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REVIEW PAPER

A review of the physiological effects of microgravity and innovative formulation for space travelers

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Abstract

During the space travel mission, astronauts' physiological and psychological behavior will alter, and they will start consuming terrestrial drug products. However, factors such as microgravity, radiation exposure, temperature, humidity, strong vibrations, space debris, and other issues encountered, the drug product undergo instability This instability combined with physiological changes will affect the shelf life and diminish the pharmacokinetic and pharmacodynamic profile of the drug product. Consequently, the physicochemical changes will produce a toxic degradation product and a lesser potency dosage form which may result in reduced or no therapeutic action, so the astronaut consumes an additional dose to remain healthy. On long-duration missions like Mars, the drug product cannot be replaced, and the astronaut may relay on the available medications. Sometimes, radiation-induced impurities in the drug product will cause severe problems for the astronaut. So, this review article highlights the current state of various space-related factors affecting the drug product and provides a comprehensive summary of the physiological changes which primarly focus on absorption, distribution, metabolism, and excretion (ADME). Along with that, we insist some of the strategies like novel formulations, space medicine manufacturing from plants, and 3D printed medicine for astronauts in longer-duration missions. Such developments are anticipated to significantly contribute to new developments with applications in both human space exploration and on terrestrial healthcare.

Keywords Space travel · Weightlessness · Fluid shift · Medicine effect · Pharmacokinetic and pharmacodynamic · Stability · Dosage forms

Abbreviations

NASA	National Aeronautics and Space Administration
ISS	International Space Station
ADME	Absorption, distribution, metabolism, elimination
SLEP	Shelf-life extension program
ICH	International Council for Harmonisation
RH	Relative humidity
LEO	Low: earth orbit
IV	Intravenous fluid
IVGEN	Intravenous fluid generation
PK	Pharmacokinetic
PD	Pharmacodynamic
GCR	Galatic cosmic rays
UV	Ultraviolet
GIT	Gastrointestinal tract
CO	Cardiovascular output
PP	Pancreatic polypeptide
VIP	Vasoactive intestinal peptide
CCK	Cholecytokinin
PEG	Polyethylene glycol
FTIR	Fourier transform infrared
API	Active pharmaceutical ingredient
SV	Stroke volume
ANP	Atrial natriuretic peptide
HU	Hindlimb unloaded
UGT	Uridine diphosphate Glucuronlytranferase
OCT	Organic Cation Transporter
IHA	Immune Hemolytic Anemia
HDBR	Head-down bed rest
LB	Loureirin
SMEDDS	Self-micro-emulsifying drug delivery system

Extended author information available on the last page of the article

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Introduction

Space exploration has become an inevitable part of many countries, as NASA (National Aeronautics and Space Administration), together with five other space agencies, including the European Space Agency, Israel Space Agency, Canadian Space Agency, Japan Space Agency, and the Australian Space Agency, has planned for the Artemis program to establish the facilities in the moon for the human mission to longer duration program Mars [1]. In recent years, many companies have come forward for the exploration of space tourism. But, one important task in human space programs is to keep astronauts fit and healthy within the physiological changes caused by microgravity or weightlessness. In the international space station, the drug products were replaced within a year, whereas for the longer duration of the mission, it is impossible to replace the medication [2].

During a six-month mission aboard the International Space Station (ISS) in 2017, the medication consumption of six crew members was monitored using the Dose Tracker system. It indicated an average of 453 prescription uses per crewmember, or around four pills weekly. It was found that there was underreported medication use in medical records from previous space missions without a dose tracker system. That means astronauts were using many medicines and more doses of medicines during space travel to remain healthy [3]. However, multiple factors like physiological changes, psychological behavior, and radiation present in the space environment influence or reduce the effectiveness of the medications used by the astronaut [4].

Some of the countermeasures were adopted for the physiological changes like exercise (treadmills, stationary bike, breathing exercise), adequate hydration, medical monitoring (telehealth), and psychological support (telepsychiatry, telepsychotherapy, and LunaNet) [5–8]. The data from medical records gathered across various space missions highlights instances of reduced pharmacological efficacy of the drug product. These potential changes transpire in two ways one at instability rooted in the physicochemical changes of drugs and the microgravity effect on the absorption, distribution, metabolism, and elimination (ADME).

To better characterize and reduce the danger of a future exploratory spacecraft mission. This review aims to focus on three main sections: the impact of the drugs, alteration in the physiological changes primarily focusing on ADME, and the novel formulation strategies that can be adopted to the astronaut for the longer duration mission. Special attention was highlighted to the novel strategies for formulation, such as nano/micro-sized particles, self-micro or nano-emulsifying drug delivery systems, and the cocrystal. In particular, the space community involved in human spaceflight finds this to be a high-priority disciplinary scientific topic, which poses a significant challenge and presents opportunities for advancing human space exploration. Addressing these issues is critical for ensuring the health and safety of astronauts on long-duration missions, as well as for developing effective medical treatments and countermeasures.

Impact of outer space environment on drugs

During space exploration, stored pharmaceuticals in the space shuttle experience a space environment depending on the length of a space mission. When spacecraft leaves the Earth's atmosphere, it experiences microgravity, hypergravity, radiation exposure, excessive vibrations, humidity and pressure conditions, space debris, highly virulent microbes, and dense vacuum. Along with that, the temperature and humidity will remain under control in the spacecraft [9].

Other challenges pharmaceuticals face are radiations, such as charged particles, galactic cosmic rays, X-rays, and gamma rays deflected into the outer space environment in the presence of the magnetic field. Some highly energetic protons, electrons, and heavy ions are the particles trapped in the Van Allen belts [10]. This trapped radiation and the radiation in outer space will penetrate inside the ISS or the spacecraft. The space radiation will hit the spaceship, fragmenting from highly charged particles into a more significant number of low atomic particles that will cause chaotic radiation inside the spacecraft. For longer space missions, this radiation will cumulate inside the spaceship [11].

Space radiation

Space is filled with various types of radiation, broadly classified into two categories: non-ionizing (low energy) and ionizing (high energy) radiation [12]. Ionizing radiation includes alpha particles (fast-moving helium atom nuclei), beta particles (high-speed electrons or positrons), gamma rays, X-rays, and galactic cosmic radiation (GCR) originating from outer space, solar cosmic rays, and trapped particles. On the other hand, non-ionizing radiation encompasses radio frequencies, microwaves, infrared, visible light, and ultraviolet (UV) light. These types of radiation have lower energy levels than ionizing radiation [13].

When high-energy cosmic rays interact with the atmosphere or spacecraft materials, they produce secondary particles, such as neutrons and secondary protons, contributing to the overall radiation exposure [14]. There are two main ways that radiation reacts. During direct ionization in the absence of moisture or water, the drug product interacts with

the radiation leading to physical and chemical degradation like changes in color, hardness, malleability, solubility, degradation of chemical bond radiolysis, polymerization, racemization, etc. When radiation interacts in the presence of water, it hydrolyses the water molecule. It produces free radicles of water ($H_2O^{\cdot+}, OH, H_3O^+, H^{\cdot}, O^{\cdot}, H_2, e^-$), which are stable for a longer duration and can degrade drugs in liquid and semisolid formulations. It is called the effect of indirect ionization.

There are different case studies showing the effect of radiation on degradation. Once the drug product is flown in the ISS or nanosatellite, the causes of instability concerning the radiation will impact either the drug substance or the inactive substance present on the drug product. Wotring Virginia E. investigated various formulations of Aspirin and Ibuprofen; she found that the formulation of aspirin-containing starch, cellulose, stearate, or dextrose was more stable than alumina or silica contained in another formulation and with ibuprofen brands containing excipients of PEG, polysorbate, and hypromellose shows faster degradation [15]. Bhayani et al. [16] examined the stability in simulated space radiation of amlodipine besylate drug substance and tablet. They found that the additional peak in FTIR analysis by the proton irradiation and two radiolytic impurities detected in LC–MS/MS were caused by the gamma irradiation. Also, diclofenac, ciprofloxacin, and metoprolol were irradiated with the same ionizing radiation. They also found significant degradation in the proton irradiation of the drug substance and tablet. The API solution and liquid dosage are susceptible to degradation once gamma radiation is provided [17].

Vibrations

The vibrations in the spacecraft can be caused by various sources, including the liftoff, propulsion system, thruster and engines, mechanical components inside the spacecraft, and external interactions. In order to do that, solar winds, micrometeoroids, and gravitational forces are considered minor vibrations, but consequently, they will cumulate over a period. Drug products are subjected to high vibrations during space travel; for shorter duration missions like lunar orbital and Low Earth Orbital (LEO) initially, the movement of the spaceship at 1G level (Earth gravity) passes through a hypergravity area with 8-9G at the surface of the Earths sphere and escapes from the Van Allen belts into microgravity, the drug product will experience different gravity (G values) and magnetic field [18]. Simultaneously, for the deeper mission, Mars, the spacecraft must travel different physical environments, including gravity, hypergravity, microgravity, different G values, thruster & engine, and the mechanical components inside the spacecraft. These different physical properties will impair the quality of medicines, affecting the drug product's physical stability [19].

Direct reports are not available regarding the impact of vibration on space medicine. Oakey et al. evaluated the insulin with different packaging to quantify the level of vibration stability during the transit via two drone deliveries. The vibration was significantly higher in both drone transits than in road transport. This Actrapid® insulin passes the BP turbidity evaluation and indicates the absence of insoluble aggregates. Establishing frequency-dependent sensitivity of drug products in different modes of vibration is a precondition to planning for medicine. So, further systematic study is essential to evaluate the effect of vibrations on the physical stability of medicine flown to space [20].

Microgravity and hypergravity effects on space medicine

Numerous factors affect medicinal products, but gravity, hypergravity, and microgravity will have a minor interaction during space exposure. On Earth, due to the gravity effect, dosage forms like injection, suspension, emulsion etc., have less physical stability compared to solid dosage forms like tablets, capsules etc. But in microgravity conditions, sedimentation of suspension and flocculation, coalescence of globules in emulsion will not occur, leading to physical stability of dosage forms. But then, microgravity will influence the packaging model of the liquid dosage form. As both the suspension and emulsion in the conventional packaging don't move upward or downward, they will start to float in the bottle, and the air in the container will not come out and will remain dispersed with the dosage form. Normally, crew members have to spin the container for the content to reach the neck of the bottle, and they will squeeze to expel it [21]. Dispensing such liquid and semisolid dosage forms in the required quantity is difficult in microgravity. There is a possibility of uneven dispensing of the dosage form at the time of use, which can lead to significant variation in the therapeutic action of the dosage form. So, primary packaging material and dispensing techniques are very important in delivering a unit dose of the dosage form at a particular time to astronauts.

Injectables like normal saline 5% dextrose and lactated Ringers are necessary to maintain astronaut homeostasis, as 115 out of 442 conditions of medical disorders have been recognized as potentially requiring IV treatment during space missions [22]. Indeed, it has some limitations in the zero gravity, sucking out the injection from ampoules, bubble inclusion in the IV fluid, the flow of fluid from the cannula, and excessive air present at the injector can't be removed as it was dispersed with the drug. This air embolism, unfortunately, if injected, will cause potentially fatal problems to the astronaut. Apart from that, injectables are available in solid powder form, which can be suspended in water for injection at the time of use. Such dosage

forms are more convenient to handle compared to liquid injectables. Equipment called Intravenous Fluid Generation (IVGEN) was designed and developed by NASA scientists in 2010 to produce sterile IV saline fluid from the ISS potable water using a purification technique. They produced six 1.5 L bags of purified water out of these two bags for 0.9% of the normal saline solution [23]. In 2021, IVGEN mini was developed for mixing techniques and enlargement of IV parental formulation development in the outermost environment. They used two mixing techniques: magnetic stir bar and vibrating wall induced for efficient IV fluid mixing [24].

Stability of medicine in the space environment

As numerous factors cause the instability of drug products in the space environment; radiation is one of the major factors [25]. The Earth's atmosphere and the magnetosphere protect us from various radiation, including ionizing and non-ionizing radiation. Various kinds of ionizing radiation like X-rays, gamma rays, and high Z energetic particles like protons, neutrons, and electrons [26, 27]. Radiation plays a major role in the instability of drug products like solar cosmic rays and galactic cosmic rays. All these radiations were produced from the stellar cloud collisions and the radiation trapped into the Van Allen belt [28].

The insights of stability analysis can determine the shelf life of the drug product. The ICH International Council for Harmonisation structured the stability guidelines corresponding to the mean temperature and associated humidity conditions [29]. However, the expert working group analyzed all the parameters of environmental conditions in various regions. After several research investigations, they drafted the guidelines for ICH Q1 [30]. In addition to that, the FDA further investigated the pharmaceutical under the (SLEP) Shelf-Life Extension program. This SLEP analysis has extended the shelf life of many pharmaceutical drug products [31]. However, the crewmembers' safety must be ensured with the proper conception of how drug products behave in the unique space environment. NASA and other space agencies have implicated a forthcoming number of research works specifically to understand pharmaceutical instability [32].

Some pharmaceuticals are heat liable, affecting the drug product's shelf life. Astronauts commonly use drug products such as lidocaine, amoxicillin, melatonin, and olanzapine as they are heat-labile [33]. Drastic changes in the temperature in the space will affect the active moiety of the drug product. Unfortunately, when consumed by astronauts, this formed degradation derivative in the drug product may cause severe health problems [34].

Microgravity: human physiological variability effect on drug bioavailability

Exposure to the microgravity (μG) environment of space flight causes several physiological changes in the body. As of today, most of the physiological changes experienced in space have been fairly well characterized and understood. The human body's homeostasis pathway will be strongly influenced by gravitation that monitors various routine processes and takes appropriate action as required. Exposure to microgravity, cumulative radiation, altered circadian cycle, and psychological shift will heavily impact the homeostasis pathway in chronic space conditions. Altered human anatomy and physiology will adapt to the spacecraft environment, leading to space adaptation syndrome and alternation in homeostatic system development. This altered homeostatic system affects several biochemical processes, including processes that take part in drug absorption, distribution, metabolism, and elimination (ADME) properties in the body. Currently, the intake of medicine by the astronaut will significantly influence ADME, reducing the drug's potency and efficacy. Here, we will discuss different changes observed in humans in microgravity conditions and their impact on the efficacy and safety of medicines.

Gastrointestinal modifications

In spaceflight, most of the drugs are consumed by the oral route, yet an alternate route of administration will have tactical difficulties, as mentioned above. For oral medications, it is important to get absorbed from GIT for drug efficacy. Alteration in stomach empty time, intestine transit rate, and gut microbiome can lead to alteration in drug efficacy and, finally, PK/PD. Apart from that, drug dissolution in GI fluid also gets altered due to alterations in the solubility of solid drug particles in the surrounding liquid [35]. The study conducted by Afonin BV on astronauts under microgravity states that gastric and pancreatic secretion levels increase. These changes of increased secretion of gastric juice and lowered pH might be caused by the hemodynamic changes in the venous of the abdominal body part. Further, the studies of 4 months of bedrest affirm the increased level of pepsinogen in the blood and the urine sample [36].

Several investigations on EUROMIR-94 mission regarding the gastric content analyzed that the level of pancreatic polypeptide (PP), secretin, motilin, and vasoactive intestinal peptide (VIP) were increased in the fasting period; subsequently, the plasma cholecystokinin (CCK) level decreased. Additionally, on chronic conditions for

4 weeks, there is an increasing level of CCK, VIP, neurotensin, motilin, and insulin. But PP, gastrin somatostatin, and motilin levels remain the same [37].

Stomach emptying time

On chronic microgravity exposure, the fluid content in the stomach will be altered, leading to two main essential factors that will affect the PK/PD of the drug profile [38]. Such factors are the kinetic moment of solid and liquid matter. The physical properties of the drug and the content inside the stomach will changed during spaceflight. Microgravity conditions may significantly affect the stomach's ability to distinguish particle sizes. Since no gravitational force can discriminate between a high- and low-density particle, no dependence on density would be anticipated. The kinetic energy of a drug, especially its velocity due to pressure effects produced by the stomach, drug particle/particle present at the stomach, and drug particle/gastric wall collisions, would thus appear to be more critical for emptying the GIT [39]. As some drugs are absorbed in a particular window of the GIT, during microgravity exposure, the food and drug intake will remain in the stomach for a more extended period as no gravity is acting on it. It will float in the fluid content, and the drug's kinetic energy will remain to move toward the lower pyloric sphincter. In this case, the stimulation of the peristaltic moment will be delayed as the fed state content has to reach a particular area, and it takes a longer time for gastric emptying compared to the terrestrial condition [40].

Intestinal transit rate

During space flight, microgravity will cause cardiovascular deconditioning, reducing the splanchnic blood flow and a higher rate of space motion sickness, which triggers the vestibular otolith organ. This stimulation will alter the acid secretion and modify the normal electrolyte balance [41]. This changes the muscles' ability to contract, which disrupts the rhythmic contractions of GIT and, eventually, disturbs the usual pattern of intestinal transit and gastric emptying. Consequently, drugs like diphenhydramine, aspirin, and ibuprofen are to be rapidly absorbed to treat immediate symptoms. The weakly acidic drug shows its maximum absorption in the stomach due to longer stays in the stomach. But for the weakly basic drugs, the absorption will take place in the intestine as there will be a delay in the disintegration/dissolution of the drug product in the gastric fluid, slowing of the kinetic moment, and delay in the contraction of the peristaltic tone will affect the PK of the drug product [42].

Gut microbiome

Specific cues like nutrition, lessened or inadequate caloric intake, changes in circadian rhythms, drug intake, confinement, radiation, and other conditions (microgravity, light–dark cycles) will significantly affect the function and composition of the gut microbiome [43]. Several investigations on gut microbiome were conducted on both spaceflight and ground-based analogs. Considering all the stressor factors of space conditions to the animal and human studies on the gut microbiome, dysbiosis shows the implications on gastrointestinal disease and metabolic variances [44]. Voorhies et al. investigated the astronaut microbiome in the international space station for one year, and they found that alpha diversity and richness of GI microbiota were significantly raised during the spaceflight at ISS. Indeed, the results show a relative abundance of Parasutterella in the GI microbiota, positively associated with inflammatory bowel disease. Further, there is a decrease in the GI microbiome of Pesudobutyvibrio, Fusicatenibacter, and Akkermansia, the bacterial gene with anti-inflammatory properties. These changes resulted in moderate increases in inflammatory responses, which were also observed in the crew members during the space flight [45]. Further, the studies by NASA on twin subjects confirm the alteration of individual gut microbial communities, which causes inflammation of the intestinal tract. However, it remains unclear whether this will put the astronaut at risk [46].

Since the direct observation of drugs on the increasing level of space gut microbiome has not been studied, some of the investigations provide that the gut microbiome has a direct and indirect effect on drug metabolism. Digoxin has been used for atrial flutter, atrial fibrillation, and heart failure; *Eggerthella lenta* present in the intestine shows a direct modification of digoxin. This modification leads to inactivation with the potential for variability of drug concentration and toxicity. Further, the investigation on the tacrolimus with *Faecalibacterium prausnitzii* exhibits a keto-reduced product. Moreover, the second-generation cephalosporin, cefprozil, showed an indirect action on the CYP enzymes, particularly decreasing the activity of CYP1A2, CYP3A4, and CYP2C19. Likewise, the diverse and healthy microbiome was essential for the appropriate function of drug-metabolizing enzymes, but caution should be taken on the intake of drugs metabolized by CYPs [47].

Effect on cardiac deconditioning

Astronaut body fluid is transferred from the lower part of the body to the upper thoracic region. It will appear as a puffy or moon face in the initial stages. This exposure will substantially decrease pressure in the intrathoracic area that simultaneously affects the cardiac muscle to expand, along

with the reduction of central venous pressure. In the early stages of microgravity, the size of the heart chamber expands by 20% [48]. On chronic adaptation to the space, the cardiovascular output (CO) and the stroke volume (SV) increased by 35 and 41%, which causes the stretching of atrial muscle to release an enormous amount of atrial natriuretic peptide (ANP) and messenger cGMP. This increases vascular permeability and shifts the intravascular fluid and electrolyte to the extravascular system (Fig. 1) [49].

Starling-Landis proposed a hypothesis that the gravitational fluid flow has four forces that will maintain the fluid equilibrium between the intravascular and the interstitium: plasma and interstitial colloid osmotic pressure, capillary blood, and interstitial fluid pressure. When entering microgravity, members will face cardiac deconditioning with the following mechanism: decreased sensory and mechanical stimulation and reduced hydrostatic pressure [50]. This mechanism will alter the Starling-Landis hypothesis, stating that in microgravity, both the acceleration and tissue weight drop to zero and thus decrease interstitial fluid pressure and increase transmural pressure [51, 52]. Furthermore, the reduction of hydrostatic pressure on the crew member does not correlate with vascular capillaries and tissue fluid, as the precapillary sphincter and vascular tone control them [53, 54]. Several investigations on the ISS, Apollo astronauts and subsequent missions on the simulated cardiovascular studies reveal that cardiac deconditioning can also occur by greater carotid-cardiac (baroreflex) vagal sensitivity reduction [55, 56]. This diminished baroreflex sensitivity affects heart rate control and augments the muscle sympathetic nerve activity. After the post-space mission, the astronauts face orthostatic intolerance; nearly 65–70% of the crew members faint upon returning to Earth [57–59]. Thus, baroreflex attenuates both the heart's vagal control and carotid parasympathetic, illustrating the increased heart rate during orthostatic intolerance [60]. As the cardiac deconditioning continues in long-duration space travel, the plasma volume decreases by 15–18%. Reduction of plasma volume (hypovolemic condition) will alter the drug-receptor interaction. This will result in reduced hepatic blood flow, which leads to the inability of drugs to metabolize, thereby decreasing the clearance. This condition of microgravity changes the function of ion channels or, affects the drug products' pharmacokinetic and pharmacodynamic profile [61, 62]. So far today, only six human studies have been carried out to analyze the pharmacokinetics of scopolamine/dextroamphetamine and acetaminophen during space travel [63].

Moreover, adaptation to microgravity will decrease the RBC count level by 10–12%. This adaptation was due to major hemodynamic circumstances such as fluid shift, cardiac deconditioning, bone and muscle density loss, hemoglobin concentration, and low erythropoietin [64]. Research studies onboard ISS for the longer duration mission will potentially induce hemoglobin degradation, as there was a 54% increase in hemolysis observed on the postflight [62, 65]. Simionato et al. investigated the *in-vitro* approach of erythropoiesis in different levels of pO_2; it shows that at the hypoxia stage, the RBC counts increased. These produced

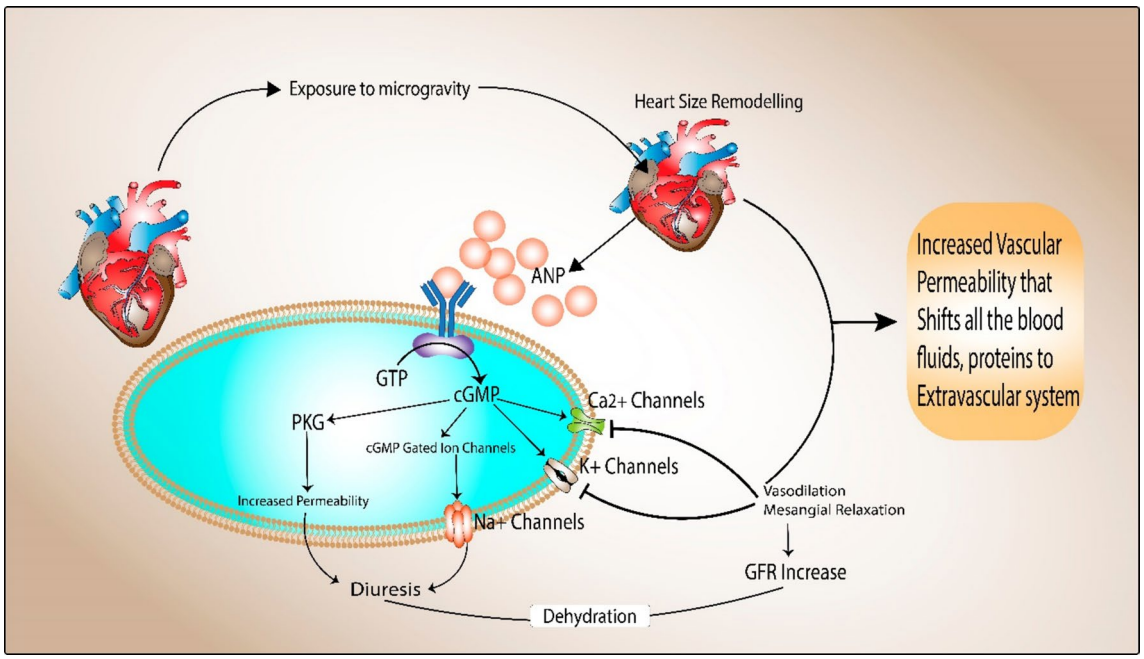

Fig. 1 Alteration of blood circulation in microgravity leads to heart remodeling, increased ANP peptide, activation of cGMP pathways, diuresis, and vascular permeability shifts, resulting in moon face appearance

reticulocytes have a significant difference in concavity, reduced cell volume, and higher levels of glycolytic activity compared to a higher level of oxygen [66, 67]. Moreover, they confirmed no changes in the cell deformability, cytoskeletal protein, and enzymes. At the initial stages of spaceflight, there is an increasing level of RBC count (reticulocytes), and beyond 10 days, the concentration of hemoglobulin proceeds to normal as in the Earth's condition [68]. This increases the hematocrit level in the plasma; as the crew members are exposed to the chronic condition, the drug binding to RBC is higher, which causes a lower clearance level. Zhu et al. examined the effect of higher altitude exposure on acetaminophen and metformin hydrochloride to analyze the pharmacokinetic parameters. As the $t_{½}$ and AUC of these drugs were significantly decreased, the following clearance and bioavailability decreased. Further, they quantified the protein expression of uridine diphosphate glucuronlytransferase UGT1A1 and organic cation transporter OCT2. Both the protein and mRNA expression were significantly reduced under the higher altitude. So, the pharmacokinetic and pharmacodynamic investigation should be reconsidered for the optimal dose for the astronaut during microgravity exposure [69].

Effect on drug-plasma protein binding

Daria et al. investigated 18 cosmonauts to quantify 125 proteins in the blood plasma. The samples were collected 30 days before the launch and the 1st and 7th days after the mission. They analyzed 19 proteins showing significant differences; the levels of S100-A9, a myeloid zinc and calcium-binding protein, significantly regulating the immune and inflammatory process increased [70]. The concentration of this protein increases its extracellular function, including antimicrobial, proinflammatory, and apoptosis-inducing activities. This protein can be predicted for the risk of myocardial infarction, recurrent cardiac attacks, and atherosclerosis.

Moreover, all the other proteins were reduced to maintain homeostasis in the microgravity environment, and these decreases in the protein concentration were caused by other factors such as emotional stress, overloads at the landing stage, and alteration of cardiac rhythm [71]. To determine the pharmacokinetics of the drug product, drug-protein interaction plays a crucial role as the protein-drug binding has the potential to change over the drug's half-life and is an important observation over the longer mission duration [72]. It plays a major role in the bioavailability and distribution of API or drug, as a higher molecular mass of complex protein-drug binding will be limited to crossing the biological membrane [73]. In addition, reduced plasma in the microgravity condition will ultimately reduce the protein concentration in the intra-vascular region. Since only a limited number of proteins will attach to the natural active compound, the concentration of drugs in the tissue binding increases. This leads to saturation or supersaturation of the receptor, which will significantly reduce their pharmacological action [74].

Effect on drug metabolism alterations

As the crewmember travels on a long-duration mission, the hepatocytes in the liver modify its configuration and dimensions. The activity of metabolism and detoxification will significantly impact the drugs taken by the crewmembers [75]. Zhang et al. investigated the simulated microgravity effect on liver enzymes and pharmacokinetics studies of Folic acid in rats. They analyzed that Folic acid was metabolized by methyl tetrahydrofolate reductase, Methionine synthase, and Cystathionine beta-synthase. The expression of these enzymes was modified on a four-week simulated microgravity tail suspension model that decreases the AUC and Cmax of folic acid [76].

Zong et al. examined the liver metabolism in rhesus macaques on long-term microgravity exposure. This study carried over a 42-day head-down bed rest (HDBR) simulated model in which they analyzed the level of both transcriptome and metabolome [77]. The livers of HDBR monkeys accumulated fat vacuoles and inflammatory cells, and there was minor liver damage and an increased level of ANGPTL3 in the blood [78]. The liver sample analysis also found the down and up-regulation genes of innate immune and lipid metabolism. Ranade et al. investigated the hindlimb unloading (HU)-induced hepatic cellular processes in mice. The controlled and HU groups were treated daily with the vehicle and 4-phenylbutyrate. They examined that HU models express hepatic atrophy with down-regulation of genes involved in liver metabolism. This significantly affects the signaling pathway associated with cytochrome P450 [79]. One of the Cytochrome P450 enzymes, CYP2D6, was responsible for the metabolism of many drugs, as codeine which is metabolized into morphine. The microgravity causes the CYP2D6 to accelerate into a rapid metabolizer that can lead to unfavorable respiratory complications. Another CYP enzyme, CYP3A4, was most abundantly present in humans and highly sensitive to the metabolism of drugs [80]. Uncertainly, if microgravity induces this enzyme, it will reduce the efficacy of the drug product consumed by the astronaut, and there is the possibility of taking additional doses, which can lead to potential toxicity to the crewmembers [81].

Chen et al. Investigated the Loureirin B (LB), a compound used for pain relief and improving blood circulation of astronauts from Microgravity and radiation. They examined the lead metabolite using a rat liver microsome in the simulated microgravity and their isoform changes in the Cytochrome P450 [82]. It was found that the LB follows

the Michaelis–Menten equation, and the CYP enzymes involved in metabolism are CYP1A2, CYP2D1, CYP2C11, and CYP3A2. The study suggested that the clearance of LB was increased by the 3rd day and 14th day of simulated microgravity. Anselm et al. investigated the potential alterations in the metabolic pathway of the mice floating on the spaceflight project "Bion-M1". They analyzed the proteomic expression of 12,206 peptides, and 1086 proteins were identified using mass spectrometry. The data shows that 218 proteins were upregulated and 224 down-regulated after the post-flight adaptations. They also found that peroxisome proliferate-activated receptor pathways and bile acid secretion are altered due to increased reconstituted protein levels and CYP family expression.

On the other hand, mice that remained 30 days in space showed enhanced CYP2C29, CYP1A2, and CYP2E1 levels. The former two CYP subtype contents reverted to the baseline level seven days after landing, while the enhanced CYP2E1 expression remained significant. Rats flown for 12 days had more CYP4A1 than usual, but the other CYP genes evaluated did not alter [83]. For a preclinical investigation, animal models were utilized to predict the pharmacokinetic similarity before initiating clinical studies. The Fig. 2 summarizes the different CYP enzymes present in the human and animal models for both the space and simulation studies [84–87].

To summarize the above physiological alteration with the pharmacokinetic and pharmacodynamic data suggested to support the development of strategies for the optimal doses for the astronaut during long-term spaceflight, cardiac deconditioning, protein binding, GIT modifications, liver metabolic processes, and the gut-liver axis should be continuously examined for the safety of crewmembers.

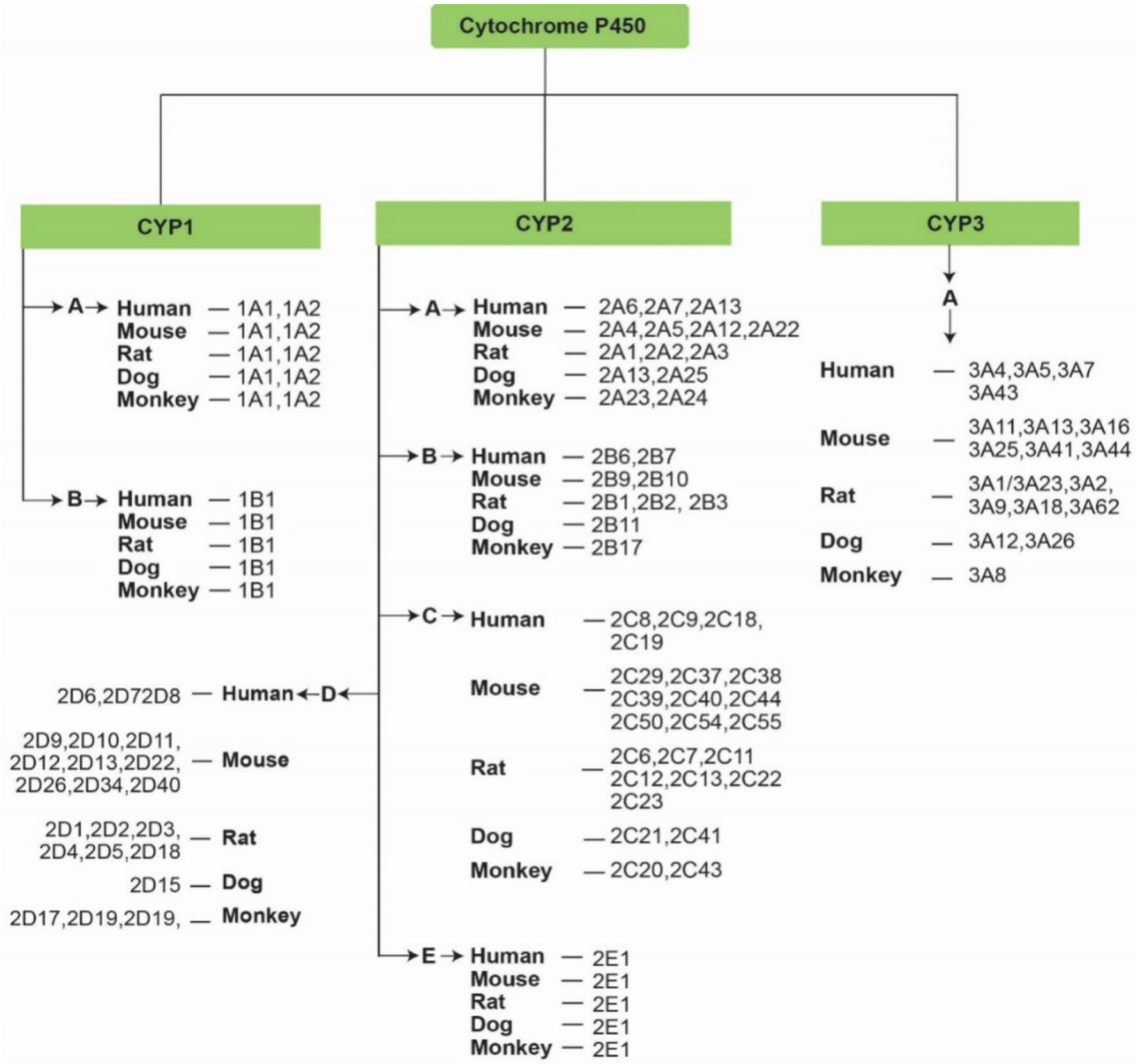

Fig. 2 Comparative overview of CYP enzymes in human and animal models for space and simulation studies

Novel strategies for space pharmaceutical formulation

Stability issues of drug products can increase during long-duration missions, which ultimately reduce the pharmacological effect of the drug. Some strategic approaches can be used to overcome these instability issues of drug products. Moreover, pharmaceutics formulation insights have evolved in many research aspects using computational modeling and molecular dynamics [88, 89]. Recently, In-silico modeling has evolved in predicting the solvation and crystallization formation ability with different solvent molecules. Later, the AI and machine learning era gained minimal laboratory work with cost efficiency. Along with these techniques, molecular quantum physics has evolved to predict the drug payload in different nanocarriers, such as lipids and polymers. These molecular dynamics simulations will provide insight into different excipients with drugs. Additionally, we insist that some of the novel approaches can be implemented for the astronaut's longer duration mission (Fig. 3).

Use of antioxidants as an excipient in formulations

Medicine excipients, including pyridoxine, nicotinamide, and mannitol, will have radiation-protection properties that have been proven terrestrial in sterilization. Another alternative was the addition of antioxidants; if the dosage form has reactive oxygen species, it will lead to its instability. In addition, changing or including excipients in the regulation must illustrate the drug product's safety, potency, and efficacy. The approval of this drug product will be treated as the regulatory process for a new drug product [90].

Novel drug delivery system

The administration of smart drug delivery systems provides various advantages over the conventional dosage form not only in terrestrial conditions but also in the case of microgravity conditions, as the gravitational vector G values play a major role in the aggregation or flocculation of the nanoparticle/nanoemulsion. In microgravity conditions, reduced gravitational force G values will have the advantage of increasing the stability of the nano and microemulsion.

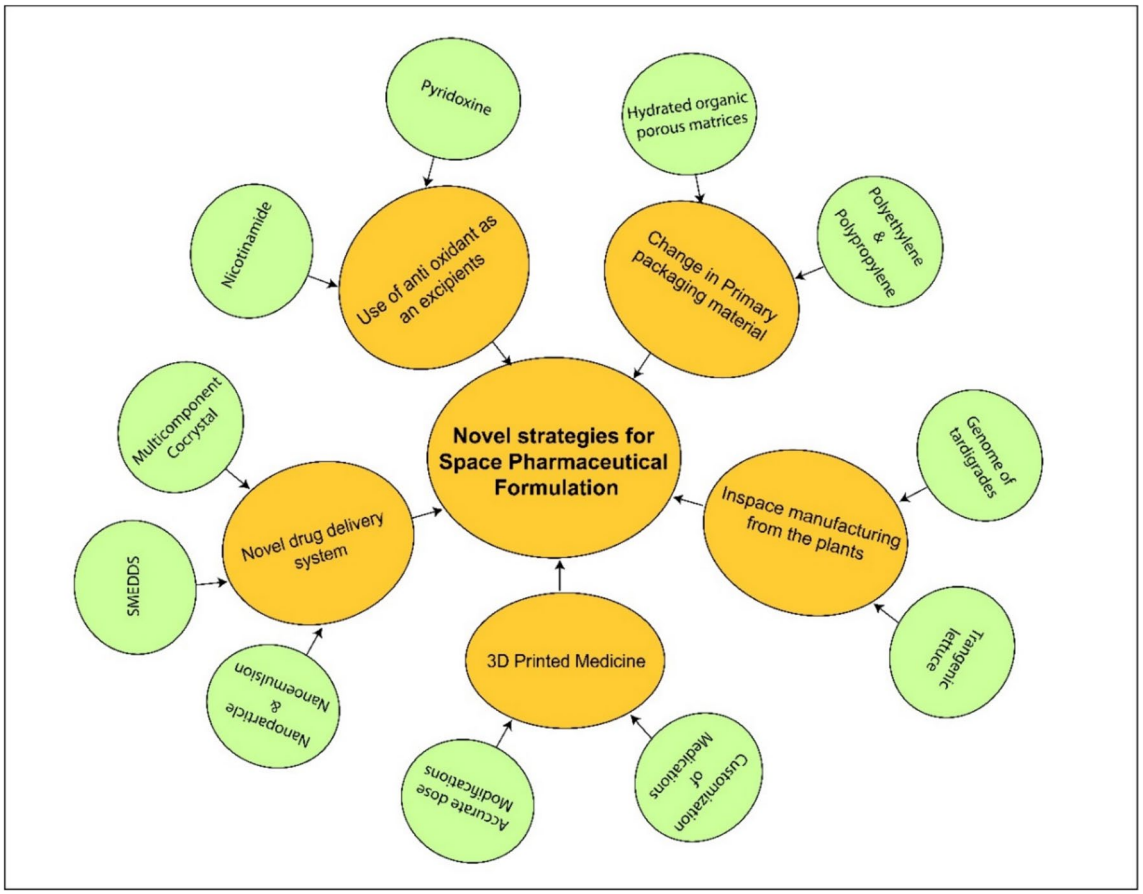

Fig. 3 Innovative astronaut pharmaceutical strategies

Dantuma et al. investigated the stability of nanoemulsion in microgravity conditions using a 3D clinostat. They found that the nanoemulsion of various dosage forms was stable throughout 7 days, in which the globule size of the formulation was also reduced [91, 92].

Nanoparticle and nanoemulsion

In addition, nanoparticle transport through a specialized uptake mechanism enhances the bioavailability of the dosage form. Likewise, it protects the drug from hydrolytic and enzymatic degradation by encapsulating it with polymeric nanomaterial. They also provide targeted drug delivery by attaching some conjugates with the polymer. Moreover, it will provide the photostability of the photolabile drugs. The desonide was loaded into nanoencapsulation using an oil core acai oil and medium chain triglycerides; it was found that the nano-encapsulated formulations show photostability against UV-A and UV-C radiations. Acai oil prevents the desonide from photodegradation rather than medium-chain triglycerides [93]. The solid lipid nanoparticle integrated with hydrogel for the leflunomide drug incorporated into tween-80, phospholipon G90, and Compritol 888 ATO shows promising protection against sunlight exposure. The Leflunomide enclosed in the amber container was found to have 80% drug content after sunlight exposure [94].

Moreover, curcumin was a polyphenol compound that had high degradability in case of light exposure. The nanoprecipitation was prepared using the green surfactant curcumin incorporated into poly lactic-co-glycolic acid to enhance the photolabile properties. The sample was irradiated with laser light at 633 nm compared to pure curcumin [95]. In addition, the prepared nanoparticle shows efficient protection against laser light exposure in that 13-fold increased solubility. Further, the studies of ellagic acid encapsulated into β-cyclodextrin nanosponges show a remarkable photostability property. The prepared ellagic acid-loaded nanosponges were irradiated using the UV-A light. They analyzed that the degradation of the ellagic acid was higher at the initial stage. This was due to free ellagic acid in the nanosponges; after, its physical barrier was protected against UV radiation [96].

Self micro-emulsifying drug delivery system

The self micro-emulsifying drug delivery system (SMEDDS) shows a promising drug delivery system for the hydrophobic drug substances. As it is an isotropic mixture of oil, surfactant, and co-surfactants. It will promptly convert into oil in a water emulsion system when it reaches the gastrointestinal tract [97]. Additionally, it promotes bioavailability by increasing the solubility of the drug product in the gastric and intestinal fluid. As well as it also enhances the photostability of the drug substance. The methotrexate SMEDDS prepared by tween 80, plurol, and castrol oil was formulated using the spray dryer in the solid carrier [98]. This methotrexate-loaded SMEDDS was carried over for the photostability studies for 12 weeks. They identified a small change in the color changes from yellow to orange in the pure methotrexate after exposure to the light sources. As in the case of the SMEDDS, it exhibits a promising effect on the photostability of methotrexate. Despite methotrexate exploration on the surface, the attached solid dispersion technique explains the studies in UVA/UVB. Consequently, they analyzed that this technique prevents the photodegradation caused by irradiation. The photostability investigation on the resveratrol-loaded SMEDDS shows almost 85% of the optimal formulation's drug content [99].

Multicomponent cocrystal

Cocrystal was one of the blooming strategies in the pharmaceutical industry. It provides various advantages of increasing the bioavailability and stability parameters, including thermal, moisture, oxidative, and photo stress [100, 101].

Reiko Teraoka et al. investigated the furosemide cocrystal with different coformer of caffeine, urea, and nicotinamide. After irradiation with a D65 fluorescent lamp for 90 days, they identified that the cocrystal formed by nicotinamide showed 1.3% chemical degradation. Similarly, carbamazepine was a photolabile drug in that the succinic acid and saccharin form one cocrystal produced higher stability [102]. Additionally, the nutrient molecule ubiquinol was highly oxidized in the presence of air, converted into ubiquinone, and reduced ubiquinol. The newly formed cocrystal with 3,4-dihydroxybenzoic exhibits higher stability under stressed conditions [103]. Likely, drug-drug cocrystal will also show a prominent synergistic effect, and the possible dose of the formulation can be reduced. It also enhances the higher photostability, as levofloxacin, an antibacterial agent, exhibits various degradation products upon light exposure. The levofloxacin-paracetamol cocrystal reveals a drastic improvement in physical and photostability [104].

In space medicine manufacturing from plants

On Earth, the efficacy of numerous medications tends to diminish after a year or six months, posing a challenge for Mars expeditions that may take twice as long. The limited storage capacity of spacecraft further complicates the issue, making it impractical to carry several years; worth of emergency medications. However, researchers at TRISH (Translational Research Institute for Space Health) are focused on finding a solution through the exploration of synthetic biology—a cutting-edge approach to pharmaceutical production [105]. By manipulating natural substances, they aim to create medications with enhanced stability, addressing the

critical problem of drug manufacturing in space. This innovative field shows promising potential for revolutionizing the way medications are developed and used in space missions [106]. Scientists are exploring ways to enhance human radiation resistance, and they have made significant progress by studying the genomes of tardigrades, which possess remarkable tolerance to ionizing radiation. Meanwhile, space missions already rely on plants as essential cargo [107].

NASA provides funding to various organizations to carry out a research project to look at the viability of utilizing plants for pharmaceutical manufacture in space. A study team has created a transgenic lettuce that can produce parathyroid hormone (PTH), a crucial protein drug, to address bone loss, a major problem astronauts encounter. PTH, granulocyte-colony stimulating factor (GCSF), and granulocyte–macrophage colony-stimulating factor (GMCSF) genes were inserted into three different types of lettuce seedlings. This inventive lettuce can produce the required drugs to stop bone deterioration in space. The team successfully introduced the human parathyroid hormone gene into the plant's DNA. This discovery opens the door to quick drug manufacture from genetically altered plants, which might be crucial for combating infectious disease outbreaks during space missions. With additional developments in this area, we might be able to find novel ways to protect the health and well-being of astronauts during protracted space travel.

3D printed medicine

Modern technologies, such as space manufacturing, offer potential solutions to the challenges faced in long-duration space missions. Among these advancements, 3D printing stands out as a particularly promising approach. NASA and Made in Space, Inc. sent the first 3D printer to the International Space Station in 2014, marking a significant milestone in off-planet manufacturing [108].

3D printing allows for the customization of medications in ways that traditional methods cannot achieve. By carefully selecting materials and adjusting settings, it becomes possible to modify both tablets' external and internal structures. Due to technological advancements, drugs may now be made as powders that dissolve more quickly than traditional tablets, increasing their efficacy [109]. Additionally, 3D printing enables accurate dose modifications catered to an individual's physical state. It can also be utilized to produce loose porous pills, ease swallowing, and develop transdermal microneedle patches to reduce discomfort during medication administration. The revolutionary potential of 3D printing technology might lead to a metamorphosis in the production and distribution of drugs in the future. Its capabilities in space and on Earth have the potential to revolutionize medical treatments, making them more personalized, efficient, and accessible [110].

Change of primary packaging material

The primary packaging for drug products used is the strips and blister in which one part has been covered with aluminum foil. This material has not been used for space pharmaceuticals as the nuclei from the radiation will strike the aluminum foil, producing the secondary particle. This secondary particle will affect the medicine present inside, which causes the formation of unstable drug products [111, 112]. Similarly, to prevent the physical instability caused by the rocket propulsion system, thruster, and engine, the packaging material should be critically evaluated to meet the specific requirements of the pharmacopeia. Therefore, new polymer technologies and non-metals can be used to avoid the consequence of daughter ions cumulations and physical instability. Using a variety of high-density polyethylene impregnated with tungsten and boron impregnated will act as the shielding effect for the radiation [113, 114].

Further, multiple layers with hydrated organic porous matrices will provide the attenuation and deflection characteristics. Even so, the ideal packaging material has to be subjected to long-term storage and use for future missions. The choice of the medium should consider the radiation sensitivity and the expansion of shelf life.

Conclusion

Effective medical therapy plays an important role in successful human space missions. During space missions, the effect of medicine depends on both aspects: physiological changes in astronauts and physicochemical changes in drug products. The physiological adaptation on the space mission is the critical parameter for the absorption, distribution, metabolism and excretion (ADME) of the drug product for the therapeutic action. Further, the data from the previous missions on GIT modification, cardiac deconditioning, protein binding, and the liver metabolic process will suggest support for the development of therapeutic doses for a longer duration of the mission.

The stability of pharmaceuticals depends on the length and duration of space missions. For short-duration space missions such as lunar or International Space Station (ISS) missions, data generated from the accelerated stability and SLEP studies will pave the way to understanding the physicochemical changes in the selected drug products. Proper selection of primary and secondary packaging material can avoid physicochemical changes in the drugs due to excessive vibration during space missions. Apart from that, novel drug formulation strategies like SMEDDS, the use of antioxidant excipients, and cocrystal development will be very helpful for the stability of drug products.

But for the longer duration mission, it is important to manufacture drugs using 3-D techniques or genetically modified plants at the time of use to get stable drug products. Such developments are anticipated to significantly contribute to new developments with applications both in space and on Earth.

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Declarations

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References

1. Hoffman SJ (1997) Human exploration of Mars: the reference mission of the NASA Mars exploration study team. National Aeronautics and Space Administration, Lyndon B. Johnson Space Center
2. Blue RS, Bayuse TM, Daniels VR, Wotring VE, Suresh R, Mulcahy RA, Antonsen EL (2019) Supplying a pharmacy for NASA exploration spaceflight: challenges and current understanding. npj Microgravity 5(1):14. https://doi.org/10.1038/s41526-019-0075-2
3. Wotring V (2019) Spaceflight pharmacology. Principles of clinical medicine for space flight, pp 815–840. https://doi.org/10.1007/978-1-4939-9889-0_27
4. Nikolaev DV, Shchelykalina SP, Korostylev KA, Semenova VV, Kolesnikov VA, Vassilieva GY (2022) Measurement and computational procedures of bioimpedance analysis to assess human postural instability in clinical and space medicine research. In: 2022 24th International conference on digital signal processing and its applications (DSPA). IEEE, pp 1–6. https://doi.org/10.1109/DSPA53304.2022.9790757.
5. Krittanawong C, Singh NK, Scheuring RA, Urquieta E, Bershad EM, Macaulay TR, Crucian BE (2022) Human health during space travel: state-of-the-art review. Cells 12(1):40. https://doi.org/10.3390/cells12010040
6. Sibonga J, Matsumoto T, Jones J, Shapiro J, Lang T, Shackelford L et al (2019) Resistive exercise in astronauts on prolonged spaceflights provides partial protection against spaceflight-induced bone loss. Bone 128:112037. https://doi.org/10.1016/j.bone.2019.07.013
7. Leblanc A, Matsumoto T, Jones J, Shapiro J, Lang T, Shackelford L, Ohshima H (2013) Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight. Osteoporos Int 24:2105–2114. https://doi.org/10.1007/s00198-012-2243-z
8. Seoane-Viano I, Ong JJ, Basit AW, Goyanes A (2022) To infinity and beyond: strategies for fabricating medicines in outer space. Int J Pharm X 4:100121. https://doi.org/10.1016/j.ijpx.2022.100121
9. Stewart LH, Trunkey D, Rebagliati GS (2007) Emergency medicine in space. J Emerg Med 32(1):45–54. https://doi.org/10.1016/j.jemermed.2006.05.031
10. Scully RR, Basner M, Nasrini J, Lam CW, Hermosillo E, Gur RC, Ryder VE (2019) Effects of acute exposures to carbon dioxide on decision making and cognition in astronaut-like subjects. npj Microgravity 5(1):17. https://doi.org/10.1038/s41526-019-0071-6
11. National Academies of Sciences, Engineering, and Medicine. Space radiation and astronaut health: managing and communicating cancer risks
12. Singleterry RC Jr, Blattnig SR, Clowdsley MS, Qualls GD, Sandridge CA, Simonsen LC et al (2011) OLTARIS: On-line tool for the assessment of radiation in space. Acta Astronaut 68(7–8):1086–1097. https://doi.org/10.1016/j.actaastro.2010.09.022
13. Sihver L, Mortazavi SMJ (2019) Radiation risks and countermeasures for humans on deep space missions. In: 2019 IEEE aerospace conference. IEEE, pp 1–10. https://doi.org/10.1109/AERO.2019.8742175
14. Mehta P, Bhayani D (2017) Impact of space environment on stability of medicines: challenges and prospects. J Pharm Biomed Anal 136:111–119. https://doi.org/10.1016/j.jpba.2016.12.040
15. Wotring VE (2016) Chemical potency and degradation products of medications stored over 550 earth days at the international space station. AAPS J 18:210–216. https://doi.org/10.1208/s12248-015-9834-5
16. Bhayani D, Naik H, Nathaniel TN, Khan S, Mehta P (2019) Simulated space radiation: Investigating ionizing radiation effects on the stability of amlodipine besylate API and tablets. Eur J Pharm Sci 137:104982. https://doi.org/10.1016/j.ejps.2019.104982
17. Bhayani D, Mehta P, Patel M, Naik H, Nathaniel TN, Khan S (2022) Ground-based selected ionizing space radiation effects on stability of APIs and their formulations. J Pharm Biomed Anal 220:115019. https://doi.org/10.1016/j.jpba.2022.115019
18. Fontaine J (2008) Towards the use of diamond-like carbon solid lubricant coatings in vacuum and space environments. Proc Inst Mech Eng Part J J Eng Tribol 222(8):1015–1029. https://doi.org/10.1243/13506501JET323
19. Thirsk R, Kuipers A, Mukai C, Williams D (2009) The spaceflight environment: the International Space Station and beyond. CMAJ 180(12):1216–1220. https://doi.org/10.1503/cmaj.081125

20. Oakey A, Waters T, Zhu W, Royall PG, Cherrett T, Courtney P, Jelev N (2021) Quantifying the effects of vibration on medicines in transit caused by fixed-wing and multi-copter drones. Drones 5(1):22. https://doi.org/10.3390/drones5010022
21. Malhotra A (2022) Pharmaceutical liquid dosage forms in space: looking toward the future by learning from the past. In: Handbook of space pharmaceuticals. Springer, Cham, pp 97–112. https://doi.org/10.1007/978-3-030-05526-4_16
22. McQuillen JB et al (2011) Final report for intravenous fluid generation (IVGEN) spaceflight experiment
23. DeVon G et al (2011) "IVGEN," presented at the Technology Showcase, Cleveland, OH. Available: https://ntrs.nasa.gov/citations/20150010343. Accessed 24 July 2023
24. Ray KM et al (2023) Intravenous Fluid Generation Mini (IVGEN Mini) Summary and Related Research. E-20087. https://ntrs.nasa.gov/citations/20220012816. Accessed 24 July 2023
25. Friedberg W, Copeland K (2011) Ionizing radiation in earth's atmosphere and in space near earth (No. DOT/FAA/AM-11/9). United States. Office of Aerospace Medicine
26. Yasuda H, Sihver L (2022) Broadening the selection criteria for Astronauts undertaking long–term space travel. Front Nucl Med 2:997718. https://doi.org/10.3389/fnume.2022.997718
27. Corliss WR (1968) Space Radiation. Atomic Energy Commission, Division of Technical Information
28. Wang Q, Xie C, Xi S, Qian F, Peng X, Huang J, Tang F (2020) Radioprotective effect of flavonoids on ionizing radiation-induced brain damage. Molecules 25(23):5719. https://doi.org/10.3390/molecules25235719
29. Rignall A (2017) ICHQ1A (R2) stability testing of new drug substance and product and ICHQ1C stability testing of new dosage forms. ICH quality guidelines: an implementation guide, pp 3–44. https://doi.org/10.1002/9781118971147.ch1
30. Mehrotra DV, Hemmings RJ, Russek-Cohen E, ICH E9/R1 Expert Working Group (2016) Seeking harmony: estimands and sensitivity analyses for confirmatory clinical trials. Clin Trials 13(4):456–458. https://doi.org/10.1177/1740774516633115
31. Khan SR, Mohammad A, Khan MA, Faustino PJ (2016) Critical importance and quality evaluation of drug delivery autoinjectors in the FDA-DOD shelf life extension program (SLEP). AAPS J 18:801–803. https://doi.org/10.1208/s12248-016-9910-5
32. Reichard JF, Phelps SE, Lehnhardt KR, Young M, Easter BD (2023) The effect of long-term spaceflight on drug potency and the risk of medication failure. npj Microgravity 9(1):35. https://doi.org/10.1038/s41526-023-00271-6
33. Thamthaweechok N, Thamlikitkul V, Tiengrim S (2018) Heat stability of antibiotics commonly used in food animals and agriculture in Thailand. J Med Assoc Thail 101(7)
34. Pranil T, Moongngarm A, Loypimai P (2020) Influence of pH, temperature, and light on the stability of melatonin in aqueous solutions and fruit juices. Heliyon. https://doi.org/10.1016/j.heliyon.2020.e03648
35. Afonin BV, Sedova EA (2012) Digestive system functioning during simulation of microravity effects on humans by means of immersion. Hum Physiol 38:776–780. https://doi.org/10.1134/S036211971207002X
36. Afonin BV (2013) Analysis of possible causes activation a stomach and pancreas excretory and incretory function after completion of space flight on the international space station. Fiziol Cheloveka 39(5):62–70
37. Chen Y, Yang CM, Han QL (2012) The effects of simulated weightlessness on plasma ghrelin, plasma VIP and gastrointestinal motility. Chin J Gastroenterol Hepatol 1(1):55–58
38. Amidon GL, DeBrincat GA, Najib N (1991) Effects of gravity on gastric emptying, intestinal transit, and drug absorption. J Clin Pharmacol 31(10):968–973. https://doi.org/10.1002/j.1552-4604.1991.tb03658.x
39. Braddock M (2017) Ergonomic challenges for astronauts during space travel and the need for space medicine. J Ergon 7(221):2. https://doi.org/10.4172/2165-7556.1000221
40. Jamil F, Kumar S, Sharma S, Vishvakarma P, Singh L (2011) Review on stomach specific drug delivery systems: development and evaluation. Int J Res Pharm Biomed Sci 2(4):14271433
41. Kast J, Yu Y, Seubert CN, Wotring VE, Derendorf H (2017) Drugs in space: pharmacokinetics and pharmacodynamics in astronauts. Eur J Pharm Sci 109:S2–S8. https://doi.org/10.1016/j.ejps.2017.05.025
42. Devadasu VR, Deb PK, Maheshwari R, Sharma P, Tekade RK (2018) Physicochemical, pharmaceutical, and biological considerations in GIT absorption of drugs. In: Dosage form design considerations. Academic Press, pp 149–178. https://doi.org/10.1016/B978-0-12-814423-7.00005-8
43. Schneeman BO (2002) Gastrointestinal physiology and functions. Br J Nutr 88(S2):S159–S163. https://doi.org/10.1079/BJN2002681
44. Turroni S, Magnani M, Kc P, Lesnik P, Vidal H, Heer M (2020) Gut microbiome and space travelers' health: state of the art and possible pro/prebiotic strategies for long-term space missions. Front Physiol 11:553929. https://doi.org/10.3389/fphys.2020.553929
45. Voorhies AA, Mark Ott C, Mehta S, Pierson DL, Crucian BE, Feiveson A et al (2019) Study of the impact of long-duration space missions at the International Space Station on the astronaut microbiome. Sci Rep 9(1):9911. https://doi.org/10.1038/s41598-019-46303-8
46. Schmidt MA, Meydan C, Schmidt CM, Afshinnekoo E, Mason CE (2020) The NASA twins study: the effect of one year in space on long-chain fatty acid desaturases and elongases. Lifestyle Genom 13(3):107–121. https://doi.org/10.1159/000506769
47. Tsunoda SM, Gonzales C, Jarmusch AK, Momper JD, Ma JD (2021) Contribution of the gut microbiome to drug disposition, pharmacokinetic and pharmacodynamic variability. Clin Pharmacokinet 60:971–984. https://doi.org/10.1007/s40262-021-01032-y
48. Clément G (2011) Fundamentals of space medicine, vol 23. Springer, Cham
49. Jirak P, Mirna M, Rezar R, Motloch LJ, Lichtenauer M, Jordan J, Jung C (2022) How spaceflight challenges human cardiovascular health. Eur J Prev Cardiol 29(10):1399–1411. https://doi.org/10.1093/eurjpc/zwac029
50. Hargens AR, Richardson S (2009) Cardiovascular adaptations, fluid shifts, and countermeasures related to space flight. Respir Physiol Neurobiol 169:S30–S33. https://doi.org/10.1016/j.resp.2009.07.005
51. Hargens AR, Bhattacharya R, Schneider SM (2013) Space physiology VI: exercise, artificial gravity, and countermeasure development for prolonged space flight. Eur J Appl Physiol 113:2183–2192. https://doi.org/10.1007/s00421-012-2523-5
52. Ly V, Velichala SR, Hargens AR (2022) Cardiovascular, lymphatic, and ocular health in space. Life 12(2):268. https://doi.org/10.3390/life12020268
53. Macias BR, Liu JH, Otto CA, Hargens AR (eds) (2017) Intracranial pressure and its effect on vision in space and on earth: vision impairment in space. World scientific
54. Parazynski SE, Hargens AR, Tucker B, Aratow M, Styf J, Crenshaw A (1991) Transcapillary fluid shifts in tissues of the head and neck during and after simulated microgravity. J Appl Physiol 71(6):2469–2475. https://doi.org/10.1152/jappl.1991.71.6.2469
55. Norsk P (2020) Adaptation of the cardiovascular system to weightlessness: surprises, paradoxes and implications for deep space missions. Acta Physiol 228(3):e13434. https://doi.org/10.1111/apha.13434

56. Evans JM, Knapp CF, Goswami N (2018) Artificial gravity as a countermeasure to the cardiovascular deconditioning of spaceflight: gender perspectives. Front Physiol 9:716. https://doi.org/10.3389/fphys.2018.00716
57. Verheyden B, Liu J, Beckers F, Aubert AE (2010) Operational point of neural cardiovascular regulation in humans up to 6 months in space. J Appl Physiol 108(3):646–654. https://doi.org/10.1152/japplphysiol.00883.2009
58. Waters WW, Ziegler MG, Meck JV (2002) Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. J Appl Physiol 92(2):586–594. https://doi.org/10.1152/japplphysiol.00544.2001
59. Xu D, Tremblay MF, Verma AK, Tavakolian K, Goswami N, Blaber AP (2020) Cardio-postural interactions and muscle-pump baroreflex are severely impacted by 60-day bedrest immobilization. Sci Rep 10(1):12042. https://doi.org/10.1038/s41598-020-68962-8
60. Blaber AP, Goswami N, Xu D (2022) Prolonged unloading of the cardiovascular system during bedrest and spaceflight weakens neural coupling between blood pressure and heart rate. Acta Astronaut 195:567–573. https://doi.org/10.1016/j.actaastro.2022.03.009
61. Eyal S, Derendorf H (2019) Medications in space: in search of a pharmacologist's guide to the galaxy. Pharm Res 36:1–13. https://doi.org/10.1007/s11095-019-2679-3
62. Trudel G, Shahin N, Ramsay T, Laneuville O, Louati H (2022) Hemolysis contributes to anemia during long-duration space flight. Nat Med 28(1):59–62. https://doi.org/10.1038/s41591-021-01637-7
63. Dello Russo C, Bandiera T, Monici M, Surdo L, Yip VLM, Wotring V, Morbidelli L (2022) Physiological adaptations affecting drug pharmacokinetics in space: what do we really know? A critical review of the literature. Br J Pharmacol 179(11):2538–2557
64. Garratty G, Arndt PA (2014) Drugs that have been shown to cause drug-induced immune hemolytic anemia or positive direct antiglobulin tests: some interesting findings since 2007. Immunohematology 30(2):66–79. https://doi.org/10.21307/immunohematology-2019-100
65. Trudel G, Shafer J, Laneuville O, Ramsay T (2020) Characterizing the effect of exposure to microgravity on anemia: more space is worse. Am J Hematol 95(3):267–273. https://doi.org/10.1002/ajh.25699
66. Simionato G, Rabe A, Gallego-Murillo JS, van der Zwaan C, Hoogendijk AJ, van den Biggelaar M et al (2022) In vitro erythropoiesis at different PO2 induces adaptations that are independent of prior systemic exposure to hypoxia. Cells 11(7):1082. https://doi.org/10.3390/cells11071082
67. Curry FRE (2005) Atrial natriuretic peptide: an essential physiological regulator of transvascular fluid, protein transport, and plasma volume. J Clin Investig 115(6):1458–1461. https://doi.org/10.1172/JCI25417
68. Arndt PA, Garratty G (2005) The changing spectrum of drug-induced immune hemolytic anemia. In: Seminars in hematology, vol 42, no 3. WB Saunders, pp 137–144. https://doi.org/10.1053/j.seminhematol.2005.04.004
69. Zhu JB, Yang JX, Nian YQ, Liu GQ, Duan YB, Bai X et al (2021) Pharmacokinetics of acetaminophen and metformin hydrochloride in rats after exposure to simulated high altitude hypoxia. Front Pharmacol 12:692349. https://doi.org/10.3389/fphar.2021.692349
70. Wanat K (2020) Biological barriers, and the influence of protein binding on the passage of drugs across them. Mol Biol Rep 47(4):3221–3231. https://doi.org/10.1007/s11033-020-05361-2
71. Pastushkova LK, Kashirina DN, Brzhozovskiy AG, Kononikhin AS, Tiys ES, Ivanisenko VA, Larina IM (2019) Evaluation of cardiovascular system state by urine proteome after manned space flight. Acta Astronaut 160:594–600. https://doi.org/10.1016/j.actaastro.2019.02.015
72. Kashirina DN, Percy AJ, Pastushkova LK, Borchers CH, Kireev KS, Ivanisenko VA et al (2019) The molecular mechanisms driving physiological changes after long duration space flights revealed by quantitative analysis of human blood proteins. BMC Med Genom 12:97–105. https://doi.org/10.1186/s12920-019-0490-y
73. Smith SA, Waters NJ (2019) Pharmacokinetic and pharmacodynamic considerations for drugs binding to alpha-1-acid glycoprotein. Pharm Res 36(2):30. https://doi.org/10.1007/s11095-018-2551-x
74. Daryaee F, Tonge PJ (2019) Pharmacokinetic–pharmacodynamic models that incorporate drug–target binding kinetics. Curr Opin Chem Biol 50:120–127. https://doi.org/10.1016/j.cbpa.2019.03.008
75. Yang JQ, Jiang N, Li ZP, Guo S, Chen ZY, Li BB, Cui Y (2020) The effects of microgravity on the digestive system and the new insights it brings to the life sciences. Life Sci Space Res 27:74–82. https://doi.org/10.1016/j.lssr.2020.07.009
76. Zhang Y, Zhao J, Jing J, Zhang R, Zhou X, Gao J et al (2021) Effects of simulated weightlessness on metabolizing enzymes and pharmacokinetics of folic acid in SD rats. Biol Pharm Bull 44(2):162–168. https://doi.org/10.1248/bpb.b20-00299
77. Zong B, Wang Y, Wang J, Zhang P, Kan G, Li M et al (2022) Effects of long-term simulated microgravity on liver metabolism in rhesus macaques. FASEB J 36(10):e22536. https://doi.org/10.1096/fj.202200544RR
78. Kersten S (2021) ANGPTL3 as therapeutic target. Curr Opin Lipidol 32(6):335–341. https://doi.org/10.1097/MOL.0000000000000789
79. Ranade A, Khan AA, Gul MT, Suresh S, Qaisar R, Ahmad F, Karim A (2023) Suppression of endoplasmic reticulum stress reverses hindlimb unloading-induced hepatic cellular processes in mice. Biochimica et Biophysica Acta (BBA)-General Subjects 1867(9):130422. https://doi.org/10.1016/j.bbagen.2023.130422
80. Cahilog Z et al (2022) Astronaut health & performance in space—a review IAC 2022
81. Anselm V, Novikova S, Zgoda V (2017) Re-adaption on earth after spaceflights affects the mouse liver proteome. Int J Mol Sci 18(8):1763. https://doi.org/10.3390/ijms18081763
82. Chen B, Guo J, Wang S, Kang L, Deng Y, Li Y (2018) Simulated microgravity altered the metabolism of loureirin B and the expression of major cytochrome P450 in liver of rats. Front Pharmacol 9:1130. https://doi.org/10.3389/fphar.2018.01130
83. Paxton J (ed) (2012) Topics on drug metabolism. BoD–Books on Demand
84. Martignoni M, Groothuis GM, de Kanter R (2006) Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction. Expert Opin Drug Metab Toxicol 2(6):875–894. https://doi.org/10.1517/17425255.2.6.875
85. Turpeinen M, Ghiciuc C, Opritoui M, Tursas L, Pelkonen O, Pasanen M (2007) Predictive value of animal models for human cytochrome P450 (CYP)-mediated metabolism: a comparative study in vitro. Xenobiotica 37(12):1367–1377. https://doi.org/10.1080/00498250701658312
86. Puccinelli E, Giovanni Gervasi P, Longo V (2011) Xenobiotic metabolizing cytochrome P450 in pig, a promising animal model. Curr Drug Metab 12(6):507–525. https://doi.org/10.2174/138920011795713698
87. Sinz M, Wallace G, Sahi J (2008) Current industrial practices in assessing CYP450 enzyme induction: preclinical and clinical. AAPS J 10:391–400. https://doi.org/10.1208/s12248-008-9037-4

88. Bergström CA, Charman WN, Porter CJ (2016) Computational prediction of formulation strategies for beyond-rule-of-5 compounds. Adv Drug Deliv Rev 101:6–21. https://doi.org/10.1016/j.addr.2016.02.005
89. Abd-Algaleel SA, Abdel-Bar HM, Metwally AA, Hathout RM (2021) Evolution of the computational pharmaceutics approaches in the modeling and prediction of drug payload in lipid and polymeric nanocarriers. Pharmaceuticals 14(7):645. https://doi.org/10.3390/ph14070645
90. Celestino MT, Magalhães UDO, Fraga AGM, Carmo FAD, Lione V, Castro HC et al (2012) Rational use of antioxidants in solid oral pharmaceutical preparations. Braz J Pharm Sci 48:405–415. https://doi.org/10.1590/S1984-82502012000300007
91. Sinha A, Behera A (2022) Chapter 8—Nanotechnology in the space industry. In: Denizli A, Alencar MS, Nguyen TA, Motaung DE (eds) Nanotechnology-based smart remote sensing networks for disaster prevention. Micro and Nano Technologies. Elsevier, pp 139–157. https://doi.org/10.1016/B978-0-323-91166-5.00005-7
92. Dantuma DM, Elmaddawi R, Pathck Y, Grenha AM, de Oliveira R, Paludo C et al (2015) Impact of simulated microgravity on nanoemulsion stability? A preliminary research. Am J Med Biol Res. https://doi.org/10.12691/ajmbr-3-4-4
93. Rosa P, Friedrich ML, Dos Santos J, Librelotto DRN, Maurer LH, Emanuelli T et al (2019) Desonide nanoencapsulation with acai oil as oil core: Physicochemical characterization, photostability study and in vitro phototoxicity evaluation. J Photochem Photobiol B Biol 199:111606. https://doi.org/10.1016/j.jphotobiol.2019.111606
94. Alhelal HM, Mehta S, Kadian V, Kakkar V, Tanwar H, Rao R et al (2023) Solid lipid nanoparticles embedded hydrogels as a promising carrier for retarding irritation of leflunomide. Gels 9(7):576. https://doi.org/10.3390/gels9070576
95. Kumari A, Guliani A, Shukla AK, Kumar S, Acharya A (2020) Green surfactant based synthesis of curcumin loaded poly lactic-co-glycolic acid nanoparticles with enhanced solubility, photostability and anti-biofilm activity. J Drug Deliv Sci Technol 59:101884. https://doi.org/10.1016/j.jddst.2020.101884
96. Sharma K, Kadian V, Kumar A, Mahant S, Rao R (2022) Evaluation of solubility, photostability and antioxidant activity of ellagic acid cyclodextrin nanosponges fabricated by melt method and microwave-assisted synthesis. J Food Sci Technol. https://doi.org/10.1007/s13197-021-05085-6
97. Kim DS, Cho JH, Park JH, Kim JS, Song ES, Kwon J, Kim DW (2019) Self-microemulsifying drug delivery system (SMEDDS) for improved oral delivery and photostability of methotrexate. Int J Nanomed. https://doi.org/10.2147/IJN.S211014
98. Giri BR, Kim JS, Park JH, Jin SG, Kim KS, Din FU et al (2021) Improved bioavailability and high photostability of methotrexate by spray-dried surface-attached solid dispersion with an aqueous medium. Pharmaceutics 13(1):111. https://doi.org/10.3390/pharmaceutics13010111
99. Thota SK, Dudhipala N, Katla V, Veerabrahma K (2023) Cationic solid SMEDDS of Efavirenz for improved oral delivery: development by central composite design, in vitro and in vivo evaluation. AAPS PharmSciTech 24(1):38. https://doi.org/10.1208/s12249-022-02495-3
100. Liu L, Wang JR, Mei X (2022) Enhancing the stability of active pharmaceutical ingredients by the cocrystal strategy. CrystEngComm 24(11):2002–2022. https://doi.org/10.1039/D1CE01327K
101. Singh M, Barua H, Jyothi VGS, Dhondale MR, Nambiar AG, Agrawal AK et al (2023) Cocrystals by design: a rational coformer selection approach for tackling the API problems. Pharmaceutics 15(4):1161. https://doi.org/10.3390/pharmaceutics15041161
102. Yutani R, Haku R, Teraoka R, Tode C, Koide T, Kitagawa S, Fukami T (2019) Comparative evaluation of the photostability of carbamazepine polymorphs and cocrystals. Crystals 9(11):553. https://doi.org/10.3390/cryst9110553
103. Bofill L, de Sande D, Barbas R, Prohens R (2020) New cocrystal of ubiquinol with high stability to oxidation. Cryst Growth Des 20(8):5583–5588. https://doi.org/10.1021/acs.cgd.0c00749
104. Shinozaki T, Ono M, Higashi K, Moribe K (2019) A novel drug-drug cocrystal of levofloxacin and metacetamol: reduced hygroscopicity and improved photostability of levofloxacin. J Pharm Sci 108(7):2383–2390. https://doi.org/10.1016/j.xphs.2019.02.014
105. Saei AA, Omidi AA, Barzegari A (2013) Screening and genetic manipulation of green organisms for establishment of biological life support systems in space. Bioengineered 4(2):65–71. https://doi.org/10.4161/bioe.22286
106. Mortimer JC, Gilliham M (2022) SpaceHort: redesigning plants to support space exploration and on-earth sustainability. Curr Opin Biotechnol 73:246–252. https://doi.org/10.1016/j.copbio.2021.08.018
107. De Martinis D, Hitzeroth II, Matsuda R, Soto Pérez N, Benvenuto E (2022) Engineering the plant biofactory for the production of biologics and small-molecule medicines—volume 2. Front Plant Sci 13:942746. https://doi.org/10.3389/fpls.2022.942746
108. Li Q, Kucukkoc I, Zhang DZ (2017) Production planning in additive manufacturing and 3D printing. Comput Oper Res 83:157–172. https://doi.org/10.1016/j.cor.2017.01.013
109. Park BJ, Choi HJ, Moon SJ, Kim SJ, Bajracharya R, Min JY, Han HK (2019) Pharmaceutical applications of 3D printing technology: current understanding and future perspectives. J Pharm Investig 49:575–585. https://doi.org/10.1007/s40005-018-00414-y
110. Zhu X, Li H, Huang L, Zhang M, Fan W, Cui L (2020) 3D printing promotes the development of drugs. Biomed Pharmacother 131:110644. https://doi.org/10.1016/j.biopha.2020.110644
111. Chakravarti A, Gowthamarajan K, Venkatesan J (2022) A brief introduction to the universe of space medication. J Med Pharm Allied Sci 11(2):4770–4776. https://doi.org/10.55522/jmpas.V11I2.2946
112. Reichard J, Lehnhardt K, Young M, Easter B (2022) Analysis of the effect of spaceflight on drug potency to quantify the risk of medication failure for exploration space missions. https://doi.org/10.21203/rs.3.rs-1720710/v1
113. Putcha L, Taylor PW, Boyd JL (2011) Biopharmaceutical challenges of therapeutics in space: formulation and packaging considerations. Ther Deliv 2(11):1373–1376. https://doi.org/10.4155/tde.11.115
114. Du B, Daniels VR, Vaksman Z, Boyd JL, Crady C, Putcha L (2011) Evaluation of physical and chemical changes in pharmaceuticals flown on space missions. AAPS J 13:299–308. https://doi.org/10.1208/s12248-011-9270-0

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