubility [20].

To establish cosmic-ray stability on ISS we selected ibuprofen as an API that was formulated as a solid tablet [21]. Importantly, ibuprofen was used in the space shuttle program [22] and as an ISS emerging medication [23]. Ibuprofen treats fever, aches, pain arthritis, and more. It is from a class of medications called NSAIDs, nonsteroidal anti-inflammatory drugs.

Ibuprofen is of research interest, therefore, for radiation-degradation, and additionally because of its large-scale manufacture of *ca*. 45,000 tonne per year in 2019 [24]. Reported ibuprofen degradation studies have included photo-catalytic, photo-catalytic chemically oxidative, thermal oxidative, enzymatic, cavitation and environmental degradative pathways [25–29].

Because an ISS study is necessarily a 'one-off, single experiment' challenging to routinely repeat [1,7], ground-based-radiation experiments were designed at a similar dose as controls. These advantageously permit establishing the effect of a selected radiation i.e., alpha, beta or, gamma, and importantly to replicate experiments. The objective was to design a formulation capable of protecting ibuprofen from cosmic rays; a space-specific tablet formulation with boosted drug stability. Nineteen (19) different tablets that encompassed seven (7) formulations, each with parametric variation of the medicine, were used. These excipient compositions i.e., solid contents forming a matrix for a drug, were selected to stabilize (or destabilize) ibuprofen in space. Each composition was replicated at least three (3) times both in ISS and on Earth, (Houston, USA). Significantly, because of this taxonomy there is a sample size of 120 tablets, which contrasts importantly to reported ISS studies, that lacked either control or appropriate sample size [11,30].

Importantly for the first time, this study was conducted with medicine tablets on both the inside the station and on an outer platform of ISS, namely, that part which is exposed to harsh outer space, or MISSE (Multipurpose International Space Station Experiment) for similar periods of time [31]. This designed exposure to unprotected cosmic ray radiation establishes how medicine behaves when in a harsher environment to that shielded in ISS and anticipates Moon and Mars missions.

2 Methodology

2.1 Materials

See Supplementary Material.

2.2 Tablet compression

See Supplementary Material.

2.3 Earth-simulated space radiation

See Supplementary Material.

2.4 Packaging of tablets and launch / space experiment

Tablets were encased in a home-made aluminum (Al)-based packet, resembling the 'blister' packs of commercial tablet products (see Fig. 1). The foil thickness was 0.07 mm (PET/ALU/PE Doypack®, made from polyethylene terephthalate (PET), Al as middle layer and polypropylene (PE), Flexico Group), Supplementary Material, Figure S2.

Launch to ISS: On 02 October 2020, 60 tablet blister samples were sent to the ISS National Laboratory Facility using Northrup Grumman as launch provider (Mission, NG-14) on an Antares rocket, Figure S2, Supplementary Material. Launch site was Wallops Island, Virginia (USA).

The mission was planned and administered by Space Tango, Lexington, Kentucky (USA). During travel to ISS the samples were stored in a storage-cube (CubeLab). The duration of the experiment was nearly exactly 12 month, with splashdown in a SpaceX CRS-23 Dragon cargo capsule on 01 October 2021. Sixty (60) control samples stayed for this time in Lexington, Earth. Flight and ground control samples were shipped *via* post-express services from, and to, Australia.

Launch to ISS for installation on MISSE Platform: By 20 February 2021, 60 tablet blister samples were sent to the Multipurpose International Space Station Experiment (MISSE platform), outside ISS, using Northrup Grumman as launch provider (Mission, NG-15) with an Antares rocket, Fig. 2, Supplementary Material. Launch site was Wallops Island, Virginia (USA). The mission was planned and administered by Aegis Aerospace, Houston, Texas (USA) in collaboration with Space Tango, Lexington, Kentucky (USA). During travel to ISS the samples were stored in the MISSE carrier. The duration of the experiment was in total 328 days in orbit with external (outside of the pressurized ISS module) exposure of 256 day. The tablets returned in the SpaceX CRS-24 Dragon cargo capsule on 24 January 2022. Six (6) identical control samples stayed for this time in Houston. Flight and control samples were shipped *via* post-express services, from and to, Australia.

MISSE-14 Timeline	
Launch	20-Feb-21
Transferred external (through airlock)	19-Apr-21
Transferred inside ISS	31-Dec-21
Landing	24-Jan-22
Total days in orbit (day)	328
Days external (unpressurized) on ISS (day)	256

2.5 Analytical procedure

See Supplementary Material.

3 Results and Discussion

3.1 Cosmic-ray protection concepts

The tablet form studied is the most common manufactured dosage form [32]. The active pharmaceutical ingredient, API, ibuprofen is embedded in an excipient matrix. We selected fewer excipients than in some

commercial tablets to permit a systematic variation of composition and identification of single excipient effect, whilst adhering to a total tablet number < 20, determined by the maximal size of the tablet blister and payload for ISS, Table 1. We selected inorganic excipients only, following Kaplan's research studying SiO2 protection of silk and collagen in an MISSE-6 experiment [33].

Based on informed conjecture that Earth formulation concepts might not provide sufficient shelf-life, i.e., drug stability in space, formulation was based on three (3) concepts with potential for radiation protection, Figure 2, namely: 1) *Manufacturing-inherent dilution of API in excipient matrix* - Only inorganic ingredients, chemically inert and adsorbing part of the cosmic radiation were selected. These give shielding from alpha, beta and UV rays, but not gamma rays; 2) *Enrichment of tablet with atoms of high atomic mass known to absorb particle rays (alpha, protons)* - Iron oxide (Fe_2O_3) and titanium oxide (TiO_2) were selected as highest-atomic number elements, used either dispersed or as a coating. Whilst there are elements with greater atomic number, these are often toxic and, therefore, uncommon in formulations. The concept is to shield alpha rays (and UV) – it is not clear whether there is potential to shield from electrons and gamma rays; 3) *Targeted molecular complexation of ibuprofen with excipients that change electronic structure of ibuprofen and, potentially, stability*. This concept combines 1) and 2), without excipients with potential for molecular interactions e.g., *via* molecular modelling.

3.2 Excipient Case: Investigation on ISS and MISSE

Whilst there are reported findings on drug formulation stability at ISS, these do not involve a systematic experimental design. We obviate this in the present work *via* systematic variation of excipient composition, compiled into Case studies, Table 1. As is seen in the table, the Base and API Dilution case tablets have, respectively, a fixed (25% by mass) and varied (2% to 18%) ibuprofen content; Iron Oxide comprises four (4) tablets, respectively, containing 1 mg, 10 mg, 18 mg, and 25 mg iron oxide; Excipient three (3) tablets with a variation of content of three other excipients, with 12.5% and 25%; Vitamin C comprises two (2) tablets with a variation of ibuprofen content (2% and 12.5%); Flavor of a single tablet with a significantly greater flavor content of 15% compared to the other tablets (1% to 2%); Titania of four (4) tablets with a variation of ibuprofen content of 20.5% to 25%. The ibuprofen content is set high, up to 25%, comparable with commercial NSAID products, e.g. Advil tablets comprise 200 mg ibuprofen (42%) in 475 mg total weight (determined by weighing).

Inorganic materials only were used as excipients and were selected to provide elemental excipient function needed for tablet manufacture, Figure 3. Colorants were taken as these might support shielding from cosmic rays, because they absorb part of electromagnetic spectrum and are materials common in protective shielding of Earth tablets. Significantly, the inorganic materials used have a lunar mineral counterpart, Figure 3. In principle, therefore, the excipients could be manufactured on the Moon from these lunar minerals. Vitamin C was also added as an organic molecule and as antioxidant and color stabilizer. Iron oxide (Fe_2O_3) is the only colored ingredient used, and with other excipients and drug Concept 2, Figure 3, gives rise to a visible change of tablet coated with 25 % and 1% iron oxide due to its intense red colour as filler of coating, Figure 3.

3.3 Simulated-space radiation in Earth facility

3.3.1 Radiation dose Earth-space

Radiation facilities at our site (Adelaide) simulate cosmic radiation. This advantageously permits significant numbers of samples to be assessed and to add to ISS/MISSE, for improved mechanistic understanding.

Cosmic-ray dose at ISS Between June 2008 and March 2009, a mean absorbed dose rate of 0.319 mGy day^{-1} was reported for 12 sites within the Japanese module 'Kibo' [34]. In 2022, the mean total absorbed dose reported at ISS was 0.353 mGy day^{-1} over 1584 day based on a passive-dosimeter [35]. The majority of absorbed dose was from low LET particles of < 10 keV and *ca*. 4 % was from high LET particles of > 10 keV. During a journey to, say, Mars, the accumulated radiation exposure will be *ca*. 0.464 mGy day^{-1}, and each day spent on the Martian surface will add an extra 0.210 mGy day^{-1} [36]. Therefore, the ISS dose rate is in the range 0.32 mGy day^{-1} to 0.35 mGy day^{-1} = 0.117 Gy $year^{-1}$ to 0.128 Gy $year^{-1}$, and compares with 0.28 Gy h^{-1} and 3.36 G day^{-1} for beta radiation, and the laboratory-delivered dose-rates of 0.28 Gy h^{-1} and 3.36 G /day^{-1} for beta radiation and 0.10 Gy s^{-1} for alpha radiation. These both are lowest dose-rates practical with our equipment, meaning that 1 h beta radiation simulates *ca*. 2 year ISS. Additionally, 5 h beta radiation simulates *ca*. 11 years at ISS.

Cosmic-ray dose at MISSE A 2021-study reported a mean dose rate of 0.632 mGy day^{-1}, measured at the exposure facility (EF) which is located outside the Japanese Kibo module over a 3-year period from May 2015 to July 2018 [37]. This is greater than the dose rate inside ISS, 0.32 mGy day^{-1} to 0.35 mGy day^{-1} because of the Earth magnetosphere deflecting the majority of heavy-charged radiation.

3.3.2 Alpha radiation

A particle irradiator (Americium-241, radioactive foil source) was used to assess effectiveness of high-atomic number, Concept 2 to shield ibuprofen formulated in tablets from alpha radiation. No apparent degradation was found in any of the 27 tablets following an accumulated dose of 3.1 x 10^{11} Gy s^{-1}, importantly, a value significantly greater than typical space radiation at ISS (*see* Supplementary Material). Seventeen (17) tablets comprised the Base case, API Dilution, Iron oxide, and Titania. With the initial thickness of 15 mm no degradation of ibuprofen was apparent. The tablets were dispersed to a group with 6 mm to 8 mm, and another with 3 mm to 5 mm. With the least thickness of 3 mm tablets exhibited no apparent ibuprofen degradation, most likely a result of the fact that alpha radiation has low penetration depth and the tablet was a compressed, solid matrix, hence the alpha particles were fully absorbed in only a small mass fraction of the total tablet, stopping in a thin surface layer of no more than 20 μm thick.

Pure ibuprofen (powder, 4 mg) without shielding of an excipient matrix was then assessed under alpha radiation. Degradation of ibuprofen was apparent in all three (3) identical samples with content reduced

by 87% to 0.54 mg, Figure 4a.

Thin layer chromatography (TLC) provided a relatively facile means to identify ibuprofen degradation products *via* comparison of elution time, the peak position on the TLC sheet, with known products. Two (2) were selected for comparison that were found in photocatalytic ibuprofen degradation [26]. 4'-isobutylacetophenone was identified, confirming that decarboxylation and oxidation occurred, whilst the known degradation product 4-acetyl benzoic acid was not found [26], Figure 4a. Significantly, 4'-isobutylacetophenone is a neurotoxin with 10 x times greater toxicity than ibuprofen [38].

The finding of one product *via* TLC, Figure 4b, appears a contradiction to the UHLPC analysis showing >10 peaks (= products), Figure 4a. This might be explained by an insufficient separation, vaporization (low boiling point), lack of UV activity, or incapability to be washed out from the excipients because it was not soluble and irreversibly adsorbed. This was not further investigated.

3.3.3 Beta radiation

Strontium-90 radioactive source at 0.28 Gy h^{-1}, equivalent to *ca*. 2 year travel at ISS, was used for a 1 hour beta radiation experiment. For alpha radiation, the 36 tablets comprising the Base case, API Dilution, Iron Oxide, and Titania with a thickness ranging from 15 mm to 3 mm. The accumulated dose was set to reflect *ca*. 5 year space radiation at ISS. Significantly, no tablets exhibited ibuprofen degradation, including the 3 mm tablets and those exposed at greater dose.

Within *ca*. 5 h of radiation exposure, half of the ibuprofen was degraded, Figure 5. Electrons are known to attack with organic matter[39] and ibuprofen at the carboxyl group to give hydroxylated ibuprofen derivatives *via* hydroxycyclohexadienyl radical intermediates[40]. Conditions inside ISS are oxidative promoting beta radiation composition, and those outside ISS reductive. Hydroxylated ibuprofen derivatives were established in the ISS study. Importantly, this means electrons are a part of cosmic radiation that needs to be considered for shielding of ibuprofen from degradation.

3.3.4 X-ray radiation

Tablets were exposed to X-ray photon beams at a peak photon energy of 6 MV generated by a Varian medial linear accelerator calibrated by dosimeters traceable to the Australian Primary Standards Laboratory for ionising radiation. The Base case with significant iron oxide in the coating was compared with a tablet without coating and neither iron oxide nor titania; keeping the Base case-set ratio of API-excipients. Both tablets exhibited reduction in ibuprofen with increasing gamma dosage, however, the greater iron-oxide, coated tablet, exhibited less loss, Figure 6. Maximum reduction in ibuprofen was *ca.* 15 % for the uncoated tablet, which shows that iron oxide is also relevant to protect from X-rays.

An overall comparative summary of ibuprofen tablet (*formulated*) degradation by gamma radiation on Earth is presented as Table 2. Doses of 0.6 Gy and 60 Gy were used. Ibuprofen degradation was up to 21%. Gamma radiation is known to penetrate deeply, including into solid dosage tablet

formulations [41]. Three (3) samples out of five (5) exhibits increase in degradation with gamma dosage from 0.6 Gy to 60 Gy, whilst two (2) exhibit a decrease. The latter could be a result of varying tablet composition, common in tablet manufacturing, Figure S2 and [42], which then would apply to all results given. Degradation is greater for the low Titania case than for high. It is all but absent when using titania and iron oxide as excipients, whilst degradation is apparent when using $CaHPO_3$ only.

These findings are in agreement with those reported that evidence gamma radiation decreased ibuprofen concentration with increasing absorbed dose [43]. A 100 % degradation was found for a concentration of ibuprofen of 28.3 mg L^{-1} and a dose 1.1 kGy. This study identified hydroxylated and isobutyl degradation products were found, findings that agree with those reported [43].

3.4 Space radiation inside ISS - The astronauts' cabin

3.4.1 Ibuprofen degradation under ISS cosmic rays

Table 3 summarizes ibuprofen content from tablets from ISS spaceflight and stored at 'ground' control on Earth (Houston, Texas, USA), as established *via* ultra-high-performance liquid chromatography (UHPLC). Descriptor.

It is seen in Table 3, the ISS tablets exhibit similar reduced ibuprofen content for flight and ground samples, except for 1% Iron Oxide case which lost nearly all ibuprofen (25%). Importantly, six (6) of seven (7) tablets did not chemically degrade significantly following nine (9) month exposure on ISS, and 10 of 19 did not exhibit a significant change onboard ISS (green-color coding). Samples with high ibuprofen content are relatively more degraded, as is evidenced by the yellow-color marking for the seven (7) circumstances, Table 3. The presence of vitamin C reduced ibuprofen stability. Some organic excipients are known to decrease ibuprofen stability, and their own reactive decomposition intermediates might autocatalyze ibuprofen decomposition. The Titania case exhibits reduced ibuprofen content as compared to the API Dilution and Iron Oxide cases.

Tablets inside ISS are largely shielded from mild beta rays or soft X-rays, and it can be reasonably assumed that alpha rays are absent. It is concluded that ISS findings that shielding by an Al-blister combined with solid formulation ensures ibuprofen stability and agree with simulated findings in the herein reported measurements at the Prescott Environmental Luminescence Laboratory (PELL) on Earth (Adelaide, Australia).

3.4.3 TLC degradation analyses

The 1% iron oxide content tablet exhibiting greatest degradation at ISS was analyzed with thin layer chromatography (TLC), Figure 7. The determination of a strong signal of a degradation product confirms the finding of almost complete vanishing of ibuprofen, Table 3. The degradation product is hydrophilic, as it stays on the TLC start-line when exposed to fluid transport with a polar solvent over a hydrophilic solid phase. Therefore, these are more hydrophilic than ibuprofen.

3.5 Space radiation outside ISS (MISSE mission) – Galactic cosmic rays

3.5.1 Ibuprofen degradation under MISSE cosmic rays - (UHPLC)

Six (6) tablets were exposed outside ISS on MISSE platform under harsh conditions of cosmic-rays, Table 4.

UHPLC analyses established ibuprofen content following MISSE exposure. As is evident by orange- and red-color coding of data of Table 5 a significant degradation of ibuprofen occurred *via* exposure to cosmic rays under less protected conditions than at ISS. High iron oxide content prevents significant loss in ibuprofen and Flavor case tablet. The three (3) other tablets including, Base case degraded > 0.5 of ibuprofen content, with the Titania tablet degrading all ibuprofen content. Two (2) tablets had ibuprofen degraded for the (ground) control.

The Titania case tablet, comprising the greatest amount of titania of all, exhibited the greatest reduction of ibuprofen content, Table 5. Titania is known to be a photocatalyst for UV-photon degradation [44], meaning it fosters this pathway of ibuprofen degradation in our study.

The Flavor case exhibited preservation of ibuprofen content. The flavor in each tablet is composed of a mixture of three commercial flavor additives, which themselves are mixtures of flavor molecules. The flavor additive malty-biscuity contains myrcene, a terpene, and acetic cider contains 4-ethyl phenol, having a methylene group activated by the phenol aromatic core. These structures are known to be scavengers of free radicals, produced by collision of high energy electrons with molecules through high energized radiation. It is hypothesized, therefore, that this radical-scavenging mechanism for stabilization has been in place for our ISS and MISSE studies.

It is concluded that the degree of ibuprofen degradation on MISSE platform evidences that commercial shielding by Al-blisters is not sufficient to shield medicine outside spacecraft and space habitats, and possibly, therefore, in deep space of the Moon and Mars, far from LEO.

UHPLC analyses permits determination of the number of degradation products, additional to ibuprofen, Figure 9a. API High Dilution and Base case tablets exhibit > 10 degradation products; most of these are evidenced to the right of the central ibuprofen peak, and two (2) to the left, Figure 8. Degraded product is not meaningfully apparent for Vitamin C and Titania cases, in which ibuprofen content decreased significantly, Table 4.

This finding confirms shows that non-extractable or non-detectable (UHPLC) degradation products resulted.

3.5.2 Ibuprofen degradation under MISSE cosmic rays

Gas chromatography-mass spectrometry (GC-MS) findings compared for Base case tablet against analytical standards confirmed cleavage to 2-phenylpropionic acid and to unidentified (‘unknown’)

degradation products, Figure 9a. Compounds A and B were identified as impurities in commercial ibuprofen by tested and verified with ibuprofen standard.

MISSE tablets were analyzed for ibuprofen relative to 2-phenylpropionic acid and the unknown degradation product(s) together with impurities A and B, Figure 9b. Content of 2-phenylpropionic acid is greatest in Iron Oxide and Base cases. It was present in moderate (descriptor-rated) in three (3) other tablets. The Iron Oxide and Flavor case tablets were found to be stable under MISSE, exhibit degradation only to two or three products, respectively, and not showing a multiplicity of degradation products as in Figure 10.

Liquid chromatography-mass spectrometry (LC-MS) was used to determine all degradation products. Sixty (60) were established in LC, however, just six (6) of these were matched to known molecules in ibuprofen degradation literature [26,45,46] and ibuprofen decontamination databases, e.g. [47] listing 100 impurities. Consecutive products were derived using technically different means of decomposing ibuprofen, including photo-catalytic, photo-catalytic chemically oxidative, thermal oxidative, enzymatic, cavitation, and environmental degradative pathways.

Six (6) molecules were analyzed in detail, providing a semi-quantitative score of the signal intensity for these, Figure 10.

Acetic acid is not commonly reported in ibuprofen degradation; however, it is an essential component of one of three (3) flavor mixtures that were added to all tablets aboard ISS, namely, ‘acetic cider’ (flavoractive). All six (6) tablets, therefore, exhibited strong acetic acid signals of the same order of magnitude. 4-ethyl benzaldehyde was strongest for tablets of Iron Oxide and Titania cases, and is a known degradation product in the thermal oxidative degradation of ibuprofen on Earth. It is an irritant, with a toxicological classification, Table 5. 4-isopropylbenzoic acid is found strongest for the degradation of tablets of API Dilution and Flavor cases, it is also known in thermal oxidative degradation of ibuprofen on Earth, is an irritant and is toxic, Table 5. 4-isopropyl styrene is in greatest amounts formed during degradation of tablets of Iron Oxide and Titania cases. Significantly, it is not reported for the degradation analyses considered, and might show a degradation route with cosmic rays, not been found on Earth. 4-isopropyl phenol exhibited strong signals for all six (6), with the exception for Flavor cases which exhibited a medium signal. It is an irritant and is toxic, Table 5. 2-[4-(1-hydroxy-2-methylpropyl)-phenyl]propanoic acid was evident with strong intensity in four (4) cases, however medium for Base and High-Dilution cases, it is an irritant and toxic, Table 5. Hydroxy-ibuprofens are reportedly part of the natural ibuprofen metabolism pathway and are located in the tissues of liver and kidney, and cells of membrane and cytoplasm [48].

The Titania and Iron Oxide cases exhibited greatest degradation amongst the five (5) detected ibuprofen follow-up products, excluding flavor agent acetic acid. The four (4) other cases have lesser degradation, although still at a medium level. The five (5) molecules are found in all six (6) cases, with the exception of 4-ethyl benzaldehyde, being absent in the Base case. 4-isopropyl phenol and 2-[4-(1-hydroxy-2-

methylpropyl)phenyl]propanoic acid were found with a high degree of degradation in a majority of cases, showing those degradation pathways are superior.

For the two (2) molecules of the six (6) that exhibited no full-molecular match to reported ibuprofen degradation, correspondence to reported chemical transformations is given. Several literature reported degradation products that rely on the same chemical transformation and the five identified products from ISS are representative for this. An oxidation e.g., to a hydroxyl group or elimination e.g., of carbon dioxide, is considered as the main transformation, whilst subtle differences in the outcome are not considered e.g. keto group instead of aldehyde group.

4 Conclusions

Bespoke ibuprofen solid (tablet) formulation concepts for cosmic-ray protection have been used for the first time in a systematic testing of radiation protection for medicinal formulations used in space. Previous reporting on tablets and medicinal formulations at International Space Station (ISS) were commercial pharmacy products.

An excipient matrix is a potent concept medicinal formulation for space drug shelf-life in space, as additionally, is an aluminum cover on tablets for ISS, resembling a commercial shield using Al-blister packaging. Significantly, reported ISS experiments did not use commercial packaging as shield. Importantly, Earth findings confirmed that a solid formulation tablet protects from alpha and beta rays, however, is not sufficient to prevent damage from gamma rays.

Highly significantly, the inorganic materials used for excipients have lunar mineral counterparts and, therefore, have potential to be manufactured in space. Commercial tablets compromise organic excipients. Our experiment demonstrated that use of only lunar-made excipients can be sufficient for a space-manufactured medicinal product.-

It is concluded that commercial ibuprofen formulations would likely not have sufficient shelf-life in lower Earth orbit at ISS. This appears consistent with reported findings on cosmic-ray stability of medicines at ISS exhibiting degradation for particular medicines. Shielding of tablets with only inorganic excipients with high content of iron oxide, evidenced boosted ibuprofen stability and, importantly, without iron oxide the tablets exhibit significant loss. The iron oxide lowers ibuprofen degradation both inside and outside ISS. Flavor additives have apparent shielding, possibly because of ability for radical scavenging.

Because space experiments are ‘on-off ‘events currently challenging to routinely repeat, it is concluded that Earth experiments simulating extreme conditions support actual findings from experiments in space. Earth analyses led to establishing molecular mechanisms and gaining of insight into processes in space and extreme environment(s).

An advantage of combining Earth experiments is that the effect of single radiation sources can be devolved, however, in ISS this is not readily practical. Earth experiments are therefore important.

These Earth radiation experiments, however, cannot directly replace space experiments.

Declarations

Declaration of competing interests

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tables

Tables 1 to 5 are available in the Supplementary Files section

Figures

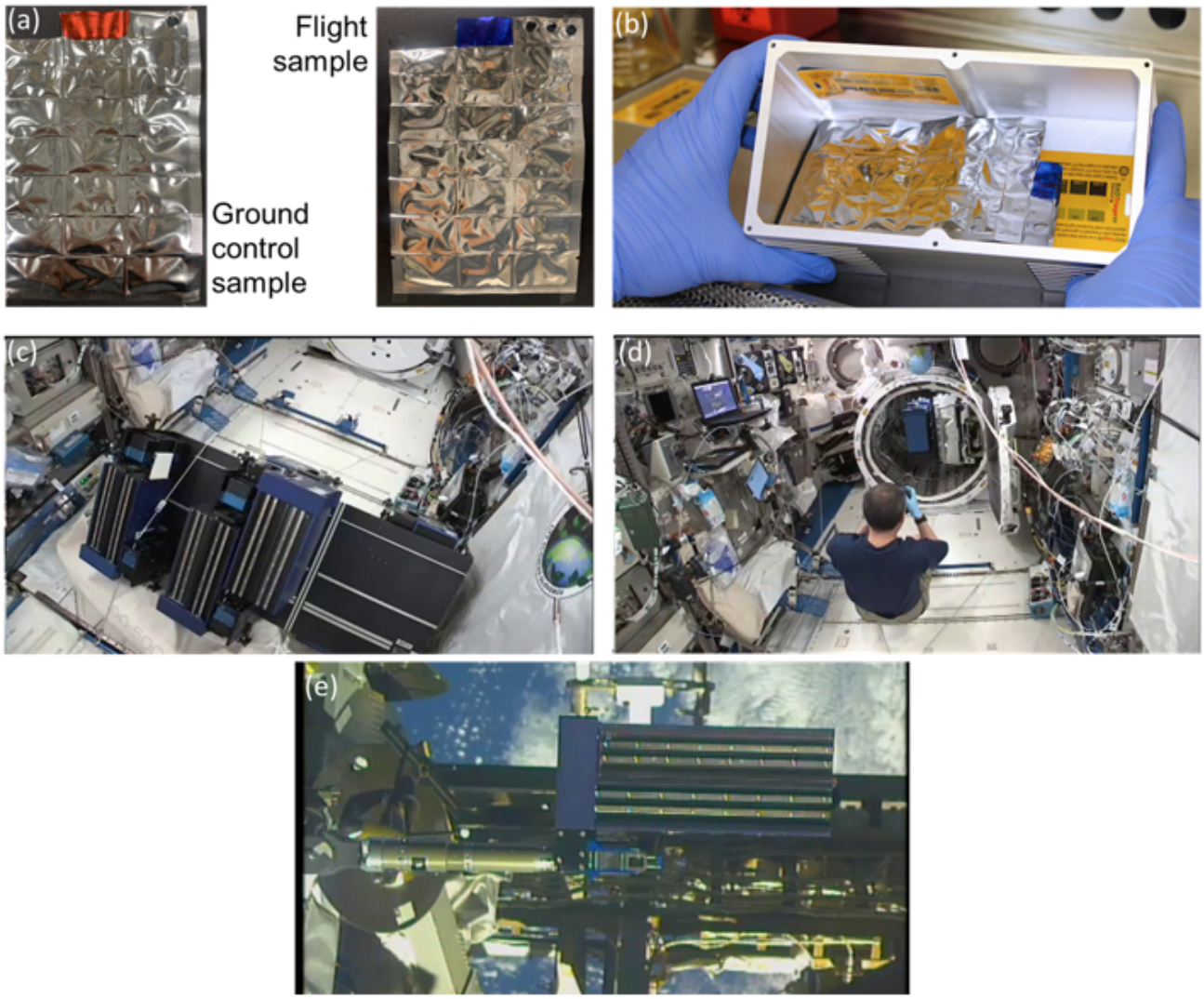

Figure 1

Packaging of ibuprofen specimens for space mission. (a) Tablets are packed in Al-blister that is color-coded for identification for flight (blue) and control (red). (b) Flight samples placed in a storage-cube. (c) MISSE experiment pack containing blister samples assembled at ISS. (d) Discharging of the MISSE experiment package from ISS to MISSE. (e) MISSE experiment pack on outer MISSE platform, outside ISS.

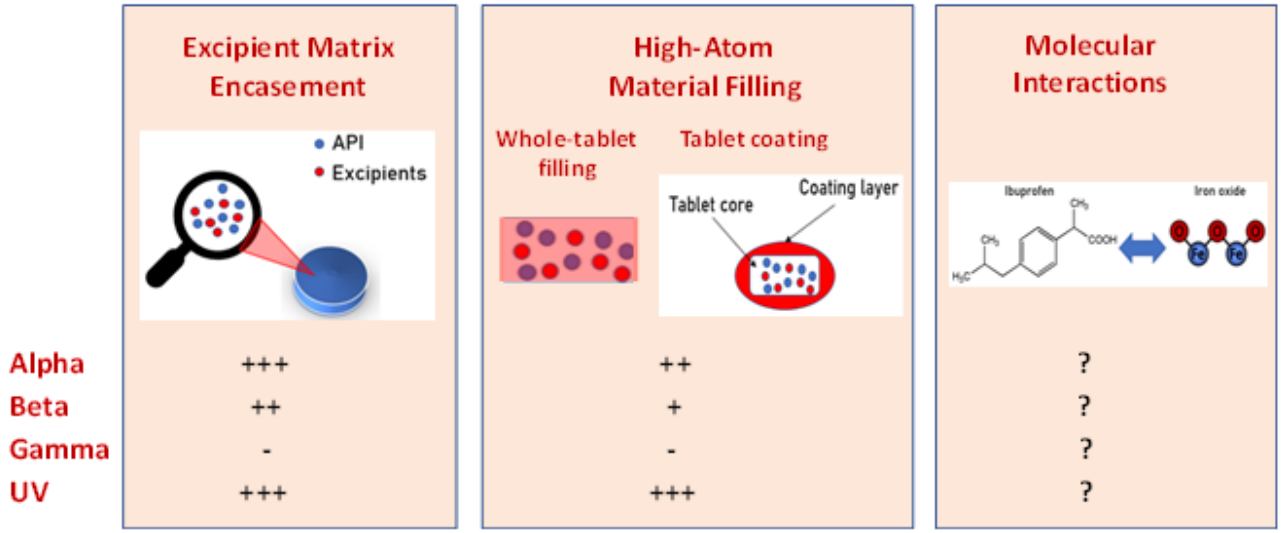

Figure 2

Concepts for radiation shielding used in ISS-MISSE where (+) = expected contribution to radiation protection, and (-) = negligible effect.

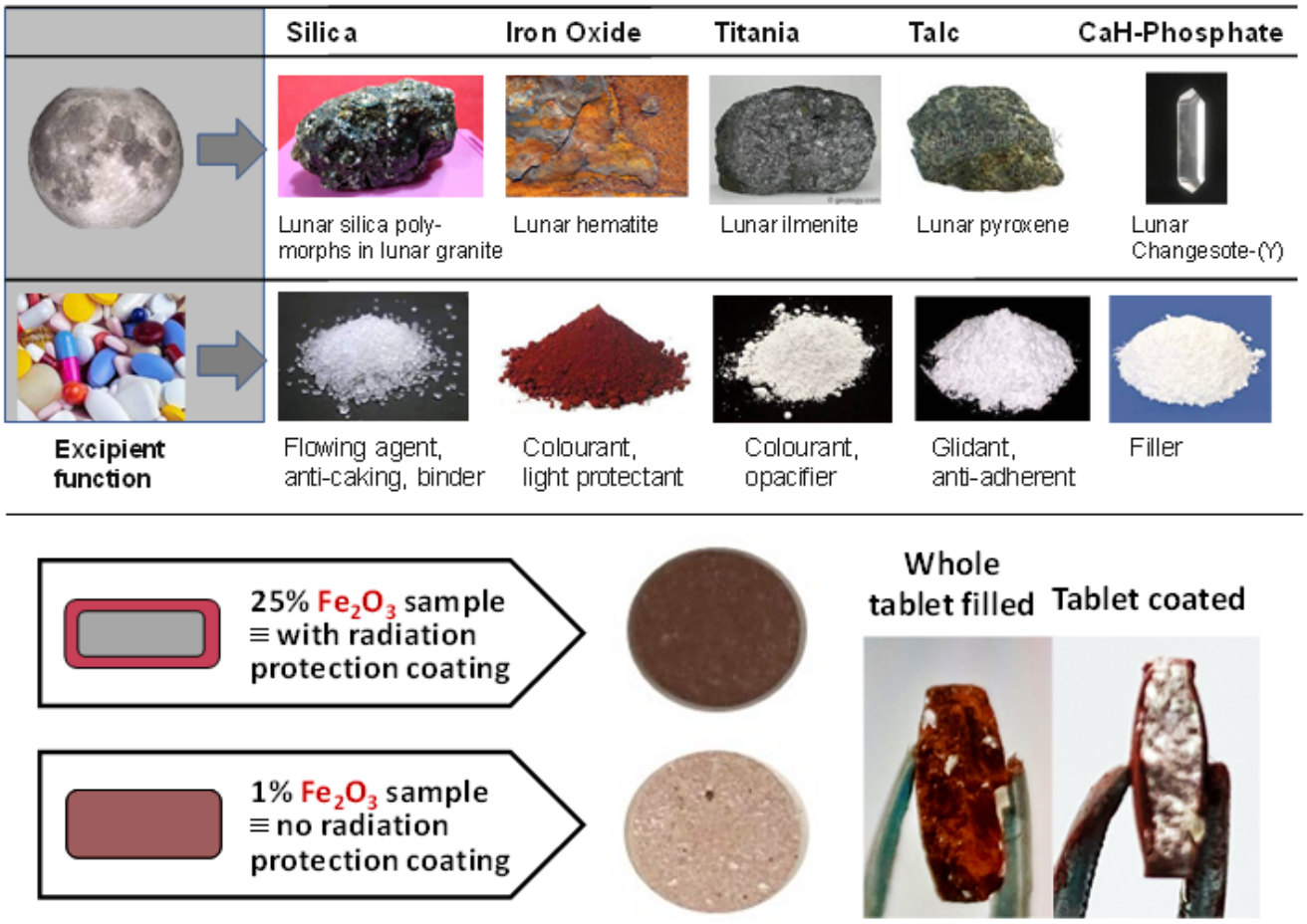

Figure 3

Common inorganic excipients used for making tablets and lunar counterpart mineral, top, and; Heavy coated iron oxide tablet, and low iron oxide coating, bottom.

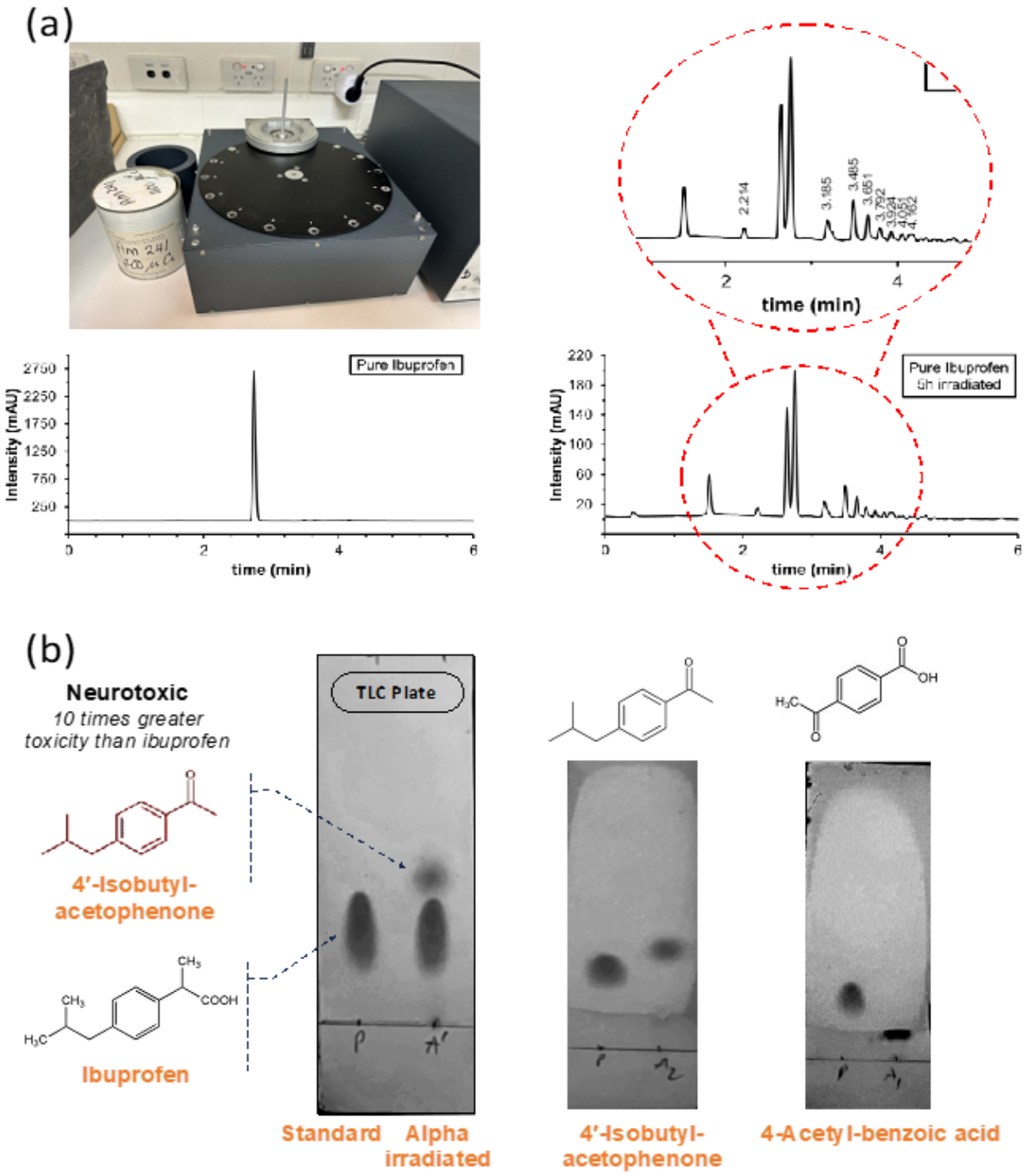

Figure 4

(a) Degradation of pure ibuprofen (non-formulated) by alpha radiation on Earth. (b) Pure ibuprofen (non-formulated) degradation products by alpha radiation on Earth as determined via thin-layer chromatography (TLC).

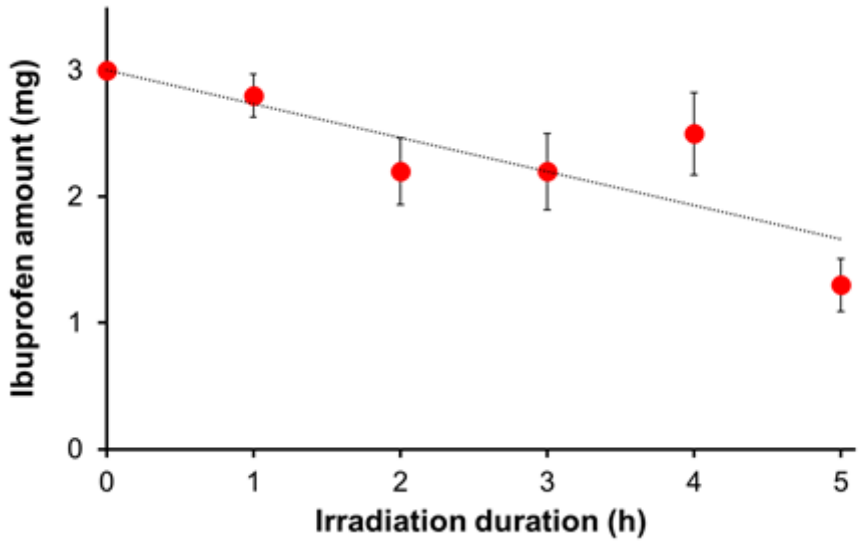

Figure 5

Degradation of pure ibuprofen (non-formulated) by beta radiation on Earth.

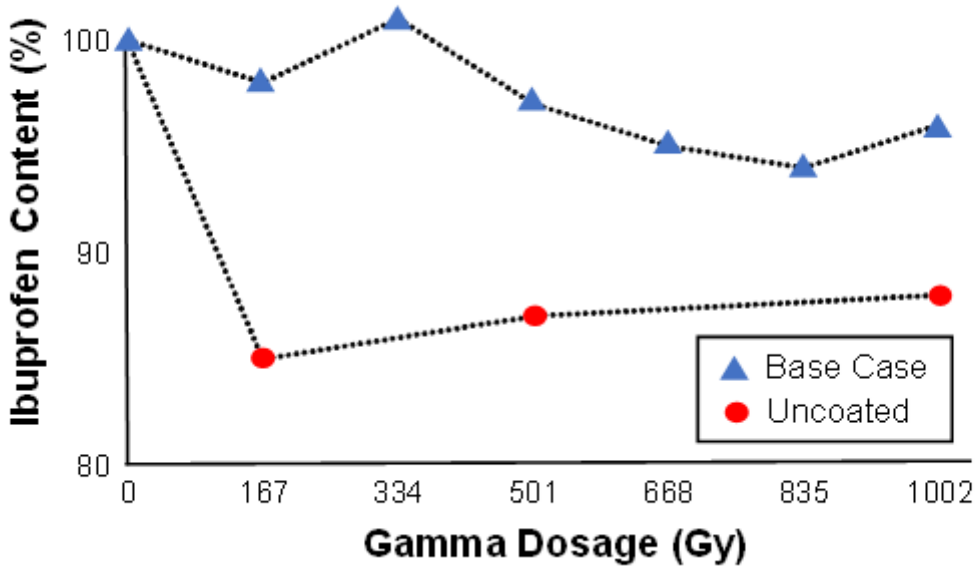

Figure 6

Degradation of ibuprofen tablet (formulated) by gamma radiation on Earth for Base case, coated and Base case, uncoated.

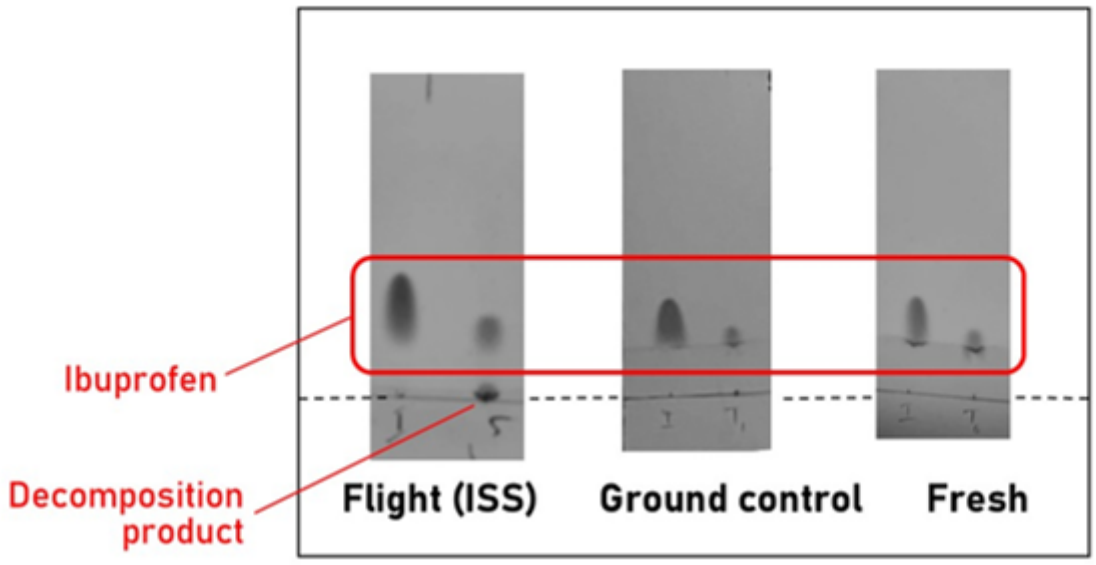

Figure 7

Analysis via thin layer chromatography (TLC) of degradation products of 1% iron oxide tablet exposed at ISS. A strong peak for a degradation product is seen at the start-line for the ISS-TLC.

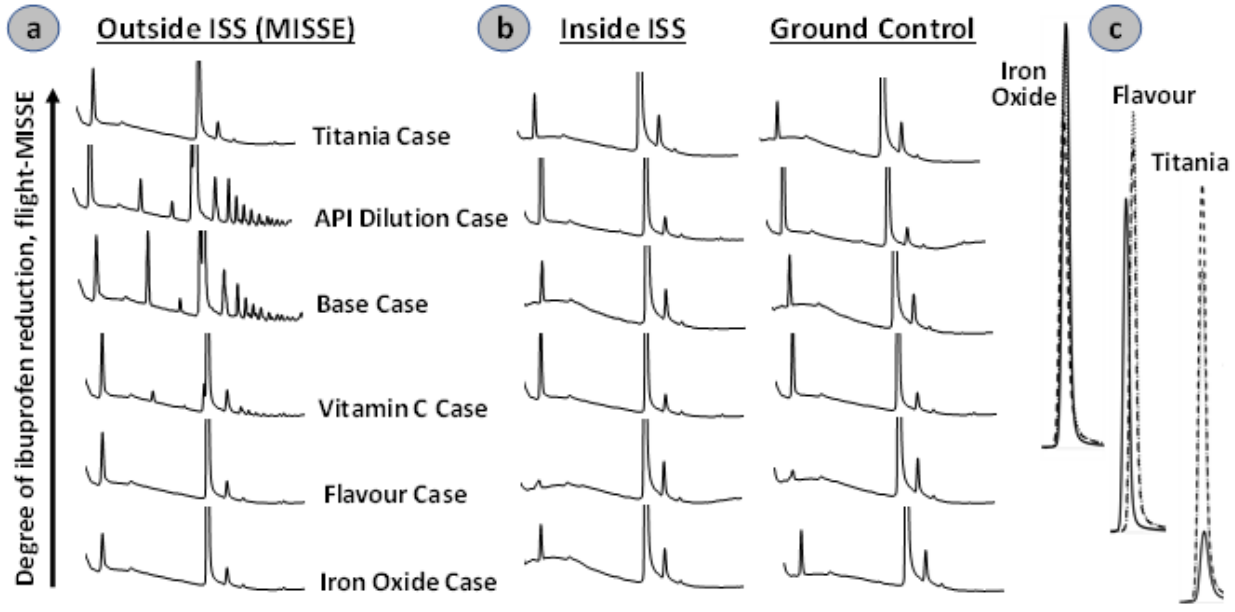

Figure 8

a) UHPLC profiles for tablets exposed to cosmic rays outside ISS at MISSE platform. b) UHPLC profiles inside ISS and ground control samples. c) Ibuprofen peaks for distinct cases.

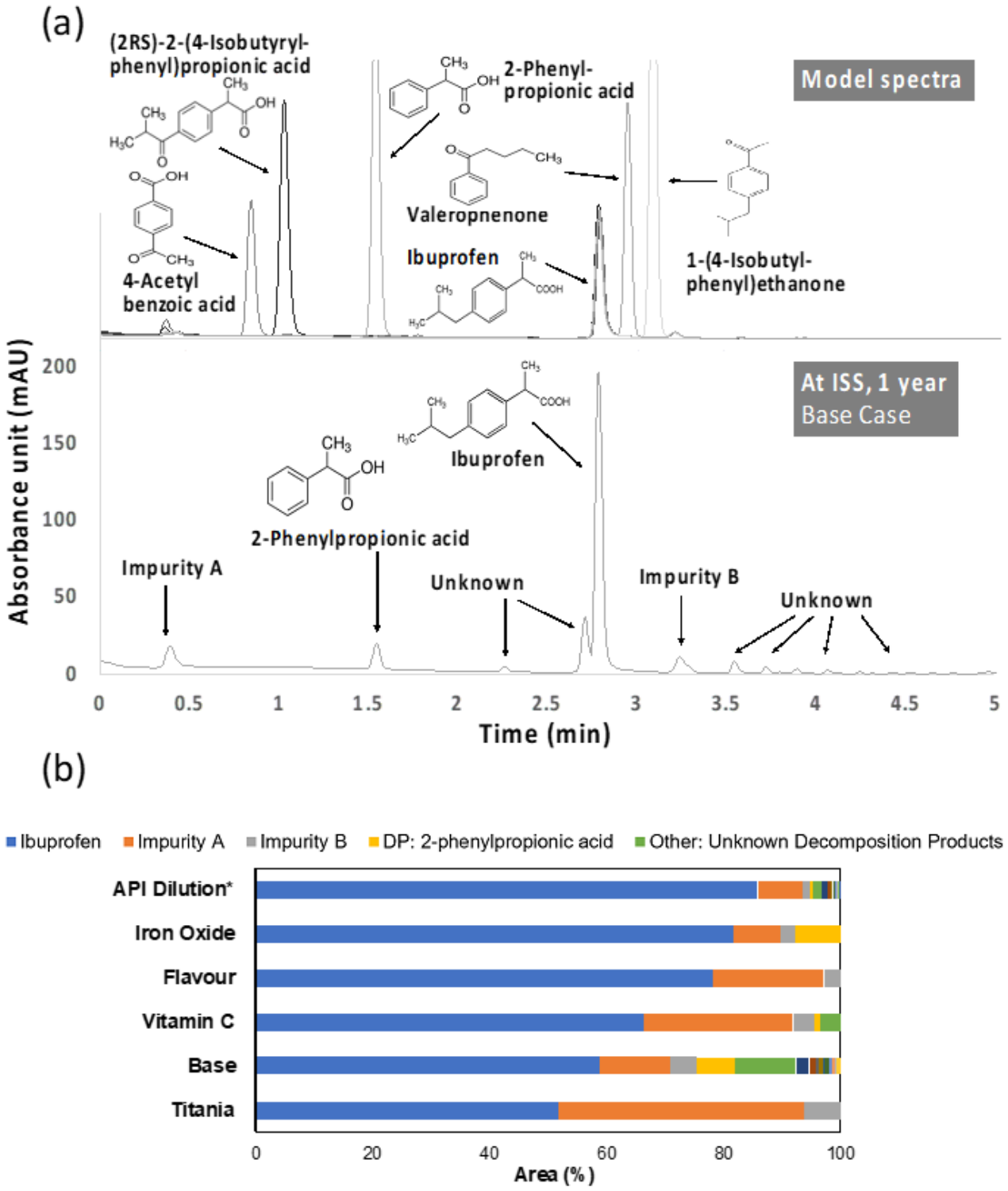

Figure 9

(a) Model spectra for reported ibuprofen degradation products, Top. UHPLC chromatogram for Base case tablet exposed to cosmic rays outside ISS at MISSE platform, Bottom. (b) Share of ibuprofen, impurities and degradation products for different cases of tablets exposed at MISSE as determined via UHPLC.

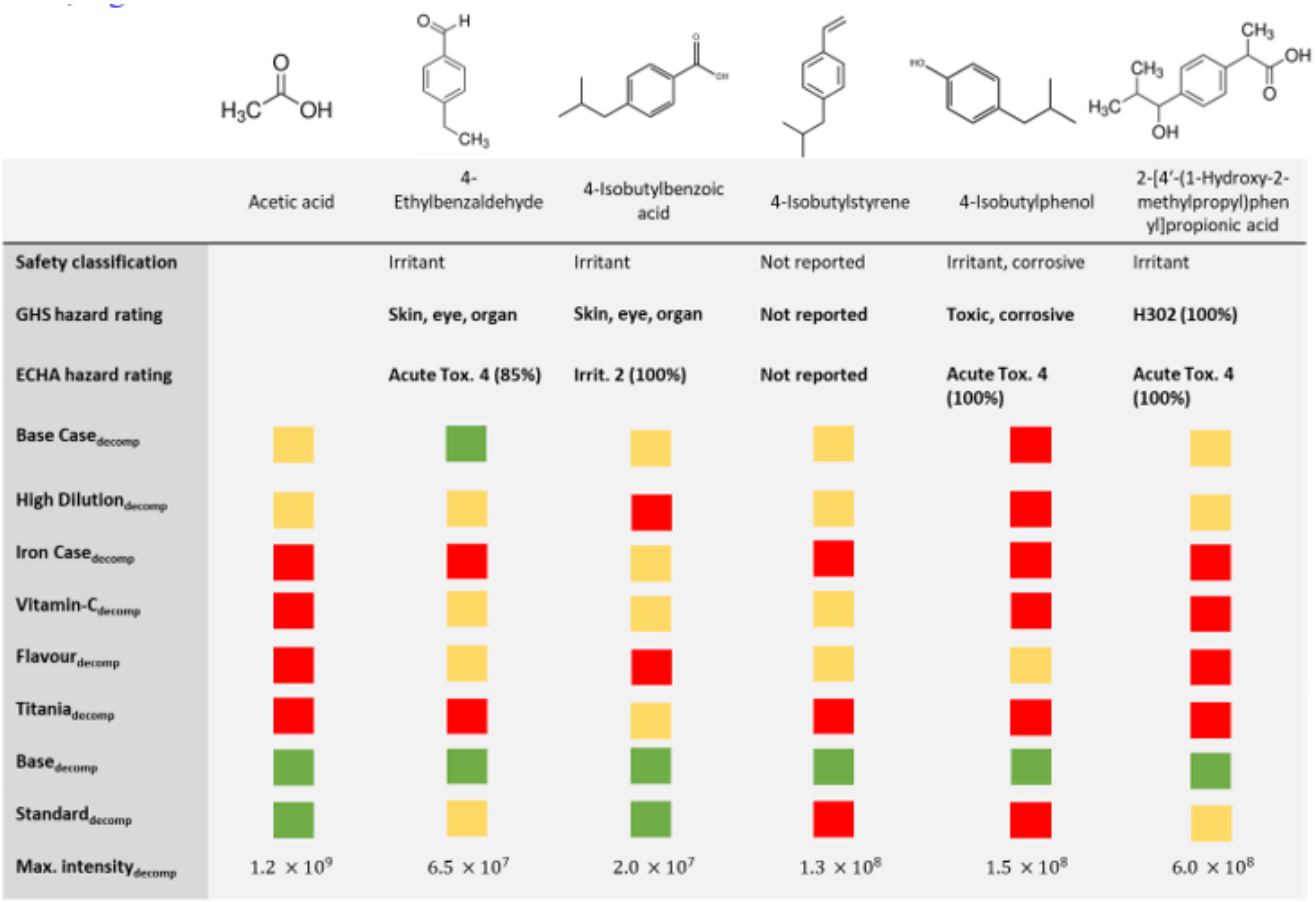

Figure 10

Six (6) ibuprofen degradation products identified via LC-MS, and semi-quantified. Color code is, strong (red), medium (orange) and very weak-absent (green). Maximal intensity is presented.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterialsv5.docx
- Tables.docx