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Letter

Microplastics Entry into the Blood by Infusion Therapy: Few but a Direct Pathway

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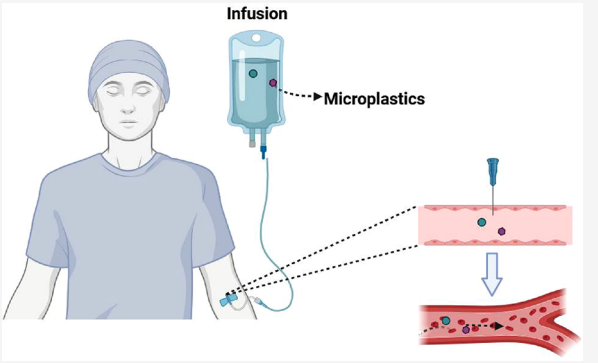
ABSTRACT: Microplastic pollution is now ubiquitous in the environment, making human exposure to microplastics unavoidable. This results in the detection of microplastics in human bodies, including blood. However, the pathways through which microplastics enter the bloodstream still need to be clarified, despite the studies of several direct and indirect routes. Herein, the potential occurrence of microplastics in infusion therapy sets, including glass infusion bottles, plastic infusion bottles, plastic infusion bags, and plastic infusion tubes, was investigated. The results showed that a total of eight microplastics, ranging from 4 to 148 μm in size, were identified from three PP-bottled infusion, three PE-bagged infusion, and one glass-bottled infusion, consisting of PE, PA, PS, and PC, while no particles were detected in infusion tubes. The samples containing microplastics accounted for 11.66% of the total samples with 1−2 particles/unit. Although microplastics were detected in infusion solutions, microplastic exposure to the bloodstream via infusion therapy is minimal, owing to their low abundance. Nevertheless, these findings suggested that infusion therapy might be a direct pathway of microplastics entering the bloodstream, partially or fully explaining the presence of microplastics in human blood and tissues.



KEYWORDS: *Plastic particles, Exposure pathway, Infusion therapy, Blood, Health risk*

1. INTRODUCTION

Microplastics are defined as plastic particles of "≤5 mm" diameter. Recently, they have been regarded as emerging contaminants, although these tiny particles were discovered in the 1970s.[1] The widespread and persistent presence of microplastics in the environment has raised public concerns regarding their potential health risks. A recent study detected microplastics in human blood, with an average concentration of 1.6 μg/mL in 17 of 22 healthy volunteers, indicating that microplastics have entered human bloodstreams.[2] Furthermore, Wu et al.[3] observed the presence of 87 plastic particles with diameters ranging from 2.1 to 26.0 μm in 16 human thrombi, and a statistically significant association between microparticle abundance and blood platelet levels was further established. These findings implied that the tiny plastic particles in the human circulatory system might pose threats to human health. Given that microplastics have been identified successively in the human placenta, newborns, and meconium,[4−6] concerns about the pathways of microplastics entering the bloodstream circulatory are rising.

Generally, microplastics can enter humans through ingestion, inhalation, and dermal contact. Among these pathways, ingestion, and inhalation are the primary routes because of their widespread detection in food and air.[7−10] For example, cultured bivalves contain an average of 0.47 ± 0.16 and 0.36 ± 0.07 items/g of microplastics,[11] while billions of microplastics and nanoplastics could be released from plastic teabags into warm tea.[12] Consequently, an average of 39,000 to 52,000 microplastics are ingested only through foods by common Americans annually, while the number increases to 74,000 and 121,000 when inhalation is considered.[13] Once these microplastics cross biological barriers and enter the bloodstream, human health might be affected seriously.[14−16] According to a report by FAO,[17] however, microplastics larger than 150 μm are virtually impossible to be absorbed, and even the uptake of 20-μm particles is also limited. Although the results of several laboratory tests suggest that nanoplastics are capable of penetrating biological barriers,[18−20] conclusive evidence of their presence in human blood is unavailable

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owing to the limitations of current analytical methods. In addition, the small intestine provides an effective barrier against particle uptake, including microplastics and nanoplastics, and hinders the intracellular uptake of larger particles because of their incompatibility with intestinal epithelial cells (approximately 10 μm).[21] Therefore, the presence of microplastics in blood could not be adequately explained by ingestion and inhalation, particularly for particles larger than 10 μm.[3]

Intravenous infusion therapy (IV therapy) is widely used in clinical practice, owing to its quick and effective pain relief. However, using plastic infusion bottles, bags, and syringes might also directly introduce plastic particles into the bloodstream. Herein, we hypothesized that microplastics could be introduced into the bloodstream during IV therapy if the infusion solution contains microplastics. After all, it is similar to a toxic diffusion way by transinjection, a classic drug study model.[22−24] Once in circulation, parts of microplastics might pass through barriers by simple diffusion and finally accumulate in blood and tissue medium,[25] increasing their toxicity. To confirm this hypothesis, microplastics were identified in infusion solutions packaged in plastic bottles and bags commonly used in clinical settings. Meanwhile, infusion solutions with glass bottles and plastic infusion tubes were also sampled to determine the potential source of microplastics. Finally, the possibility of human exposure to microplastics was evaluated via IV therapy. These findings will improve the understanding of the occurrence of microplastics in the human bloodstream, particularly the transfer and accumulation of microplastics in human tissues and organs.

2. METHODS AND MATERIALS

2.1. Sample Collection. Plastic infusion bottles and bags with 0.9% sodium chloride solution were purchased from a common pharmacy store, including 15 polypropylene(PP)-bottled infusions (500 mL/bottle) and 15 polyethylene(PE)-bagged infusions (1000 mL/bag). These infusion sets are commonly used to treat diseases in hospitals. In addition, 15 plastic infusion tubes (60 cm in length) and 15 glass-bottled infusions (500 mL/bottle) were obtained from a local hospital. The polymers of these infusion sets were identified individually by using the Agilent Cary 630 Fourier-transform infrared spectrometer (Figure 1).

2.2. Sample Treatment. The entire operation process for isolating microplastics was conducted following the guideline previously established in our laboratory with minor modifications.[26] Before treatment, the outside surface of infusion bags and bottles was carefully cleaned three times with ultrapurified water. Then, the lids of each unit were removed, and the solutions were directly filtered through a 0.8-μm pore size and 2.5 cm diameter silver filter membrane (Sterlitech, USA) using a glass filter. Then, 100 mL of purified water was added to the filtering device and retained for 20 min to eliminate potential sodium chloride residues in the silver membrane. Subsequently, these silver membranes were individually stored in clean glass Petri dishes for further analysis.

To detect the possible shedding of microplastics from infusion tubes, six glass infusion bottles obtained from the above tests were first rerinsed thrice with purified water. Then, 500 mL of purified water was poured into each bottle and connected to a set of infusion tubes. The purified water was then collected dropwise using another clean glass bottle via an infusion tube, simulating a clinical process of IV therapy. The remaining procedures were identical with those described above.

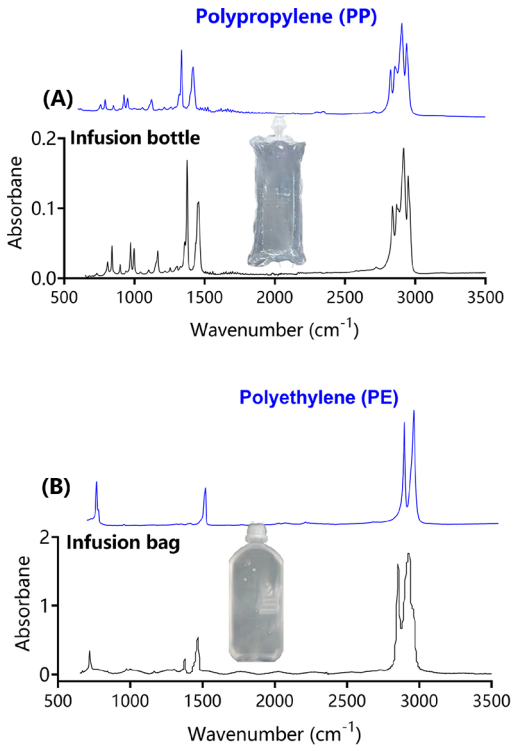

Figure 1. Polyethylene infusion bags (A) and polypropylene infusion bottles (B) identified by the FT-IR spectrum.

2.3. Microplastic Identification. To capture all particles on the filters, the filter membrane was first observed directly under an optical microscope with a 10-fold magnification. Once particles more than 1.0 μm with a 3D shape were found, a micro-Raman spectrometer (Scientific DXR2xi, USA) was further used to identify the corresponding polymers in confocal mode with Thermo Scientific DXRTM2xi Raman Imaging software. The following condition was set: 785 nm excitation wavelength with 3.1 μm spot size approximately, 5-s integration time at the wavenumber range of 500−2000 cm^{-1} under a laser power of 24 Mw. The spectrum of each particle was searched against the built-in libraries to confirm its polymer using the library search tool within the OMNICxi software. Particles only with >75% matching ratio (Hit quality index) and significant characteristic peak anastomosis were concerned as microplastics.

2.4. Quality Assurance and Quality Control. All treatment processes were implemented on an ultraclean platform to prevent background contamination. Cotton clothing and powder-free nitrile gloves were worn throughout the experiments. Glass bottles and silver membranes used in this study were thoroughly rinsed with purified water, which was filtered three times through 0.8-μm pore size silver membranes. During the simulation and filtration procedures, all bottles and dishes were promptly covered with aluminum foil paper. Furthermore, all preparation and analysis were conducted in unique rooms without ventilation and low activities. Three procedural blanks were performed using purified water to evaluate background contamination during processing and analysis. No microplastics were detected in these blank samples.

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3. RESULTS AND DISCUSSION

3.1. Microplastics Characteristics in Infusion Solutions. In the current study, 60 samples were individually investigated, and finally, 8 transparent tiny fragments were identified in a total of 7 samples (Table 1). Namely, 3 fragments were detected in 3 plastic infusion bottles, 4 fragments in 3 plastic infusion bags, one fragment in one glass infusion bottle, and no particle was found in plastic infusion tubes. These fragments consisted of polyethylene (PE, 4), polyamide (PA, 2), polycarbonate (PC, 1), and polystyrene (PS,1), and their sizes ranged from 4 to 148 μm (Figure 2).

Table 1. Microplastics Were Detected in Infusion Solutions[a]

Samples	No.	Number	Polymer	Size (μm)	Shape	HQI
PP-bottled infusion	#1	n.d.	n.d.	n.d.	n.d.	n.d.
	#2	n.d.	n.d.	n.d.	n.d.	n.d.
	#3	n.d.	n.d.	n.d.	n.d.	n.d.
	#4	n.d.	n.d.	n.d.	n.d.	n.d.
	#5	n.d.	n.d.	n.d.	n.d.	n.d.
	#6	n.d.	n.d.	n.d.	n.d.	n.d.
	#7	n.d.	n.d.	n.d.	n.d.	n.d.
	#8	n.d.	n.d.	n.d.	n.d.	n.d.
	#9	n.d.	n.d.	n.d.	n.d.	n.d.
	#10	1	PA	59	fragment	97
	#11	n.d.	n.d.	n.d.	n.d.	n.d.
	#12	n.d.	n.d.	n.d.	n.d.	n.d.
	#13	1	PE	114	fragment	99
	#14	1	PE	151	fragment	94
	#15	n.d.	n.d.	n.d.	n.d.	n.d.
Glass-bottled infusion	#1	1	PS	16	fragment	97
	#2	n.d.	n.d.	n.d.	n.d.	n.d.
	#3	n.d.	n.d.	n.d.	n.d.	n.d.
	#4	n.d.	n.d.	n.d.	n.d.	n.d.
	#5	n.d.	n.d.	n.d.	n.d.	n.d.
	#6	n.d.	n.d.	n.d.	n.d.	n.d.
	#7	n.d.	n.d.	n.d.	n.d.	n.d.
	#8	n.d.	n.d.	n.d.	n.d.	n.d.
	#9	n.d.	n.d.	n.d.	n.d.	n.d.
	#10	n.d.	n.d.	n.d.	n.d.	n.d.
	#11	n.d.	n.d.	n.d.	n.d.	n.d.
	#12	n.d.	n.d.	n.d.	n.d.	n.d.
	#13	n.d.	n.d.	n.d.	n.d.	n.d.
	#14	n.d.	n.d.	n.d.	n.d.	n.d.
	#15	n.d.	n.d.	n.d.	n.d.	n.d.
PE-bagged infusion	#1	n.d.	n.d.	n.d.	n.d.	n.d.
	#2	n.d.	n.d.	n.d.	n.d.	n.d.
	#3	n.d.	n.d.	n.d.	n.d.	n.d.
	#4	n.d.	n.d.	n.d.	n.d.	n.d.
	#5	n.d.	n.d.	n.d.	n.d.	n.d.
	#6	1	PE	4	fragment	75
	#7	1	PE	70	fragment	95
		1	PC	148	fragment	95
	#8	n.d.	n.d.	n.d.	n.d.	n.d.
	#9	n.d.	n.d.	n.d.	n.d.	n.d.
	#10	n.d.	n.d.	n.d.	n.d.	n.d.
	#11	1	PA	81	fragment	94
	#12	n.d.	n.d.	n.d.	n.d.	n.d.
	#13	n.d.	n.d.	n.d.	n.d.	n.d.
	#14	n.d.	n.d.	n.d.	n.d.	n.d.
	#15	n.d.	n.d.	n.d.	n.d.	n.d.

[a]n.d.: not detected. HQI: hit quality index.

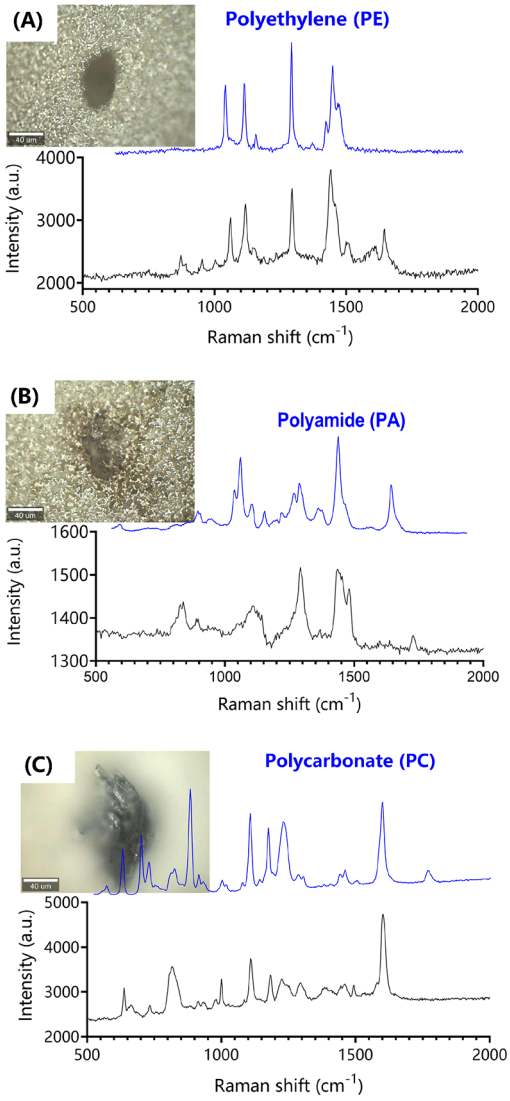

Figure 2. Microplastics in infusion detected by Raman spectrum: (A) polyethylene (PE), (B) polyamide (PA), and (C) polycarbonate (PC).

Given that microplastic contamination is ubiquitous in the environment, the quality of the infusion solutions is satisfactory for patients owning to, although a few tiny plastic fragments were detected in these infusion solutions. However, the detection of microplastics in infusion solutions indicated that IV therapy might be a direct pathway for microplastics entering the bloodstream. This finding can explain, at least in part, the presence of microplastics in human blood.[2,3] Thus, microplastics are more likely to enter the human body through transfusion rather than crossing cellular barriers, which is restricted owing to limited tissue absorption mechanisms.[16] It should be pointed out that polymer-based nanoparticles are often used as vectors in drug delivery systems for precision therapy.[22−24] Compared to these nanoparticles with biocompatibility and biodegradability, however, microplastics are commonly nondegradable, which might be present for their whole lives once they enter the human bloodstream.

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In addition, some signals which were similar to those from polymers were also found on some filter membranes, but no significant particle could be observed in the micro-Raman spectra. This suggested that some smaller plastic particles might be present in the infusion solutions despite the lack of clear evidence. Notably, the sensitivity of the current approach is not adequate to identify particles <1.0 μm, such as nanoplastics. Alternatively, 500−1000 mL of plastic-bottled, plastic-bagged, and glass-bottled infusion solutions were sampled individually and analyzed using a thermal extraction−desorption coupled with GC/MS with the detection limits of 0.5 μg PS, 1.0 μg PE, and 5 μg PP (data are not shown). However, no polymer was detected in these samples, implying that the concentration of target microplastics in infusion solutions would be lower than the limits of detection. Therefore, various advanced analytical techniques with high sensitivities need to be developed for monitoring potential microplastics and nanoplastics contamination in infusion solutions in the future.

3.2. Human Exposure to Microplastic via IV Therapy. The present test detected the presence of microplastics in infusion solutions with 1−2 particle/1000 mL PE-bagged infusion and one particle/500 mL glass-bottled infusion, respectively. Generally, the infusion solutions are injected into blood through an infusion tube with an in-line filter of intravenous administration sets. The in-line filters can intercept >90% of particles with ≥5 μm diameter (https://www.weigaoholding.com), including these microplastics more than 5 μm in size. However, plastic particles with <5 μm diameter might also escape the intercept and flow directly into the bloodstream. For example, a 4 μm polyethylene (PE) microplastic was detected in a plastic infusion bag. These tiny plastic particles might accumulate in vascular walls and then interfere with or even block the bloodstream, as reported by Wu et al.[3] Despite high filtering capacity, in-line filters could not capture all particles completely and a few microplastics >10 μm might also enter the bloodstream.[27] Thus, patients who frequently receive IV therapy might be exposed to microplastics with possibilities relatively higher than those who do not.

Despite entrance through IV therapy being a direct pathway for the microplastics to enter human blood, the number of microplastic particles entering human bodies via IV therapy is absolutely small in comparison with the number of those entering humans through ingestion and inhalation. This is due to the low abundance and detection ratio of microplastics in infusion solutions. Importantly, Horvatits et al.[28] reported that the abundance of microplastics detected in liver samples from patients with cirrhosis (4.6−11.9 particles/g) was dramatically higher than those without underlying chronic liver disease (0.3−1.9 particles/g). They deduced that microplastics might cross the impaired intestinal barrier caused by chronic liver disease and then migrate to liver tissues. Schmidt et al.[29] also observed a significantly enhanced accumulation of microplastics in the inflamed mucosal areas and ulcerous lesions through biopsies compared to healthy controls, implying a possible association between microplastic uptake and/or translocation and inflamed mucosal areas.[28] In addition, Yan et al.[30] reported that the fecal microplastic levels were significantly higher in patients with inflammatory bowel disease (41.8 items/g) than in healthy individuals (28.0 items/g). Considering the previously reported findings combined with the current results, we deduced that the microplastics detected in liver and mucosal areas likely entered the body along with the infusion solutions during IV therapy rather than translocation through an impaired inflamed barrier. This implies that these patients received IV therapy and thus were exposed to more microplastics via infusion solutions than healthy individuals, resulting in more microplastics entering the bloodstream, circulating systemically, and finally accumulating in tissues. Consequently, various microplastics were detected in the human placenta,[4] liver,[28] and breast milk.[31] Therefore, the risk of exposure to microplastics for patients who often receive IV therapy should be fully assessed in the future. Furthermore, large microplastics have the potential to obstruct blood vessels owing to their relatively larger volumes compared with the diameter of the blood capillaries.[32] For example, particles >10 μm in size could be trapped in the lungs, regardless of their nature, thereby blocking the pulmonary vessels.[27] Similarly, the microplastics detected in human thrombi were all block-shaped,[3] and they might promote thrombosis and then seriously hamper blood circulation after accumulating inside the vessels.

3.3. Potential Source of Microplastics in Infusion Solutions. Plastics are widely used in various aspects of modern life. Moreover, a significant proportion of medical and clinical devices are made of plastics, potentially resulting in microplastic contamination in medical equipment and consumables, similar to what is illustrated by the current results. That is, two PE particles were identified in both PE-bagged infusion and PP-bottled infusion, respectively. It indicated that these plastic particles might shed not only from bags during production and usage but also from other sources. Certainly, it appears that the microplastics were generated from the residual materials during the production of plastic bags based on the irregular shapes and transparency of these particles. If this speculation is true, the production process of plastic bags for packaging infusion solution should be updated to properly remove the residuals from the inside of bags. In addition, plastic particles are also easily shed from packaging bags when these bags are squeezed and broken. For example, plastic containers/bags/tapes/caps can generate microplastics through simple procedures such as scissoring with scissors, tearing with hands, cutting with knives, and even twisting manually.[33] Additionally, one plastic particle was detected in a glass-bottled infusion, also indicating that microplastics detected in infusion solutions are not necessarily derived from the corresponding bottles. Alternatively, the microplastics might be introduced into infusion solutions during the processes of solution production, including water processing and bottle preparation. Notably, various tools and pipelines in pharmaceutical factories are widely made of plastics, and avoiding the use of plastics throughout production is nearly impossible. Moreover, the current quality control for monitoring the production of infusion solutions in pharmaceutical plants also does not include microplastic as one of the control sanitation indicators, and no international standards are available for controlling microplastic contamination in infusion solutions and the corresponding medical products. Thus, the updated quality control system should consider controlling microplastic as an emerging contamination to establish a strict quality control and assurance system for protecting human health.

In conclusion, this study first reported the presence of microplastics in infusion solutions. Importantly, it implied that microplastics in human blood, at least partially, are injected

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directly into the blood from IV therapy. The results are expected to enhance our understanding of the source of blood microplastics. Notably, the possibility of microplastics crossing cell walls cannot be completely ruled out, owing to the current availability of limited data. Further robust evidence is required to identify all sources of microplastics in the human circulatory system and tissues. Simultaneously, it is urgent to determine the adverse impacts of the appearance of microplastics in the bloodstream and tissues and to differentiate whether they are a potential cause or consequence of diseases resulting from human exposure to microplastics.

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Author Contributions

#Long Zhu and Mindong Ma contributed equally.

Notes

The authors declare no competing financial interest.

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